



**World Health  
Organization**

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

**SAGE**

**October 2014**

**Strategic Advisory Group of Experts  
on Immunization  
21-23 October 2014**

**Executive Boardroom  
WHO HQ, Geneva**



**World Health  
Organization**

## **SAGE October 2014**

This booklet contains key background documents for the  
meeting of the  
Strategic Advisory Group of Experts (SAGE) on immunization  
21-23 October 2014

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

<http://www.who.int/immunization/sage/meetings/2014/october>

For password, please send an e-mail to: [sageexecsec@who.int](mailto:sageexecsec@who.int)

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**Draft Agenda**  
**Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)**  
**21 – 23 October 2014**  
**EB Room, WHO HQ Geneva**

**Tuesday, 21 October 2014**

<b>Time</b>	<b>Session</b>	<b>Purpose of session, target outcomes and questions for SAGE</b>	
9:00	<b>Welcome - introduction</b>  J. Abramson, Chair of SAGE		20 min.
9:10	<b>Report from Director, IVB - Session 1</b>  Global report including key updates and challenges from regions, P. Duclos, WHO, 30 min.  Discussion: 50 min	<b>FOR INFORMATION</b>	2h
<b>10:30</b>	<b>Coffee/tea break</b>	<b>Break</b>	<b>30 min.</b>
11:00	<b>Report from Director, IVB - Session 1, (Contd.)</b>  Update on the Ebola outbreak and experimental Ebola vaccines, M.-P. Kieny or D. Wood, WHO, 15 min.  Discussion: 30 min.		
11:40	<b>Report from GAVI - Session 2</b>  Report from the GAVI Alliance, R. Newman, GAVI Alliance, 20 min.  Discussion: 20 min.	<b>FOR INFORMATION</b>	40 min.
12:20	<b>Reports from other Advisory Committees on Immunization - Session 3</b>  Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min.  Discussion: 10 min.	<b>FOR INFORMATION</b>	1h 20 min.



	Report of the Immunization Practices Advisory Committee (IPAC), C. Morgan, Chair of IPAC, 10 min.  Discussion: 10 min.		
<b>13:00</b>	<b>Lunch</b>	<b>Break</b>	<b>1h</b>
14:00	<p><b>Reports from other Advisory Committees on Immunization - Session 3, (Contd.)</b></p> <p>Report of the Immunization and vaccines related implementation research advisory committee (IVIR-AC), R. Breiman, Chair of IVIR-AC, 10 min. Discussion: 10 min.</p> <p>Report on the first meeting of the Product Development for Vaccines Advisory Committee (PDVAC), D. Kaslow, Chair of PDVAC, 10 min. Discussion: 10 min.</p> <p>Report of the Expert Committee on Biological Standardization (ECBS), E. Griffiths, Chair of ECBS, 10 min. Discussion: 10 min.</p>	<b>FOR INFORMATION</b>	
15:00	<p><b>GVAP progress report - Session 4</b></p> <p>The GVAP Secretariat Report 2014: Update on process, new indicators, &amp; dashboard, T. Cherian (For the Secretariat of the Decade of Vaccines Working Group), WHO, 15 min.</p> <p>Summary of GVAP implementation progress review and recommendations for corrective actions, N. Arora, Chair of the SAGE Decade of Vaccines Working Group, 30 min.</p>	<p><b>FOR DISCUSSION AND DECISION</b></p> <p>SAGE will be expected to produce an independent annual report on progress with the Decade of Vaccines Global Vaccine Action Plan.</p> <p>Specially, SAGE will be asked to:</p> <ul style="list-style-type: none"> <li>Review the DoV WG "Assessment report on DoV progress" based on the "GVAP Secretariat report 2014" and some Independent stakeholder submissions.</li> <li>Make recommendations on any necessary changes to the formulation of the indicators, operational definitions and/or the processes for data collection.</li> <li>Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed.</li> <li>Provide recommendations and corrective actions for Members States, regions, partners, donor agencies "SAGE Assessment report on the Decade of Vaccines progress" which will be the basis of the "progress report" for the WHO Executive Board and World Health Assembly.</li> </ul>	2h

15:45	Coffee/tea break	Break	30 min.
16:15	GVAP progress report - Session 4 (Contd.)  Discussion: 1h 15 min.	FOR DISCUSSION AND DECISION	
17:30	Cocktail		

**Wednesday, 22 October 2014**

<b>Japanese Encephalitis vaccines - Session 5</b>		
<b>08:30</b>	<p>Introduction of the topic, objectives of the session and background on Japanese encephalitis, P. Tharmaphornpias, Chair of the SAGE working group on Japanese encephalitis vaccines, 10 min.</p> <p>Vaccines available against JE, A. Barrett, Member of the SAGE working group on Japanese encephalitis vaccines, 10 min.</p> <p>Review of the evidence: vaccine immunogenicity, effectiveness, and co-administration, S. Hills, Member of the SAGE working group on Japanese encephalitis vaccines, 15 min.</p> <p>Review of the evidence: vaccine safety and other evidence review, H. Meyer, Member of the SAGE working group on Japanese encephalitis vaccines, 15 min.</p> <p>Discussion: 30 min.</p> <p>Review of proposed recommendations on Japanese encephalitis vaccines, P. Tharmaphornpias, Chair of the SAGE working group on Japanese encephalitis vaccines, 10 min.</p> <p>Discussion: 30 min.</p>	<p><b>FOR DECISION</b></p> <p>Present SAGE with the report of the SAGE working group on Japanese encephalitis vaccines and request SAGE's endorsement of the proposed recommendations. Discuss data gaps and research needs.</p> <p>Review the immunogenicity, effectiveness and safety profile of Japanese encephalitis vaccines and proposed schedules, including booster requirements and co-administration with other vaccines.</p> <p>SAGE recommendations on vaccine use will then be used to update the 2006 WHO position paper on the use of Japanese encephalitis vaccines.</p>
<b>10:30</b>	<b>Coffee/tea break</b>	<b>30 min.</b>

11:00	<p><b>Meningococcal A conjugate vaccine impact and routine immunization schedule in infants and young children - Session 6</b></p> <p>Why are we reviewing the evidence on meningococcal A conjugate vaccine and what are the questions for SAGE today? K. O'Brien, SAGE member, 5 min.</p> <p>Rollout of the meningococcal A conjugate vaccine through mass vaccination campaigns in countries of the meningitis belt, M. Djingarey, WHO, 10 min.</p> <p>Results from clinical trials in infants and young children, safety in pregnancy, and review of routine coverage data, A. Hodgson, Ghana Health Service, 15 min.</p> <p>Modeling of strategies for routine use of the meningococcal A conjugate vaccine, in the context of a dynamic vaccination program, and future evidence needs to inform vaccine policy, C. Trotter, University of Cambridge, 15 min.</p> <p>Questions for clarification: 15 min.</p> <p>What are the preferred schedules for meningococcal A conjugate vaccine for infants and young children living in countries of the African meningitis belt? K. O'Brien, SAGE member, 10 min.</p> <p>Discussion: 50 min.</p>	<p><b>FOR DECISION</b></p> <p>What are the preferred schedules for meningococcal A conjugate vaccine in infants and young children living in countries of the African meningitis belt to achieve sustainable disease control following the initial mass vaccination campaigns?</p> <p>This will lead to an update of the meningococcal position paper</p> <p>What are the gaps in policy-oriented information?</p>	2h
13:00	<p><b>Lunch</b></p> <p>Discussion: 50 min.</p>	<b>Break</b>	1h
14:00	<p><b>Global polio eradication initiative - Session 7</b></p> <p>Introduction: Issues for SAGE decisions and discussions, B. Aylward, WHO, 15 min.</p> <p>Major decisions for the OPV2 withdrawal: the report from the Polio Working Group, P. Figueroa, Chair of SAGE Working, 30 min.</p> <p>Discussion: 60 min.</p> <p>Progress towards interruption of wild poliovirus and persistent type 2 cVDPV and risk mitigation strategy, H. Jafari, WHO, 15 min.</p>	<p><b>FOR DISCUSSION AND DECISION</b></p> <p><b>For decision:</b></p> <ul style="list-style-type: none"> <li>• Type 2 risk mitigation strategy prior to OPV2 withdrawal</li> <li>• Type 2 risk assessment and response strategy after OPV2 withdrawal</li> <li>• Bio-containment strategy</li> <li>• mOPV2 stockpile policy</li> </ul> <p><b>For discussion:</b></p> <ul style="list-style-type: none"> <li>• Progress in eliminating wild and persistent cVDPV poliovirus</li> </ul>	3h
16:00	<b>Coffee/tea break</b>		30 min.

16:30	<b>Global polio eradication initiative - Session 7 (Contd.)</b>  Type 2 risk assessment and response strategy after OPV2 withdrawal, R. Sutter, WHO, 15 min.  Discussion: 15 min.  Operationalizing IPV and bOPV introduction in priority countries, M. Zaffran, WHO, 15 min.  Discussion: 15 min.		
17:30	<b>End of day</b>		

**Thursday, 23 October 2014**

<b>08:30</b>	<b>Hepatitis E vaccine - Session 8</b>  Introduction, N. Arora, Chair of the SAGE Working Group on hepatitis E vaccine, 5 min.  Hepatitis E: epidemiology and disease burden, E. Teshale, Member of the SAGE Working Group on hepatitis E vaccine, 15 min.  Questions for clarification: 10 min.  Composition, safety, efficacy and immunogenicity of the licensed hepatitis E vaccine, R. Aggarwal, Member of the SAGE Working Group on hepatitis E vaccine, 15 min.  Questions for clarification: 10 min.  Recommendations of SAGE Working Group the hepatitis E vaccine, N. Arora, Chair of the SAGE Working Group on hepatitis E vaccine, 15 min.  General discussion: 50 min.	<b>FOR DECISION</b>  Present SAGE with:  1. a review of data regarding the global prevalence and burden of disease caused by hepatitis E 2. a review of safety, efficacy, immunogenicity, cost effectiveness and programmatic issues related to the hepatitis E vaccine 3. the hepatitis E vaccine pipeline  SAGE will be expected to provide recommendations on the use of hepatitis E vaccine.	2h
<b>10:30</b>	<b>Coffee/tea break</b>	<b>Break</b>	<b>30 min.</b>
<b>11:00</b>	<b>Vaccine hesitancy - Session 9</b>  Introduction. J. Eskola, Chair of the SAGE Vaccine Hesitancy Working Group, 10 min.  Deliverables and conclusions, N. MacDonald, Member of the SAGE Vaccine Hesitancy Working Group, 25 min.  Recommendations. J. Eskola, Chair of the SAGE Vaccine Hesitancy Working Group, 15 min.  Discussion: 1h 40 min.	<b>FOR DISCUSSION AND DECISION</b>  SAGE will be presented with and asked to review and discuss the deliverables and conclusions of the Vaccine Hesitancy Working Group including: <ul style="list-style-type: none"> <li>• The definition of hesitancy</li> <li>• The Matrix of determinants of hesitancy</li> <li>• The Results of the immunization managers' survey and a systematic review of the drivers of vaccine hesitancy and their impact</li> <li>• A systematic review of strategies of vaccine hesitancy</li> <li>• The proposed indicators and survey questions</li> <li>• The Landscape of organizations dealing with hesitancy</li> </ul> SAGE will be expected to make a decision on the proposed recommendations on how deal with vaccine hesitancy.	2h 30 min.
<b>13:30</b>	<b>Closing</b>		
<b>13:40</b>	<b>End of meeting</b>		

**Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization  
21 – 23 October 2014  
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 policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of the Decade of Vaccines (DoV) Collaboration and Global Vaccine Action Plan (GVAP);
2. major issues and challenges to be addressed with respect to achieving the goals of the DoV and GVAP;
3. immunization programme response to current public health priorities;
4. major general policies, goals and targets including those related to vaccine research and development;
5. adequacy of WHO's strategic plan and priority activities to achieve the DoV and GVAP goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions;
7. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

#### **Membership**

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

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

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

1. professional affiliation (e.g., academia, medical profession, clinical practice, research institutes, and governmental bodies including national immunization programmes, public health departments and regulatory authorities);
2. major areas of expertise (e.g., influenza control, diarrhoeal diseases, respiratory diseases, research, biologics, immunization safety); and
3. the three major strategic areas of WHO's work relating to immunization (i.e., accelerating innovation, ensuring quality and safety, and maximizing access and links with other health interventions).

SAGE members, including the Chairperson, shall be nominated by the WHO IVB Director in consultation with WHO Regional Offices and other relevant WHO departments upon the proposal of an independent selection panel including representatives of key partner organizations. A public call for nominations is issued. After determination of eligibility, nominations are submitted to the selection panel. Members will be selected on the basis of their qualifications and ability to contribute to the accomplishment of SAGE's objectives.

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

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

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

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

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

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

- (1) failure to attend two consecutive SAGE meetings;
- (2) change in affiliation resulting in a conflict of interest; and
- (3) a lack of professionalism involving, for example, a breach of confidentiality.

#### **Roles and responsibilities of SAGE members**

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

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

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

#### **Meetings and operational procedures**

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

SAGE members are asked to update their declared interests before each meeting. SAGE members with potentially conflicting interests will not participate in deliberations on the specific topic(s) for which they would have a conflict of interest. SAGE member's relevant interests will be made publically available along with the meeting documentation on the SAGE website after the meeting.

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

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

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

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

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

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by the full SAGE in an open public forum. These Working Groups are established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated and could not be addressed by an existing standing WHO advisory committees. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 3.

In addition to attendance of meetings, active participation will be expected from all SAGE members throughout the year, including participation in SAGE Working Groups, video and telephone conferences as well as frequent interactions via e-mail. Review of documents may also be solicited. SAGE members may be requested to participate as observers in other important WHO departmental or cross-departmental meetings.

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

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

Version: October 2014

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

### **Purpose and decision to establish a SAGE Working Group**

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

These Working Groups are established on a time limited basis to help address specific questions identified by SAGE when the issue cannot be addressed by existing standing WHO advisory committees.

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

### **Terms of reference of the Working Groups and identification of needed expertise to serve on the Working Group**

Each Working Group operates under specific terms of reference (TORs). These TORs need to be defined within 30 days of the SAGE decision to establish the Working Group.

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

### **Working Group composition and selection of membership**

Each Working Group should include two SAGE members (one of whom functions as Chair), WHO staff (one of whom functions as the Working Group technical lead), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. This may include organizations representatives, and members of regional technical consultative groups. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict.

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

A public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of reference of the Working Group and indication of the desirable expertise. SAGE members, regional offices, WHO staff and key partner organizations will also be approached for potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests prior to being considered for membership on the Working Group. From the pool of nominees, the Working Group Chair, SAGE Executive Secretary and Lead WHO staff will propose a Working Group composition for endorsement by the SAGE Chair and the Director of the Department of Immunization, Vaccines and Biologicals. The proposed list should also identify other names and rationale for proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity in the Group.

### **Working Group Process**

WHO staff perform or coordinate, systematic assessment of the evidence such as analysis of data addressing efficacy, effectiveness, safety, feasibility, and economic aspects of immunization policy to address research questions developed by the Working Group in order to propose appropriate vaccine policy decisions.

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO D-G. SAGE Working Group Chairs, other Working Group representatives, or the Working Groups *per se* are not empowered to speak on behalf of SAGE. Rather, they are utilized by SAGE to gather and organize information upon which the SAGE can deliberate and act. Thus, while SAGE Working Groups can and should examine an area in detail and define the issues, including development of options for recommendations, the actual processes of group deliberation resulting in development of the group's consensus and final recommendations must occur in the public forum of SAGE meetings.

Effective communication and a strong working collaboration between the Working Group Chair the Lead WHO staff and the Working Group members are significant determinants of the effectiveness of a Working Group. Draft minutes of Working Group in person meetings or conference calls are produced shortly after the meetings. Once the minutes are approved by the Working Group, they are circulated to SAGE members. Depending on the Working Group, minutes may be produced by the secretariat or a Working Group member may be asked to serve as Rapporteur. Minutes are not publicly available except in the context of a SAGE session when included in the background documents.

With the Lead WHO Staff, the Chair of the Working Group develops a plan for routine operations of the Group. Working Groups accomplish most of their work through teleconferences. A set day and time for routine monthly teleconferences may be established, in order to allow standing teleconferences to be arranged and Working Group members to anticipate and reserve time

for these teleconferences. The frequency of Working Group teleconferences may be changed depending on the urgency of issues being considered by the group and the amount of preparatory work needed prior to a topic being brought up for plenary discussion and decision making at SAGE. Some Working Groups may more effectively achieve their purpose through exchange of e-mail communications with intermittent teleconferences.

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

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

#### **Management of Conflict of Interest**

The value and impact of SAGE recommendations and WHO policies and recommendations are critically dependent upon public trust in the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. Summarized Declarations of Interest are publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition. Members are expected to inform WHO on any change in relevant interests.

## **1. SAGE working group on polio (Established August 2008)**

### **Terms of Reference**

1. Prepare SAGE for the development of comprehensive policy guidance on the use of IPV in the post-eradication era in low and middle income settings, including by:

- **Reviewing long-term Polio Risks & Risk Management Strategies:**  
reviewing the long-term risks associated with live polioviruses after wild polio transmission globally, and reviewing the range of strategies for mitigating those risks in low-income settings (e.g. coordinated OPV cessation, mOPV stockpiles and response mechanism).
- **Assessing Current & Future IPV Products:**  
reviewing the existing range of IPV products, in terms of supply capacity, production cost, price, presentations, etc, and their appropriateness and suitability for low-income settings, particularly sub-Saharan Africa; and studying the IPV 'pipeline' and its implications for post-eradication IPV use in terms of potential new products (e.g. Sabin-IPV, adjuvanted-IPV, fractional dose IPV), production costs, and prices.
- **Establishing Potential IPV Policies & Implications:**  
establishing the range of IPV vaccination schedule options that could be utilized in a post-eradication world, given the difference in polio immunization objectives and polio risks compared with a polio-endemic world; and identifying and characterizing the programmatic implications, economics and opportunity costs of those policy options, for both IPV stand-alone and combination formulations, in low-income settings and particularly sub-Saharan Africa;
- **Identifying and prioritizing knowledge gaps that should be addressed to facilitate SAGE decision-making on the role(s) and options for IPV use in the post-eradication era in low-income settings.**

2. Propose key recommendations to SAGE for updating the 2003 position paper on IPV and consolidating it with other relevant documents (including the 2006 supplement to the IPV position paper) into one vaccine position paper on routine polio immunization covering both IPV and OPV and giving consideration to the ongoing polio eradication efforts.

3. Advise SAGE on technical guidance to WHO and the GPEI for the development and finalization of the overall polio eradication 'endgame strategy' to reduce long-term risks associated with OPV and to accelerate wild poliovirus eradication, including:

- policy and programmatic options for the use of different OPV formulations and IPV delivery options, and
- strategy and priorities in the related areas of outbreak response, surveillance, containment, risk assessment (esp. Vaccine Derived Polio Viruses - VDPVs), research and product development, and vaccine supply.

### **Composition**

#### *SAGE Members*

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

#### *Experts*

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

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

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

### **Terms of reference**

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

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

### **Composition**

#### *SAGE Members*

- Zulfiqar Bhutta, Aga Khan University, Pakistan
- Claire-Anne Siegrist, University of Geneva, Switzerland

#### *Experts*

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

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

### **Terms of Reference**

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

### **Composition**

#### *SAGE Members*

- Narendra Arora, International Clinical Epidemiology Network, India
- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan (SAGE member until June 2012)

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

#### *Experts*

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

#### **4. SAGE working group dealing with vaccine hesitancy (established March 2012)**

##### **Terms of Reference**

- Prepare for a SAGE review and advice on how to address vaccine hesitancy and its determinants.
- Define vaccine hesitancy and its scope
- Undertake a review of vaccine hesitancy in different settings including its context-specific causes, its expression and its impact.
- Suggest one or several indicator(s) of vaccine hesitancy that could be used to monitor progress in the context of the Decade of Vaccines Global vaccine Action Plan.
- At global, regional and national levels:
  - Perform a landscape analysis of who/what organizations are working on this issue in various settings/countries
  - Identify existing activities and strategies that have had or could have a positive impact including looking at successful strategies that have worked and are not specifically related to vaccines or even medicines;
  - Identify strategies and activities that did not work well;
  - Identify new activities and strategies that could have a positive impact;
  - Prioritize existing and new activities/strategies based on an assessment of their potential impact;
  - Outline the specific role of WHO in addressing vaccine hesitancy;
  - Identify the specific role of regional and country advisory committees.

##### **Composition**

##### *SAGE Members*

- Juhani Eskola, Chair of Working Group, National Institute of Health and Welfare, Finland
- Xiaofeng Liang, Chinese Center for Disease Control, China (SAGE Member and Chair of Working Group until April 2014)

##### *Experts*

- Mohuya Chaudhuri, Independent Journalist and Documentary Filmmaker, India
- Eve Dubé, Institut National de Santé Publique du Québec, Canada
- Bruce Gellin, Department of Health and Human Services, USA
- Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa
- Heidi Larson, School of Hygiene and Tropical Medicine, UK
- Noni MacDonald, Dalhousie University, Canada
- Mahamane Laouali Manzo, Ministry of Health, Niger
- Arthur Reingold, University of California at Berkeley, USA. (SAGE member until November 2011)
- Dilian Francisca Toro Torres, Congress of the Republic of Colombia
- Kinzang Tshering, Jigme Dorji Wangchuck National Referral Hospital, Bhutan
- Yuqing Zhou, Chinese Center for Disease Control, China

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

### Terms of Reference

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

Specifically the working group will be asked to:

- Review epidemiological data from countries that have or not experienced a resurgence of pertussis, in particular data that relates to the quality and duration of protection for wP and aP vaccines
- Review, in the context of the above, accumulated data on the usefulness of the following strategies to prevent early mortality
  - Role of vaccination of adolescents and adults
  - “Cocooning”
  - Vaccination of pregnant and lactating mothers
  - Vaccination of newborns
- Update estimates of effectiveness of 1 or 2 dose schedules against mortality
- Create optimal primary vaccination schedule and timing of booster dose(s)
- Propose, based on the above and as necessary, an update of the current recommendations on the use of wP/aP vaccine.

### Composition

#### *SAGE Members*

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

#### *Experts*

- Tom Clark, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA
- Kathryn Edwards, Vanderbilt Vaccine Research Program, Vanderbilt University School of Medicine, Nashville, USA
- Nicole Guiso, Institut Pasteur Research Unit, Institut Pasteur, Paris, France
- Scott A. Halperin, Canadian Center for Vaccinology, Dalhousie University, Halifax, Canada
- Teeranart Jivapaisarnpong, Institute of Biological Products, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand
- Daniel Levy-Bruhl, Infectious Diseases Department, Institut de Veille Sanitaire, Saint-Maurice, France
- Peter McIntyre, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Sydney, Australia
- Gabriela Moreno, Departments of Epidemiology and Immunizations, Ministry of Health, Santiago, Chile
- Carl Heinz Wirsing von König, National reference laboratory for Bordetella infections, Krefeld, Germany

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

### Terms of Reference

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

Specifically, the WG will:

- review the quality of the data on the GVAP indicators and make recommendations on changes to the formulation of the indicators, operational definitions and/or the processes for data collection;



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

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

## Composition

### *SAGE Members*

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

### *Experts*

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

## **7. SAGE Working Group on Hepatitis E vaccines (established October 2013)**

### **Terms of Reference**

The Working Group will be asked to review the evidence with respect to the following questions/issues and to propose recommendations for review by SAGE. This will lead to the publication of a WHO vaccine position paper on the use of hepatitis E. The target date of the publication of the position paper is early 2015.

- Review data regarding the global prevalence and burden of disease caused by hepatitis E virus infection.
- Review issues related to hepatitis E surveillance
- Review existing data on the safety, immunogenicity, efficacy, and cost-effectiveness of the licensed hepatitis E vaccine
- Review the hepatitis E vaccine pipeline.
- Identify potential indications and uses for the hepatitis E vaccine in the context of other hepatitis E preventive, control and treatment strategies/tools
- Provide draft recommendations on the potential use of hepatitis E vaccine.
- To summarize existing evidence on the burden of hepatitis E and on the safety, immunogenicity, efficacy, and cost-effectiveness of the licensed hepatitis E vaccine.
- To provide SAGE with summaries and analyses needed to support its discussion and recommendation process.

## Composition

### *SAGE Members*

- Narendra Arora (Chair of the Working Group), Executive director, International Clinical Epidemiology Network, India
- Xiaofeng Liang, Deputy Director General, Chinese Center for Disease Control, China

## Experts

- Emily Gurly, Associate Director for Science and Head of Outbreak and Surveillance Research Group, Center for Communicable Diseases, International Centre for Diarrheal Diseases Research, Bangladesh
- Rakesh Aggarwal, Professor Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India
- David Rein, Principal Research Scientist, NORC at the University of Chicago, Public Health Research Department, USA
- Sally Baylis, Senior scientist and quality assessor, Division of Virology, Paul-Ehrlich-Institut, Germany
- Eyasu Teshale, Centers for Disease Control and Prevention, Division of Viral Hepatitis Epidemiology and Surveillance Branch, USA
- Nilsa de Deus, Head of Research Department National Institute of Health, Minister of Health, Mozambique
- Samreen Ijaz, Clinical Scientist, R&D lead for blood borne infections, Blood Borne Virus Unit, Virus Reference Department, Public Health England, UK
- Rana Jawad Asghar, Resident Advisor, Field Epidemiology and Laboratory Training Programme, Pakistan

## 8. SAGE Working Group on Japanese encephalitis vaccines (established November 2013)

### 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 Japanese encephalitis (JE) vaccines for a SAGE review. This will lead to an update of the current (2006) JE vaccine position paper. The target date for publication of the revised vaccine position paper is 2015.

The Working Group will specifically be asked to review data relating to:

- the global prevalence and burden of disease caused by JE, including issues relating to JE surveillance
- the role of inactivated mouse-brain based JE vaccines in the context of other products
- the safety, effectiveness, and immunogenicity profile of inactivated, live attenuated, and chimeric JE vaccines\*
- the schedule and age of administration for the first dose of inactivated, live attenuated, and chimeric JE vaccines\*
- the duration of protection following immunization with inactivated, live attenuated, and chimeric JE vaccines\*
- co-administration of JE vaccines\* with other vaccines
- use of JE vaccines\* in special populations (e.g. immunosuppressed, pregnancy)
- the disease impact and cost-effectiveness of JE immunization programs
- additional critical issues that need to be considered in updating the current vaccine position paper

\*Due to the large number of available JE vaccines with limited global use, the Working Group will focus its in-depth evidence review on products with current or likely international distribution.

### Composition

#### *SAGE Members*

- Piyanit Tharmaphornpilas, Chair of Working Group, National Immunization Program, Ministry of Public Health, Thailand
- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

#### *Experts*

- Alan Barrett, Sealy Center for Vaccine Development, University of Texas Medical Branch, USA
- Susan Hills, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, USA
- Ooi Choo Huck, Sarawak Health Department, Ministry of Health, Malaysia
- Heidi Meyer, Viral Vaccines Section, Paul-Ehrlich-Institut, Germany
- Khin Saw Aye Myint, Eijkman Institute, Indonesia
- Tom Solomon, Institute of Infection and Global Health, University of Liverpool, UK
- Tomohiko Takasaki, Laboratory of Vector-Borne Viruses, National Institute of Infectious Diseases, Japan
- Shyam Upreti, Central Regional Health Directorate, Ministry of Health and Population, Nepal
- Yin Zundong, National Immunization Program, Chinese Center for Disease Control and Prevention, China

**Strategic Advisory Group of Experts (SAGE) on Immunization**

**21 - 23 October 2014**

**WHO Headquarters, Executive Boardroom, Geneva, Switzerland**

**Provisional List of Participants**

**SAGE members**

<p>Abramson, Jon (Chair) Chair Professor Department of Pediatrics Wake Forest Baptist Health 27157 Winston-Salem United States of America</p>
<p>Al-Mazrou, Yagob Secretary General Council of Health Services 12431 Riyadh Saudi Arabia</p>
<p>Arora, Narendra Kumar (Vice-Chair) Executive Director The INCLEN Trust International 110020 Delhi India</p>
<p>Bhutta, Zulfiqar (Unable to attend) Co-Director Co-Director, Robert Harding Chair in Global Child Health and Policy The Hospital for Sick Kids M5G 404 Toronto Canada</p>
<p>Eskola, Juhani Director General National Institute for Health and Welfare (THL) FI-00270 Helsinki Finland</p>
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## Chair of Immunization Advisory Committee

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Chair, Global Advisory Committee for Vaccine Safety  
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<p>Bergsaker, Marianne A Riise  Deputy Director  Department of Vaccines  Norwegian Institute of Public Health  0403 Oslo  Norway</p>
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<p>Curry, David  Executive Director  Diviosn of Medical Ethics/NYU Medical School  Center for Vaccine Ethics and Policy/University of Pennsylvania  19104 Philadelphia  United States of America</p>
<p>Da Silva, Alfred  Executive Director  Agence de Médecine Préventive (AMP)  75015 Paris  France</p>

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<p>Dubé, Eve  Member of working group on Vaccine Hesitancy  Researcher  Institut national de santé publique du Québec  G1E7G9 Québec  Canada</p>
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<p>Essoh, Téné-Alima  New Vaccines introduction / Pharmacovigilance /Vaccine safety programme  Agence de Médecine Préventive  75015 Paris  France</p>
<p>Fermon, Florence  Leader vaccination Working Group. MSF  Médecins Sans Frontières  75011 Paris  France</p>
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<p>Gellin, Bruce  Member, Vaccine Hesitancy Working Group  Deputy Asst. Secretary for Health, Director National Vaccine Program Office  Department of Health and Human Services  20201 Washington  United States of America</p>
<p>Hills, Susan  Arboviral Diseases Branch  Center for Disease Control and Prevention  CO Fort Collins  United States of America</p>
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# Weekly epidemiological record Relevé épidémiologique hebdomadaire

23 MAY 2014, 89th YEAR / 23 MAI 2014, 89<sup>e</sup> ANNÉE

No. 21, 2014, 89, 221–236

<http://www.who.int/wer>

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

The Strategic Advisory Group of Experts (SAGE) on immunization<sup>1</sup> met on 1–3 April 2014 in Geneva, Switzerland. This report provides a summary of the discussions, conclusions and recommendations.<sup>2</sup>

## Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on 3 key issues: (i) sustaining the momentum generated by the Decade of Vaccines (DoV)/Global Vaccine Action Plan (GVAP), (ii) ensuring efforts to effectively support country implementation are sufficient and (iii) identifying areas for more effective coordination and collaboration between WHO and its partners.

The upcoming 40-year anniversary of the WHO Expanded Programme on Immunization (EPI) was celebrated during World Immunization Week, 24–29 April 2014.

The report described the implementation of recent SAGE recommendations on yellow fever, hepatitis A and cholera vaccinations. In January 2014, the WHO Executive Board recommended a draft resolution for consideration by the World Health Assembly in May 2014, calling for an update of the relevant provisions in the *International Health Regulations* (Annex 7) to reflect the life-long protection conferred by 1 dose of yellow fever vaccine. The continued monitoring of the 1 dose hepatitis A vaccination programme in Argentina indicates the

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

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination<sup>1</sup> s'est réuni du 1<sup>er</sup> au 3 avril 2014 à Genève (Suisse). Le présent rapport récapitule les discussions, ainsi que les conclusions et recommandations auxquelles il est parvenu.<sup>2</sup>

## Rapport du Département OMS Vaccinations, vaccins et produits biologiques

Le rapport s'est axé sur 3 points essentiels: i) maintenir la dynamique suscitée par le Plan d'action mondial pour les vaccins (GVAP) dans le cadre de la Décennie de la vaccination, ii) veiller à ce que les efforts pour soutenir efficacement la mise en œuvre dans les pays soient suffisants et iii) déterminer les domaines pour une coordination et une collaboration plus efficaces entre l'OMS et ses partenaires.

Le 40<sup>e</sup> anniversaire du Programme élargi de vaccination (PEV) de l'OMS a été célébré lors de la Semaine mondiale de la vaccination, du 24 au 29 avril 2014.

Le rapport décrit la mise en œuvre des recommandations récentes du SAGE concernant les vaccins contre la fièvre jaune, l'hépatite A et le choléra. En janvier 2014, le Conseil exécutif de l'OMS a recommandé un projet de résolution à soumettre à l'Assemblée mondiale de la Santé en mai 2014 appelant à revoir les dispositions du *Règlement sanitaire international* (Annexe 7) pour y refléter la protection à vie conférée par une dose de vaccin anti-jaune. Le suivi continu du programme de vaccination par 1 dose de vaccin contre l'hépatite A en Argentine indique toujours une absence

WORLD HEALTH  
ORGANIZATION  
Geneva

ORGANISATION MONDIALE  
DE LA SANTÉ  
Genève

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

05.2014  
ISSN 0049-8114  
Printed in Switzerland

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

<sup>2</sup> The complete set of presentations and background materials used for the SAGE meeting of 1–3 April 2014 together with summarized declarations of interests provided by SAGE members are available at <http://www.who.int/immunization/sage/meetings/2014/april/en/>; accessed in April 2014.

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

<sup>2</sup> La série complète des communications et des documents de travail de la réunion du SAGE tenue du 1<sup>er</sup> au 3 avril 2014, ainsi que les déclarations d'intérêt fournies par les membres de ce groupe sont disponibles à l'adresse suivante: <http://www.who.int/immunization/sage/meetings/2014/april/en/>, consultée en avril 2014.

absence of breakthrough cases, and long term protection. An international cholera vaccine stockpile has been constituted and consultative meetings have taken place to start rolling out the implementation of cholera vaccination.

An overview of progress towards achieving the DoV goals was provided, noting that Member States welcomed the SAGE recommendations during the Executive Board meeting in January. SAGE applauded the initiatives to adopt and roll-out the GVAP at regional level

The report emphasized that challenges remain to reach the milestone of 90% national coverage with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) in all countries by 2015, which requires the immunization of an additional 13 million children. To reduce dropout rates between the DTP1 and DTP3 vaccinations and assess the associated missed opportunities, efforts should be made to improve country capacity to generate demand, drive their programme and in particular to improve ownership of immunization programmes. The importance of ensuring adequate country ownership was exemplified again by ongoing challenges in the African Region and SAGE emphasized the importance of sustaining current efforts. The requirements for ongoing funding and sufficient immunization staff were noted, with a particular focus on GAVI graduating countries. Concern was raised that meeting the DoV goals is behind schedule. The absorptive capacity and willingness of countries to meet the goals is also of concern and WHO needs to work with countries to follow up on country ownership including alignment of national plans of action with the GVAP, strengthening national technical advisory groups on immunization and inter-agency coordinating committees, national legal and regulatory framework for financing immunization, and country commitment to financing. An analysis of the absorptive capacity of countries to introduce new vaccines was also requested.

The need to implement new vaccines in all countries was stressed, especially in middle income countries that self-procure vaccines, as these countries include 71% of the world's children. 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.

Finally, the report addressed how vaccine research could contribute to the mapping of existing knowledge gaps, to ultimately achieve the WHO goals in this domain, highlighting the outputs of the Global Vaccine and Immunization Research Forum which took place in March 2014.

SAGE reaffirmed the need to improve data quality and enhance data management for the purpose of better operational, management and strategic decisions.

d'échecs vaccinaux et une protection de longue durée. Un stock international de vaccins anticholériques a été constitué et des réunions consultatives ont eu lieu pour commencer à utiliser ces vaccins.

Un aperçu général des progrès accomplis dans la réalisation des buts de la Décennie de la vaccination a été donné en soulignant que les États Membres ont fait bon accueil aux recommandations du SAGE lors de la session du Conseil exécutif de l'OMS de janvier. Le SAGE a complimenté les initiatives visant à adopter et à lancer le GVAP au niveau régional.

Le rapport insiste sur les défis qu'il faut encore relever pour atteindre une couverture nationale de 90% par 3 doses du vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC3) dans tous les pays d'ici 2015, ce qui nécessitera de vacciner 13 millions d'enfants en plus. Pour réduire les taux d'abandon entre le DTC1 et le DTC3 et évaluer les occasions perdues qui s'y associent, des efforts doivent être faits pour améliorer la capacité des pays à générer la demande, à mener leur programme et, en particulier, faire en sorte qu'ils s'approprient davantage les programmes de vaccination. L'importance d'une adhésion suffisante des pays a de nouveau été mise en lumière par les difficultés persistantes rencontrées dans la Région africaine, et le SAGE a insisté sur l'intérêt de soutenir les efforts actuels. Le besoin de disposer d'un financement continu et de personnels avec des effectifs suffisants a été noté, en mettant plus particulièrement l'accent sur les pays qui se qualifient au titre de l'Alliance GAVI. Des inquiétudes ont été exprimées quant au retard actuel pris dans la réalisation des buts de la Décennie de la vaccination. La capacité d'absorption et la volonté des pays d'atteindre les buts sont également un sujet de préoccupation et l'OMS doit collaborer avec eux pour suivre l'adhésion par les pays, notamment l'alignement des plans nationaux sur le GVAP, le renforcement des groupes consultatifs techniques nationaux sur la vaccination et des comités de coordination interinstitutions, les cadres légal et réglementaire nationaux pour le financement de la vaccination et la volonté de financement dans les pays. Une analyse de la capacité d'absorption des pays pour l'introduction de nouveaux vaccins a été également demandée.

Le rapport insiste sur le besoin d'introduire de nouveaux vaccins dans tous les pays, en particulier ceux à revenu intermédiaire qui se procurent eux-mêmes les vaccins et qui regroupent 71% des enfants du monde. Il a été recommandé d'envisager une plate-forme pour la couverture de la vaccination pendant la deuxième année de vie, compte tenu des doses de rappel potentiellement nécessaires et des possibilités de rattraper les vaccinations incomplètes, en enlevant la barrière artificielle mise trop souvent après le premier anniversaire.

Enfin, le rapport s'intéresse à la possibilité pour la recherche de contribuer à dresser l'inventaire des lacunes existantes dans les connaissances pour parvenir finalement aux buts de l'OMS dans ce domaine, en soulignant les résultats du Forum mondial de recherche sur les vaccins et les vaccinations qui a eu lieu en mars 2014.

Le SAGE a réaffirmé le besoin d'améliorer la qualité des informations et de renforcer la gestion des données, la finalité étant d'améliorer les décisions opérationnelles, gestionnaires et stratégiques.



SAGE congratulated the WHO South East Asia Region (SEAR) on having been certified as polio-free on 27 March 2014. This milestone means that 80% of the world population now lives in polio-free areas. Nevertheless challenges remain, as polio transmission and outbreaks were reported from several countries, in part sustained by ongoing armed conflicts and security issues. SAGE expressed its grave concerns regarding these conflicts, particularly those in Syria, Central African Republic and South Sudan, which impact on vaccination coverage and the number of outbreaks. SAGE is concerned that maternal and neonatal tetanus elimination, which is both a health and an equity issue, remains another unfinished agenda. SAGE highlighted that climate change might lead to further conflicts and that the WHO will need to consider the associated consequences on immunization programmes.

### Report from the GAVI Alliance

The Chief Executive Officer of the GAVI Alliance provided an update on recent Board decisions, the key elements under consideration for GAVI's future strategy, its policy review pipeline, and plans for replenishment of funds.

At its November 2013 meeting, the Board approved the opening of a window for Japanese encephalitis vaccines and inactivated polio vaccines (IPV), additional support for yellow fever vaccination, and a contribution to an expanded WHO-managed cholera stockpile. The Board noted future consideration for malaria immunization pending SAGE recommendations on use and availability of WHO prequalified vaccines. More evidence was requested on rabies vaccines and on influenza vaccines for pregnant women.

The GAVI Alliance has adjusted its grant management and monitoring processes aimed at increasing country ownership, lower transaction costs, and bringing the health systems strengthening and new vaccine introduction support windows together, including with improved financial oversight. By 30 March 2014, 10 countries had submitted applications to GAVI for support for IPV introduction.

Regarding the future strategy for GAVI 2016–2020, the main focus will be on: (i) maintenance of GAVI's current gross national income eligibility criteria; (ii) focused efforts on coverage and equity; (iii) increasing country ownership; (iv) considering catalytic investments to targeted areas in large countries; and (v) market shaping and access to affordable pricing for graduated countries.

A number of GAVI policies are being reviewed towards continued relevance for the future strategy including eligibility, co-financing, graduation, and operational support policies for new vaccines. GAVI's current policy of providing countries only with whole-cell pertussis (wP) in a pentavalent combination vaccine, and monovalent IPV was reaffirmed.

Le SAGE a salué la Région OMS de l'Asie du Sud-Est (SEAR), qui a été certifiée exempte de poliomyélite le 27 mars 2014. Cette étape décisive signifie que, désormais, 80% de la population mondiale vit dans des régions débarrassées de cette maladie. Des difficultés, signalées dans plusieurs pays, subsistent cependant pour interrompre la transmission de la poliomyélite et endiguer les flambées et perdurent en partie à cause des conflits en cours et des problèmes d'insécurité. Le Groupe a exprimé ses vives inquiétudes à propos de ces conflits, notamment en Syrie, en République centrafricaine et au Soudan du Sud, qui ont des répercussions sur la couverture vaccinale et le nombre de flambées. Le SAGE est préoccupé par l'élimination du tétanos maternel et néonatal, qui est à la fois une question de santé et d'équité et demeure encore à l'ordre du jour. Il a souligné que le changement climatique pouvait aviver les conflits et que l'OMS devra prendre en compte les conséquences qui en découleront pour les programmes de vaccination.

### Rapport de l'Alliance GAVI

Le Directeur de l'Alliance GAVI a fait le point sur les décisions récentes du Conseil, les éléments clés à l'étude pour la stratégie de l'Alliance à l'avenir, la révision de la politique en attente et les plans de reconstitution des ressources financières.

Lors de sa réunion en Novembre 2013, le Conseil a approuvé l'ouverture d'une fenêtre de financement pour les vaccins contre l'encéphalite japonaise et les vaccins antipoliomyélitiques inactivés (VPI), une aide supplémentaire pour la vaccination contre fièvre jaune, et la contribution à une augmentation du stock de vaccins anticholériques géré par l'OMS. Il a pris note de la vaccination antipaludique à prendre en considération à l'avenir selon les recommandations du SAGE concernant l'utilisation du vaccin et selon la disponibilité de vaccins préqualifiés par l'OMS. Davantage d'informations factuelles sur les vaccins antirabiques et les vaccins antigrippaux pour les femmes enceintes ont été demandées.

L'Alliance GAVI a ajusté ses procédures de gestion et de suivi des subventions dans le but d'accroître l'appropriation par les pays, de faire baisser les coûts de transaction et de réunir les activités de renforcement des systèmes de santé et d'introduction de nouveaux vaccins avec une amélioration de la surveillance financière. Au 30 mars 2014, 10 pays avaient présenté à l'Alliance des demandes d'aide pour l'introduction du VPI.

En ce qui concerne la future stratégie de l'Alliance GAVI pour 2016-2020, l'accent portera principalement sur: i) le maintien des critères actuels de recevabilité ayant trait au produit national brut; ii) les efforts centrés sur la couverture et l'équité; iii) le renforcement de l'appropriation par les pays; iv) les investissements à effet catalyseur consacrés à des régions ciblées dans les grands pays; et v) la structuration des marchés ainsi que l'accès à des prix abordables dans les pays qualifiés.

Un certain nombre de politiques de l'Alliance sont en cours de réexamen pour établir leur pertinence dans la perspective de la stratégie future, notamment les politiques d'éligibilité, de co-financement, de qualification et de nouvelles politiques d'appui opérationnel pour les nouveaux vaccins. La politique actuelle de l'Alliance GAVI qui est de fournir aux pays uniquement un vaccin à germes entiers contre la coqueluche sous la forme d'un vaccin pentavalent et le VPI monovalent a été réaffirmée.

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

At its December 2013 meeting, GACVS reviewed: (i) the safety profile of chimeric Japanese encephalitis, IPV, and rotavirus; (ii) allegations related to the safety of human papillomavirus (HPV) vaccines; (iii) investigations related to increased pyrogenicity of a seasonal influenza vaccine; and (iv) the development of a vaccine safety surveillance manual.<sup>3</sup> In June 2014, GACVS will hold its 30th meeting, thereby celebrating 15 years of work. SAGE noted the relevance and importance of the work of GACVS, and the complementary roles of GACVS and SAGE in assessing and managing safety issues related to vaccine use. SAGE noted that the safety of several vaccines which are known to be very safe, such as whole-cell pertussis and HPV vaccines, is periodically questioned in several countries. 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.

## Polio eradication

Following the large poliomyelitis outbreaks in the Middle East and the Horn of Africa in 2013, and an expanding outbreak in Central Africa in 2014, Member States are voicing increasing concern about the international spread of poliovirus and have requested additional WHO guidance on recommendations for the vaccination of travellers from countries where poliovirus is circulating. Upon reviewing the relevant scientific evidence, SAGE endorsed updates to the existing WHO recommendations for travellers from polio-infected countries in the WHO publication *International Travel and Health* (ITH) 2013 as follows:

1. Polio vaccination recommendations for travellers from polio-infected countries should apply to all residents and to visitors of all ages who spend >4 weeks in the country. Several lines of evidence demonstrate that older individuals play an important role in international spread of poliovirus, including observational and challenge studies and documented cases of adult travellers excreting wild poliovirus.
2. In addition to oral poliovirus vaccine (OPV), which is currently recommended in ITH for the vaccination of travellers from polio-infected countries, IPV can be used for booster doses. A recent study from Moradabad, India, demonstrated that 1 dose of bivalent OPV or IPV reduces excretion of poliovirus significantly in people previously given OPV. For people who previously received only IPV, OPV should be the choice for booster if available and feasible.
3. Resident travellers of all ages from polio-infected countries should have received 1 documented additional dose of OPV or IPV a minimum of 4 weeks and a maximum of 12 months before each

<sup>3</sup> See No. 7, 2014, pp.53–60.

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

Lors de sa réunion de décembre 2013, le Comité a passé en revue: i) les profils d'innocuité du vaccin chimère contre l'encéphalite japonaise, du VPI et du vaccin anti-rotavirus; ii) les allégations relatives à l'innocuité des vaccins contre le papillomavirus humain (HPV); iii) les investigations relatives à la pyrogénicité accrue d'un vaccin contre la grippe saisonnière; et iv) l'élaboration d'un manuel pour la surveillance de l'innocuité des vaccins.<sup>3</sup> En juin 2014, le Comité tiendra sa trentième réunion et célébrera ainsi 15 ans d'activité. Le SAGE a relevé la pertinence et l'importance des travaux du GACVS ainsi que la complémentarité des rôles du GACVS et du SAGE pour évaluer et gérer les problèmes d'innocuité relatifs à l'utilisation des vaccins. Le SAGE a noté que l'innocuité de certains vaccins connus pour leur excellent profil de sécurité, comme le vaccin à germes entiers contre la coqueluche et le vaccin anti-HPV, est périodiquement remise en question dans plusieurs pays. Il a demandé de trouver de nouvelles stratégies de communication pour que les travaux du GACVS aient un plus grand impact et contribuent à maintenir la confiance dans les vaccins.

## Éradication de la poliomyélite

Après les grandes flambées de poliomyélite au Moyen-Orient et dans la Corne de l'Afrique en 2013, puis une flambée en expansion en Afrique centrale en 2014, les États Membres expriment des inquiétudes de plus en plus vives quant à une propagation internationale des poliovirus et ont demandé à l'Organisation des orientations et recommandations supplémentaires pour la vaccination des voyageurs en provenance de pays infectés. Après avoir passé en revue les données scientifiques à ce sujet, le SAGE a approuvé l'actualisation des recommandations existantes de l'OMS pour les voyageurs en provenance de pays infectés dans l'édition 2013 de sa publication *Voyages internationaux et santé* (VIS), comme suit:

1. Les recommandations pour la vaccination antipoliomyélique des voyageurs en provenance de pays infectés doivent s'appliquer à tous les résidents ou visiteurs, quel que soit leur âge, qui ont passé >4 semaines dans le pays en question. Plusieurs données factuelles démontrent que les individus plus âgés jouent un rôle important dans la propagation internationale des poliovirus, dont des études d'observation et des études d'épreuve, ainsi que des cas documentés de voyageurs adultes excréant des poliovirus sauvages.
2. En plus du vaccin antipoliomyélique oral (VPO), actuellement recommandé dans le VIS pour vacciner les voyageurs en provenance de pays infectés, on peut utiliser le VPI pour les doses de rappel. Une étude récente à Moradabad (Inde) a démontré qu'une dose de VPO bivalent ou de VPI réduit sensiblement l'excrétion de poliovirus chez les sujets auxquels on a administré auparavant le VPO. Pour ceux qui auparavant ont seulement reçu le VPI, le VPO sera le vaccin de choix pour un rappel s'il est disponible et si c'est faisable.
3. Quel que soit leur âge, les voyageurs résidant dans des pays infectés doivent avoir reçu au moins 1 dose supplémentaire avérée de VPO ou de VPI, administrée au minimum 4 semaines et au maximum 12 mois avant chaque voyage

<sup>3</sup> Voir N° 7, 2014, pp. 53-60.

international travel. Evidence from a number of studies demonstrates that immunologically-naïve populations usually attain a maximum immune response within 4 weeks, and intestinal immunity can wane within 12 months. Travellers embarking on last minute/urgent travel that cannot be postponed should nevertheless receive 1 dose of OPV or IPV before departure if they have not received a documented dose of polio vaccine within the previous 12 months.

SAGE recognized the potential social and economic cost associated with the implementation of these recommendations but believes that they would help decrease the risk of outbreaks. In 2013, 60% of the all reported polio cases resulted from long distance importations from polio-endemic countries.

SAGE reviewed the status of IPV introduction globally, which is 1 of the 5 major criteria for judging global readiness for OPV2 withdrawal.<sup>4</sup> SAGE was informed of the outcomes of the February 2014 UNICEF tender, in which one IPV supplier has offered a price of €0.75 per dose in 10-dose vials (approximately USD 1 per dose) to GAVI-eligible countries and €1.5–2.4 per dose (approximately USD 2.1–3.3 per dose) for middle-income countries, also in 10-dose vials; another manufacturer offered a price of US\$ 1.90/dose in 5-dose vials, for any requesting country. SAGE concurred that these represent the best possible IPV prices in the near term and constitute a firm basis for proceeding with the goal of global IPV introduction by end-2015 as an integral part of the polio endgame strategy. To date, of the 194 WHO Member States, 71 (36%) have introduced IPV and 65 (34%) have decided or declared intent to introduce IPV by end-2015. SAGE reaffirmed the need for all countries to have completed planning for IPV introduction by end-2014. SAGE endorsed the proposed actions by the Immunization Systems Management Group to further accelerate decision-making to introduce IPV in the remaining OPV-using countries, particularly through increased technical assistance, enhanced communications, and potential financial support mechanisms for non-GAVI supported countries in special circumstances. SAGE reinforced the importance of conducting a technical briefing on IPV introduction for OPV-using countries during the WHA in May 2014.

SAGE reviewed the progress towards eventual confirmation of a specific date for global OPV2 withdrawal, which requires the absence of 'persistent' circulating vaccine-derived poliovirus type-2 (cVDPV2) for at least 6 months globally. SAGE was alarmed by the persistent VDPV2 circulation in northern Nigeria (since July 2005) and Pakistan (since August 2012), noting that these areas overlap with some of the last wild poliovirus reservoirs in the world. Stopping circulation of both WPVs and VDPVs requires addressing gaps in quality

international. Les faits mis en évidence par un certain nombre d'études démontrent que les populations immunologiquement naïves atteignent en général une réponse immunitaire maximale en 4 semaines et que l'immunité intestinale peut disparaître dans les 12 mois. Les voyageurs entreprenant des déplacements urgents, de dernière minute et ne pouvant être différés, doivent néanmoins recevoir 1 dose de VPO ou de VPI avant leur départ s'ils n'ont pas reçu 1 dose avérée de vaccin antipoliomyélitique au cours des 12 derniers mois.

Le SAGE a reconnu les coûts potentiels du point de vue social et économique associés à la mise en œuvre de ces recommandations, mais il estime qu'elles aideraient à diminuer le risque de flambées. En 2013, 60% de l'ensemble des cas de poliomyélite notifiés résultaient d'importations au long cours à partir des pays d'endémie.

Le SAGE a examiné la situation de l'introduction du VPI dans le monde, l'un des 5 critères majeurs pour juger de l'état de la préparation mondiale au retrait du VPO2.<sup>4</sup> Il a été informé des résultats de l'appel d'offres de l'UNICEF en février 2014, dans le cadre duquel un fournisseur de VPI a proposé un prix de €0,75 par dose en flacons de 10 doses (environ USD 1 par dose) aux pays remplissant les conditions pour une aide de l'Alliance GAVI, et de €1,5 à €2,4 par dose (environ USD 2,1-3,3 par dose), également en flacons de 10 doses, pour les pays à revenu intermédiaire; un autre fabricant a proposé un prix de USD 1,90 par dose en flacons de 5 doses pour tout pays qui en fait la demande. Le SAGE a reconnu qu'il s'agissait là des meilleurs prix possible pour le VPI à court terme et que cela constituait une base ferme pour poursuivre l'action en vue de l'introduction mondiale, d'ici fin 2015, de ce vaccin qui fait partie intégrante de la stratégie pour la phase finale contre la poliomyélite. Jusqu'à présent, sur les 194 États Membres de l'OMS, 71 (36%) ont introduit le VPI et 65 (34%) ont décidé ou déclaré une intention de le faire d'ici fin 2015. Le SAGE a réaffirmé la nécessité pour tous les pays d'avoir terminé la planification de l'introduction du VPI d'ici fin 2014. Il a approuvé les actions proposées par le Groupe de gestion des systèmes de vaccination pour accélérer davantage la prise de décisions sur l'introduction du VPI dans les pays utilisant encore le VPO, en particulier au moyen d'une assistance technique accrue et par des dispositifs potentiels d'appui financier aux pays en dehors du système de l'Alliance GAVI dans certaines circonstances spéciales. Le SAGE a insisté sur l'importance d'organiser, lors de l'AMS en mai 2014, une séance d'information technique sur l'introduction du VPI à l'intention des pays utilisant le VPO.

Le SAGE a examiné les progrès en vue de la confirmation éventuelle d'une date spécifique pour le retrait mondial du VPO2, ce qui suppose l'absence de poliovirus circulants dérivés d'une souche vaccinale de type 2 (PVDVc2) «persistants» pendant au moins 6 mois dans le monde entier. Il s'est alarmé de la circulation persistante de PVDV2 dans le nord du Nigéria (depuis juillet 2005) et au Pakistan (depuis août 2012), notant que ces régions se superposent à certains des derniers réservoirs de poliovirus sauvages dans le monde. Pour mettre un terme à la circulation des PVS comme des PVDV, il faudra corriger les

<sup>4</sup> In November 2014, SAGE will review the 2 other major readiness criteria under its remit: global access to a registered bivalent OPV for routine immunization, and monovalent OPV type-2 stockpile and response protocols.

<sup>4</sup> En novembre 2014, le SAGE examinera deux autres critères majeurs de l'état de préparation entrant dans ses attributions: l'accès mondial à un VPO bivalent homologué pour la vaccination systématique et le stock de VPO monovalent de type 2, ainsi que les protocoles de riposte.

of supplementary immunization activity (SIA), improving routine immunization coverage, increasing access, and using an appropriate mix of trivalent and bivalent OPV over the coming 10 months. SAGE emphasized that the elimination of persistent cVDPV2s by late 2014/early 2015 must be a high priority for global eradication efforts to remain on-track for major milestones of the Polio Eradication and Endgame Strategic Plan 2013–2018. SAGE urged countries to correct the mix of OPV being used in large scale immunization campaigns in areas with persistent cVDPV2 to ensure that OPV2 can be withdrawn during the 2016 low season for poliovirus transmission, as originally scheduled. SAGE reviewed and endorsed the broad outlines of the proposed approach for mitigating the risk of cVDPV2 emergence at the time of OPV2 withdrawal, including IPV introduction, routine immunization strengthening and preventive trivalent OPV SIAs in Tier 1 and selected Tier 2 countries or parts of countries. The specifics of the approach will be further elaborated by the Working Group for SAGE review in October 2014.

### Immunization supply chain

In November 2013, SAGE expressed deep concern about the mounting challenges faced by countries and recognized the need to draw the attention of all partners and encourage greater investments for strengthening in-country immunization supply chain systems. In many instances these systems were developed for EPI 40 years ago and although they have been adjusted over these decades they are not structured for the contemporary vaccine landscape.

In this April session, SAGE reviewed a deeper analysis from the approximately 70 countries that have undergone effective vaccine management (EVM) assessments to date. This provided quantified evidence on the fragility in immunization supply systems in low and lower-middle income countries, and from national store level down to service delivery level. SAGE reviewed potential innovative solutions to address these challenges and deliberated the “Call-to-Action” from the Immunization Practices Advisory Committee (IPAC).

SAGE appreciated the more in-depth review and analysis, noting that there was no solid evidence on causality between high EVM and high coverage performance. 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%.

défauts de qualité des activités de vaccination supplémentaires (AVS), renforcer la couverture de la vaccination systématique, améliorer l'accès et utiliser une combinaison appropriée de VPO trivalents et bivalents au cours des 10 prochains mois. Le SAGE a insisté sur le fait que l'élimination des PVDVc2 persistants d'ici la fin 2014/le début 2015 devait être une grande priorité pour les efforts mondiaux d'éradication, si l'on veut rester dans les temps pour les grandes étapes du Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013–2018. Il demande instamment aux pays de corriger la combinaison de VPO utilisés pour les campagnes de vaccination à grande échelle dans les régions où l'on trouve des poliovirus circulants dérivés d'une souche vaccinale de type 2 (PVDVc2), de façon à garantir la possibilité de retirer le VPO2 au cours de la «saison basse» de transmission des poliovirus en 2016, comme cela avait été initialement programmé. Le SAGE a examiné et approuvé dans ses grandes lignes l'approche proposée pour atténuer le risque d'émergence de PVDVc2, avec l'introduction du VPI, le renforcement de la vaccination systématique et des AVS «préventives» administrant le VPO trivalent dans les pays de niveau 1 et certains pays de niveau 2 ou dans des régions de ces pays. Les détails de l'approche seront davantage élaborés par le groupe de travail et étudiés par le SAGE en octobre 2014.

### Chaîne d'approvisionnement en vaccins

En novembre 2013, le SAGE s'est vivement inquiété des difficultés grandissantes auxquelles sont confrontés les pays et a souhaité attirer l'attention de tous les partenaires et encourager des investissements plus importants pour le renforcement de la chaîne d'approvisionnement en vaccins au sein des pays. Dans de nombreux cas, il s'agit de systèmes qui ont été élaborés pour le PEV il y a 40 ans, et bien qu'ayant été ajustés au cours des décennies qui ont suivi, ils ne sont plus adaptés à la situation contemporaine de la vaccination.

Lors de cette session d'avril, le SAGE a examiné une analyse approfondie portant sur environ 70 pays ayant fait à ce jour des évaluations en matière de gestion efficace des vaccins (EVM). Cela a apporté des données quantitatives sur la fragilité des systèmes d'approvisionnement en vaccins dans les pays à revenu faible ou intermédiaire, depuis le niveau de l'entrepôt national central jusqu'à celui de la prestation des services. Le SAGE a examiné les solutions innovantes potentielles pour s'attaquer à ces difficultés et a débattu de l'«Appel à l'action» lancé par le Comité consultatif sur les Pratiques vaccinales (IPAC).

Le SAGE a apprécié l'examen plus approfondi et l'analyse, notant toutefois qu'il n'existait aucune preuve solide d'un lien de cause à effet entre une gestion efficace des vaccins et de bons résultats en matière de couverture. Le SAGE a recommandé que l'évaluation de la gestion des vaccins comporte une dimension mesurant les capacités des ressources humaines et a encouragé l'OMS à utiliser ces évaluations en les alignant sur celles de l'impact de l'introduction des nouveaux vaccins pour renforcer les liens entre les problèmes de la chaîne d'approvisionnement et les résultats des programmes. Pour améliorer encore les évaluations en matière de gestion efficace des vaccins, il a été proposé d'utiliser un outil aux fins de la supervision et de mettre au point un score composite pour compléter la comparaison générale de 80%.



SAGE welcomed the presentation on the available technology and systems solutions and the ambition to push beyond traditional approaches to addressing problems. However, SAGE cautioned that not all solutions will have the same impact and should be ranked. Furthermore, some technological solutions may have unintended consequences and add complexity to the programme, or be cost-inefficient. These risks should be mitigated and well-documented so that countries can better prioritize their appropriate actions. Strategic assessments should be done at the national and subnational level to identify which solutions will have most impact. Solutions are likely to be local in terms of rank order.

SAGE commended the IPAC “Call-to-Action” as a strong advocacy document and suggested the recommendations be distilled into key messages that could be used in the GVAP report to the WHA and in the context of the 40-year anniversary of EPI. SAGE also suggested that human resource challenges be given more emphasis in the “Call-to-Action” and where possible, the level of financial investment required to address challenges be articulated.

SAGE affirmed the importance of the development of GAVI’s immunization supply chain strategy, and recognized this is a key rallying point to mobilize country-level funding in the following priority areas: supply chain design and optimization; cold chain and vaccine distribution strengthening; human resources for logistics; and logistics data for management. Members were equally pleased to note the initiative by WHO and UNICEF to develop an immunization supply chain hub to bolster the comprehensive approach to EVM. SAGE re-affirmed its future commitment to support policy recommendations that include the right incentives for countries to embrace transformational changes in their immunization supply chains and address the challenges and bottlenecks identified.

In conclusion, SAGE re-affirmed its concern about the alarming state of immunization supply chain systems in developing countries, including vaccine availability, vaccine potency, and supply chain efficiency. SAGE endorsed the IPAC “Call-to-Action” and affirmed the importance of the WHO-UNICEF Joint Statement on EVM as tools for global policy advocacy. Both need to be packaged in an effective and complementary manner. SAGE also stressed the importance of thoroughly considering immunization supply chain impact in future deliberations on introduction of new vaccines.

### **Varicella and herpes zoster vaccines**

SAGE reviewed the available data on the global prevalence and burden of disease caused by varicella and herpes zoster caused by varicella-herpes-zoster virus (VZV) according to country development status. Live attenuated vaccines are available to protect against herpes zoster and varicella. SAGE reviewed the safety, effectiveness, immunogenicity and duration of protection

Le SAGE a salué la présentation sur les technologies existantes, les solutions au niveau des systèmes et l’ambition d’aller au-delà des approches traditionnelles pour résoudre les problèmes. En revanche, il a averti que toutes les solutions n’auront pas le même impact et doivent être classées par ordre. De plus, certaines solutions technologiques pourraient avoir des conséquences indésirables et ajouter de la complexité aux programmes ou être inefficaces par rapport au coût. Ces risques doivent être atténués et bien documentés, de façon à ce que les pays puissent mieux hiérarchiser les mesures à prendre. Des évaluations stratégiques doivent être faites aux niveaux national et infranational pour déterminer les solutions qui auront le plus d’impact. Il est probable qu’en termes de classement, les meilleures seront au niveau local.

Le SAGE s’est félicité de «l’Appel à l’action» de l’IPAC, à ses yeux un puissant document de plaidoyer, et suggère de faire passer les recommandations dans des messages clés qui pourront être repris dans le rapport du GVAP à l’AMS pour le 40e anniversaire du PEV. Il propose que cet appel mette davantage l’accent sur les difficultés liées aux ressources humaines et, autant que possible, définisse le niveau des investissements requis pour les résoudre.

Le SAGE a affirmé l’importance de l’élaboration de la stratégie de la chaîne d’approvisionnement en vaccins de l’Alliance GAVI et a reconnu qu’il s’agit là d’un point de ralliement essentiel pour mobiliser les financements au niveau des pays dans les domaines prioritaires tels que: la conception et de l’optimisation de la chaîne d’approvisionnement; la chaîne du froid et le renforcement de la distribution des vaccins; les ressources humaines pour la logistique; et les données logistiques pour la gestion. Les membres ont également noté avec plaisir l’initiative prise par l’OMS et l’UNICEF pour établir une plate-forme pour la chaîne d’approvisionnement afin de soutenir une approche globale pour la gestion efficace des vaccins. Le SAGE a réaffirmé son engagement futur pour appuyer des recommandations politiques comportant les mesures justes incitant les pays à se rallier aux changements pour transformer leurs chaînes d’approvisionnement en vaccins, résoudre les difficultés et lever les blocages identifiés.

En conclusion, le SAGE a réaffirmé ses inquiétudes quant à l’état alarmant des systèmes d’approvisionnement en vaccins dans les pays en développement, notamment la disponibilité des vaccins, leur activité et l’efficacité des chaînes d’approvisionnement. Il a approuvé l’«Appel à l’action» de l’IPAC et affirmé l’importance de la déclaration conjointe de l’OMS et de l’UNICEF sur la gestion efficace des vaccins en tant qu’outil pour un plaidoyer politique à l’échelle mondiale. Les deux doivent être mis en forme d’une manière efficace et complémentaire. Le SAGE a également insisté sur l’importance d’étudier soigneusement l’impact des chaînes d’approvisionnement dans les futurs débats sur l’introduction de nouveaux vaccins.

### **Vaccins contre la varicelle et le zona**

Le SAGE a examiné les données disponibles sur la prévalence mondiale et la charge de morbidité imputable à la varicelle et au zona, provoqués par le virus varicelle-zona (VZV), selon l’état de développement des pays. Il existe des vaccins vivants atténués pour se protéger contre le zona et la varicelle. Le SAGE a examiné l’innocuité, l’efficacité, l’immunogénicité de ces deux vaccins, ainsi que la durée de protection qu’ils confèrent dans

of both vaccines in the general and in specific populations. Mathematical models informed SAGE on a possible shift in the age of occurrence of varicella with different levels of population coverage with childhood varicella vaccination and on the impact on herpes zoster incidence after introduction of varicella vaccination.

VZV causes varicella as an acute disease; thereafter the virus remains latent but can reactivate causing herpes zoster later in life. Varicella is more severe in adults than in children. Varicella is highly communicable with worldwide distribution and most persons acquire it during their lifetime. There are differences in the epidemiology of varicella between temperate and tropical climates including lesser seasonality and delayed average age of infection in the latter. Other factors affecting seroprevalence in populations include area of residence, population density, attendance at childcare and school and number of siblings in the household.

There is strong scientific evidence that varicella vaccine is safe and effective in preventing varicella-related morbidity and mortality in immunocompetent individuals.

SAGE noted that the varicella and herpes zoster disease burden is substantially lower than that of other vaccine-preventable disease such as measles, rotavirus or invasive pneumococcal diseases prior to vaccine introduction. SAGE concluded that before countries decide on the introduction of varicella vaccine into routine childhood immunization programmes, they should set up adequate disease surveillance to assess the varicella disease burden, with provision of continued surveillance after introduction of vaccination.

SAGE recommended that routine childhood immunization against varicella could be considered in countries where the disease has an important public health impact and causes a substantial socio-economic burden. However, resources should be sufficient to ensure reaching and sustaining vaccine coverage  $\geq 80\%$ , as vaccine coverage of 20%–80% would shift varicella to older ages with the risk of an associated increase of severe disease and mortality.

Those countries deciding to introduce routine childhood varicella immunization, should administer vaccination at 12–18 months of age. The number of doses administered is dependent on the goal of the vaccination programme. One dose is sufficient to reduce mortality and severe morbidity from varicella. Two doses induce higher effectiveness and should therefore be recommended in countries where the programmatic goal is, in addition to decreasing severe disease, to further reduce the number of cases and outbreaks.

Due to the increased severity of varicella in immunocompromised people, certain groups should be considered for VZV vaccination. Varicella vaccine has been shown to be safe, immunogenic, and effective in certain HIV-infected individuals. SAGE recommended that use of the vaccine should be considered in clinically stable

la population générale et dans des groupes spécifiques. Les modèles mathématiques ont indiqué au Groupe la possibilité d'une évolution de l'âge d'apparition de la varicelle selon les différents niveaux de couverture de la population par la vaccination dans l'enfance et d'un effet sur l'incidence du zona après l'introduction du vaccin.

Le VZV est à l'origine de la varicelle sous sa forme aiguë; le virus reste ensuite à l'état latent mais peut se réactiver à un stade ultérieur de la vie et provoquer le zona. La varicelle est plus grave chez l'adulte que chez l'enfant. C'est une maladie très contagieuse, répartie dans le monde entier et la plupart des gens la contractent au cours de leur existence. Il y a des différences épidémiologiques en fonction du climat, avec une saisonnalité moins marquée et un âge moyen plus élevé pour contracter l'infection dans les régions tropicales que dans les régions tempérées. D'autres facteurs influent sur la séroprévalence dans la population y compris la zone de résidence, la densité de la population, la fréquentation des crèches et des écoles, le nombre de frères et sœurs dans la famille.

On a des preuves scientifiques solides que le vaccin contre la varicelle est sûr et efficace pour éviter la morbidité et la mortalité imputables à cette maladie chez les sujets immunocompétents.

Le SAGE a relevé que la charge de morbidité imputable à la varicelle et au zona est sensiblement plus faible que pour d'autres maladies évitables par la vaccination, comme la rougeole, les infections à rotavirus ou les pneumocoques invasives avant l'introduction des vaccins correspondants. Il en conclut que, avant que les pays ne décident l'introduction du vaccin contre la varicelle dans les programmes de vaccination systématique de l'enfant, ils devraient mettre en place une surveillance adéquate de la maladie pour évaluer la charge de morbidité et prendre des dispositions pour la maintenir après l'introduction de cette vaccination.

Le SAGE a recommandé de n'envisager la vaccination systématique des enfants contre la varicelle que dans les pays où cette maladie a un impact important sur la santé publique et entraîne une charge socio-économique substantielle. Les ressources doivent cependant être suffisantes pour être sûr d'atteindre et de maintenir une couverture vaccinale  $\geq 80\%$ : une couverture comprise entre 20%-80% repousse l'âge auquel la varicelle survient et il s'y associe alors le risque d'une hausse des cas graves et de la mortalité.

Les pays qui décident d'introduire la vaccination systématique contre la varicelle dans l'enfance doivent administrer le vaccin à un âge compris entre 12 et 18 mois. Le nombre de doses à administrer dépend du but recherché par le programme de vaccination. Une dose suffit pour réduire la mortalité et la morbidité sévère dues à cette maladie. Deux doses sont plus efficaces et seront donc recommandées dans les pays dont les programmes ont pour objectif, en plus de diminuer la gravité, de faire baisser le nombre de cas et de flambées.

En raison de la gravité accrue de la varicelle chez les sujets immunodéprimés, on envisage la vaccination contre le VZV dans certains groupes. On a démontré que ce vaccin est sûr, immunogène et efficace chez certaines personnes infectées par le VIH. Le SAGE recommande d'envisager son administration chez l'enfant ou l'adulte infecté par le VIH dans un état clinique

HIV-infected children or adults with CD4+ T-cell determinations  $\geq 15\%$ , including those receiving highly active antiretroviral therapy (HAART). Non-immune individuals with a history of acute lymphocytic leukaemia and patients with certain solid tumours who have successfully completed chemotherapy and are unlikely to relapse can receive the vaccine at least 3 months after all chemotherapy is completed. Vaccine can be safely given to subjects with isolated defects in antibody production. It should not be given to those with immunodeficiency conditions that include defects in cell-mediated immunity.

Data on the immunization of health-care workers are limited and not widely representative. However, countries are strongly encouraged to consider vaccination of potentially susceptible (i.e. non-immunized and no history of varicella) health-care workers with 2 doses of varicella vaccine in settings where the risk of severe varicella in the population in direct contact with health-care workers is high, even if varicella vaccination is not included in the routine immunization schedule.

Large clinical trials and post-licensure surveillance data from high-income countries indicate that herpes zoster vaccine is safe and efficacious against herpes zoster disease, post-herpetic neuralgia and other serious herpes zoster complications. Due to limited data and the unknown burden of disease in most countries, initial evidence of waning of protection over time and uncertainty of the optimal age for vaccination SAGE cannot offer any recommendation on the routine use of herpes zoster vaccine at this time.

The recommendations by SAGE on the use of varicella and herpes zoster vaccines will be reflected in an update of the previous 1998 WHO position paper on varicella vaccines.

### Human papilloma virus vaccines

SAGE was requested to consider the optimal human papilloma virus (HPV) vaccination schedules in girls. SAGE was informed by: (i) a reminder that HVP vaccine efficacy is mediated by vaccine-induced antibodies and that HPV immunization in the younger age group was recommended based on "immunological bridging", i.e. the demonstration of similar or higher antibody titres in girls as in women in whom clinical efficacy against cervical carcinoma in situ was shown; (ii) 2 reviews on HPV immunization schedules (1 systematic review of randomized and non-randomized studies, and 1 descriptive review of observational studies), (iii) the deliberations of an ad-hoc expert consultation on HPV schedules and (iv) the European Medicines Agency-Assessment Report for Cervarix®.

SAGE concluded that the immunological evidence was sufficient to conclude that a 2-dose prime-boost schedule (given with a minimal interval of 6 months) was non-inferior in girls to a 3-dose (prime-prime-boost, at 0, 1–2, and 6 months) schedule in the same age group

stable et dont la numération des cellules T CD4+ est  $\geq 15\%$ , y compris chez ceux sous traitement antirétroviral hautement actif. Les sujets non immunisés ayant des antécédents de leucémie aiguë lymphoblastique et les patients qui ont certaines tumeurs solides et ont achevé avec succès leur chimiothérapie, et pour lesquels une récurrence est improbable, peuvent recevoir le vaccin au moins 3 mois après la fin de la chimiothérapie. On peut l'administrer sans danger aux sujets présentant des anomalies isolées de la production d'anticorps. En revanche, il ne doit pas être administré aux sujets porteurs d'une immunodéficience présentant des défauts de l'immunité à médiation cellulaire.

Les données sur la vaccination des agents de santé sont limitées et ne sont pas largement représentatives. Toutefois, il est vivement conseillé aux pays d'envisager la vaccination des agents de santé potentiellement vulnérables (par exemple, ceux qui ne sont pas immunisés ou qui n'ont pas d'antécédents de vaccination contre la varicelle) en leur administrant 2 doses dans les situations où le risque de varicelle grave dans la population à leur contact direct est élevé, même si ce vaccin ne fait pas partie du calendrier des vaccinations systématiques.

De grands essais cliniques et les données de la surveillance post-homologation dans les pays à revenu élevé indiquent que le vaccin contre le zona est sûr et efficace contre le zona lui-même, mais aussi contre les algies post-zostériennes et d'autres complications sérieuses. En raison des données limitées et de la charge de morbidité inconnue dans la plupart des pays, de données initiales sur la disparition de la protection dans le temps et de l'incertitude quant à l'âge optimal pour la vaccination, le SAGE ne peut pas pour l'instant se permettre de faire la moindre recommandation sur l'usage systématique des vaccins contre le zona.

La note de synthèse précédemment publiée par l'OMS en 1998 sur les vaccins contre la varicelle et le zona sera mise à jour en reprenant les recommandations du SAGE sur leur utilisation.

### Vaccins contre le papillomavirus humain

Il a été demandé au SAGE d'étudier les calendriers de vaccination optimaux contre le papillomavirus humain (HPV) chez les jeunes filles. Le Groupe a tiré ses informations: i) d'un rappel que l'efficacité du vaccin anti-HPV passait par des anticorps induits par la vaccination et que celle-ci était recommandée dans le groupe des jeunes sur la base d'une extrapolation (dite «immunological bridging»), c'est-à-dire la mise en évidence de titres similaires ou supérieurs en anticorps chez les jeunes filles par rapport aux femmes pour lesquelles on a montré une efficacité clinique in situ contre le cancer du col; ii) de 2 examens portant sur les calendriers de vaccination contre le HPV (1 examen systématique des études randomisées et non randomisées et 1 examen descriptif des études d'observation); iii) des résultats des délibérations d'une consultation ad hoc d'experts sur les calendriers d'administration du HPV; et iv) du rapport d'évaluation de l'Agence européenne des médicaments sur le Cervarix®.

Le SAGE a conclu que les preuves immunologiques suffisaient pour déterminer que le calendrier de deux doses (primovaccination/rappel administrés à au moins 6 mois d'intervalle) n'avait pas une efficacité inférieure chez la jeune fille au calendrier de 3 doses (2 doses de primovaccination plus un rappel

and in women in whom clinical efficacy was demonstrated. It noted that reports of the lower effectiveness of 2 doses compared with 3 doses of the vaccine against clinical outcomes in some observational studies were confounded by numerous factors, including the failure to control for the interval between doses and the inclusion of girls who were already infected with HPV. SAGE recognized that a reduction from 3 to 2 vaccine doses would bring major cost savings as well as obvious programmatic advantages, and that an increased flexibility in the intervals between doses would likely lead to increase in vaccination coverage.

SAGE reiterated the importance of targeting HPV immunization for girls aged 9–13 years, prior to initiation of sexual activity.

- A 2-dose schedule with an interval of at least 6 months between doses is recommended for girls aged <15 years (even for the girls aged ≥15 years at the time of the second dose).
- If for any reason interval between the first and second doses is shorter than 5 months, then a 3rd dose should be given at least 6 months after the first dose.
- The 3-dose schedule (0, 1–2, 6 months) remains recommended for girls >15 years of age and for immunocompromised individuals, including those known to be HIV-infected.
- These schedule recommendations apply to both the bivalent and quadrivalent vaccines.

SAGE identified gaps in knowledge that require further research but consider that this should not delay the implementation of the proposed recommendations. SAGE recommends: conducting head-to-head comparisons of various alternative schedules; ensuring the follow-up of the cohorts under study in India and to duplicate similar studies in other settings, especially in low and middle income countries (LMICs); to collect longer-term clinical effectiveness data to further define the duration of protection after 2-dose and 3-dose schedules. Because of the high level of herd protection conferred by immunization, these studies must be done in regions where high rates of vaccination have not yet been achieved. Multicentre studies in low income countries among healthy adolescent girls and among special populations (e.g. HIV-infected, malnourished adolescents, endemic malaria infection) would provide additional evidence. The cost-effectiveness and anticipated impact of 2-dose versus 3-dose vaccination in LMIC settings still need to be evaluated. Additional model and economic evaluations that consider alternative scenarios of low coverage and various assumptions on effectiveness and duration of protection in LMICs are needed.

### Pertussis vaccines

In November 2012, SAGE expressed concern about the apparent resurgence of pertussis in some industrialized countries despite high vaccine coverage with acellular pertussis (aP) vaccines, which in some settings was

à 0, 1-2, et 6 mois) dans la même tranche d'âge et chez les femmes pour lesquelles l'efficacité clinique a été démontrée. Il a noté que de nombreux facteurs, notamment le manque de contrôle de l'intervalle entre les doses et le recrutement de jeunes filles déjà infectées par le HPV, jetaient un doute sur la conclusion de certaines études d'observation faisant état d'une plus faible efficacité du calendrier à 2 doses par rapport à celui à 3 doses d'après les résultats cliniques obtenus. Le SAGE a reconnu que le passage de 3 à 2 doses vaccinales pouvait permettre des économies majeures et avoir aussi des avantages évidents pour les programmes, et que la flexibilité accrue des intervalles entre les doses aboutirait probablement à une augmentation de la couverture vaccinale.

Le SAGE a rappelé l'importance de cibler la vaccination anti-HPV sur les jeunes filles de 9 à 13 ans, avant le début de l'activité sexuelle.

- Le calendrier de 2 doses avec un intervalle d'au moins 6 mois est recommandé pour les jeunes filles âgées de <15 ans (et ceci, même pour les jeunes filles âgées de ≥15 ans au moment où la seconde dose est administrée).
- Si l'intervalle entre la première et la seconde dose est inférieur à 5 mois, une troisième dose devrait être administrée au moins 6 mois après la première.
- Le calendrier de 3 doses (0, 1-2, et 6 mois) reste recommandé pour les jeunes filles est âgée de >15 ans et pour les sujets immunodéprimés, y compris en cas d'infection connue au VIH.
- Ces recommandations valent pour les vaccins bivalents comme quadrivalents.

Le SAGE a identifié des lacunes dans les connaissances nécessitant de nouvelles études mais considère que celles-ci ne justifient pas de différer l'application des recommandations proposées. Il préconise: de procéder à des comparaisons directes des différents calendriers possibles; d'assurer le suivi des cohortes à l'étude en Inde et de faire des études similaires dans d'autres cadres, en particulier dans les pays à revenu faible ou intermédiaire; de collecter des données sur l'efficacité clinique à plus long terme pour mieux définir la durée de la protection après les calendriers à 2 et à 3 doses. En raison du niveau élevé de protection collective apportée par l'immunisation, ces études doivent être faites dans des régions qui n'ont pas encore atteint des taux de vaccination élevés. Des études multicentriques dans des pays à faible revenu portant sur les adolescentes en bonne santé et des populations spécifiques (par exemple les adolescentes infectées par le VIH ou souffrant de malnutrition, celles dans les zones d'endémie du paludisme) apporteront des données probantes supplémentaires. Le rapport coût/efficacité et l'impact anticipé de la vaccination par 2 doses plutôt que par 3 doses dans les pays à revenu faible ou intermédiaire doivent encore être évalués. Un modèle additionnel et des évaluations économiques prenant en compte plusieurs scénarios de faible couverture et diverses hypothèses sur l'efficacité et la durée de la protection dans ces pays sont nécessaires.

### Vaccins anticoquelucheux

En novembre 2012, le SAGE s'est dit préoccupé de la résurgence apparente de la coqueluche dans certains pays industrialisés malgré une couverture élevée de l'administration des vaccins anticoquelucheux acellulaires (Ca), s'associant dans certaines



associated with an increase in infant pertussis deaths. SAGE had advised countries considering a switch from wP to aP vaccines to await further SAGE guidance or to themselves carefully review the latest evidence on aP pertussis vaccine effectiveness and the possibility that such a switch may lead to a less favourable outcome in terms of pertussis disease control.

SAGE then established a pertussis working group which presented its report to SAGE. This report included a review of epidemiological data on pertussis from 19 developing and industrialized countries in various world regions which have wP- or aP-based programmes achieving high vaccine coverage rates, effective disease control, and the ability to provide high quality data. Given the natural periodicity of pertussis, disease resurgence was defined as a larger burden of disease than expected when compared to previous cycles in the same setting. The main outcome of the report is that pertussis vaccination is highly effective in reducing disease caused by *Bordetella pertussis*, with a large decline in overall global incidence and mortality compared with the pre-vaccination era in both wP- and aP-using countries. To date, there is no evidence of a widespread global resurgence of pertussis. There is however evidence that resurgence has occurred in 5 of the 19 countries reviewed, 4 of which were exclusively using aP vaccines. The increased number of cases in 1 country using wP vaccine was considered to reflect factors other than the use of this vaccine (surveillance, laboratory methods, and low vaccine coverage).

Recent modelling studies from Australia, England and Wales, and the USA, as well as data from a baboon model, supported the hypothesis that wP to aP vaccine transition may be associated with disease resurgence. Although the reasons for the resurgence were found to be complex and varied by country, SAGE concluded that the shorter duration of protection and likely reduced impact on infection and transmission conferred by aP vaccines play critical roles. The influence of changes in circulating pertussis strains on the effectiveness of aP or wP vaccines was not found to contribute to observed country level resurgence.

SAGE recommends that all children should be immunized against pertussis, with the goal of maintaining >90% coverage, as minor reductions can lead to an increase in incidence. Vaccination with 3 doses of wP or aP vaccine should be given as soon as possible  $\geq 6$  weeks of age with vaccine of assured quality.

Licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines, as aP vaccines induce a different type of immune response (higher Th2-promoting antibody responses but lower Th1 and Th17 responses), and are less effective in clearing mucosal infections. The risk of resurgence associated with the use of aP vaccines for

situations à une augmentation du nombre des décès infantiles par coqueluche. Il avait conseillé aux pays envisageant de passer des vaccins anticoquelucheux à germes entiers aux vaccins acellulaires d'attendre de nouvelles orientations de sa part ou d'examiner eux-mêmes minutieusement les données les plus récentes sur l'efficacité des vaccins acellulaires et la possibilité que ce changement pourrait entraîner des résultats moins favorables en termes de lutte contre la coqueluche.

Le SAGE a ensuite mis en place un groupe de travail sur la coqueluche qui lui a présenté son rapport. Ce document comportait un examen des données épidémiologiques sur cette maladie dans 19 pays en développement ou industrialisés dans différentes régions du monde, dotés de programmes de vaccination basés soit sur le vaccin à germes entiers soit sur le vaccin acellulaire et obtenant des taux de couverture élevés, luttant efficacement contre la maladie et ayant la capacité de fournir des données de grande qualité. Compte tenu de la périodicité naturelle de la coqueluche, la résurgence a été définie comme étant une charge de morbidité plus forte que celle attendue en comparaison des cycles précédents dans le même cadre. La principale conclusion du rapport est que la vaccination contre la coqueluche est très efficace pour réduire le nombre des cas d'infection à *Bordetella pertussis*, avec une baisse importante de la moyenne mondiale de l'incidence et de la mortalité par rapport à l'époque avant la vaccination, que ce soit dans les pays utilisant le vaccin à germes entiers ou le vaccin acellulaire. Aujourd'hui, rien n'indique une résurgence mondiale généralisée de cette maladie. Il y a en revanche des signes de résurgence dans 5 des 19 pays examinés, dont 4 utilisant exclusivement des vaccins acellulaires. On pense que l'augmentation du nombre des cas dans 1 pays utilisant des vaccins à germes entiers est due à d'autres facteurs que le vaccin utilisé (surveillance, méthodes de laboratoire et faible couverture vaccinale).

Des études récentes de modélisation en Australie, en Angleterre, aux Pays de Galles et aux États-Unis, ainsi que les données provenant d'un modèle sur le babouin, étayaient l'hypothèse que le passage du vaccin à germes entiers au vaccin acellulaire pourrait s'associer à une résurgence de la coqueluche. Bien que les raisons de celle-ci se soient avérées complexes et variables selon les pays, le SAGE a conclu que la durée plus courte de la protection conférée par les vaccins acellulaires et la diminution probable de l'impact sur l'infection et la transmission jouaient un rôle crucial. En revanche, il n'a pas été observé que les modifications des souches de coqueluche en circulation aient une influence sur l'efficacité des vaccins acellulaires ou à germes entiers et contribuent à une résurgence au niveau des pays.

Le SAGE recommande de vacciner tous les enfants contre la coqueluche, le but étant de maintenir une couverture >90%, des baisses mineures pouvant entraîner une augmentation de l'incidence. La vaccination par 3 doses de vaccin à germes entiers ou acellulaire de qualité assurée doit être administrée le plus tôt possible à partir de l'âge de  $\geq 6$  semaines.

Les vaccins acellulaires homologués pourraient avoir une efficacité initiale plus faible, conférer une immunité déclinant plus rapidement et avoir un impact plus réduit sur la transmission par rapport aux vaccins à germes entiers actuellement disponibles au niveau international, car ils induisent une réponse immunitaire de type différent (plus forte stimulation de la réponse Th2, mais réponses plus faibles des Th1 et Th17) et sont moins efficaces pour nettoyer les infections des muqueuses.

primary immunization, including increased disease in infants, compared with use of wP, indicates that countries where only a limited number of pertussis doses are used/affordable should continue to use wP vaccines for primary pertussis early infant vaccination. Thus the switch from wP to aP vaccines for primary infant immunization should only be considered if large numbers of doses (including several boosters) can be included in the national immunization schedules; this has substantial cost implications given the much higher cost of aP vaccines and higher number of doses required. Surveillance and modelling data suggest that the use of aP vaccines may result in a resurgence of pertussis after a number of years and might lead to an increased risk of death in young infants compared with programmes using wP. The magnitude and delay for this resurgence to occur are difficult to predict, given the many factors that intervene such as vaccine coverage, natural immunity, vaccine type, schedules, etc.

SAGE was also presented with a review of strategies to further reduce infant mortality. Protection against severe or fatal pertussis in infancy and early childhood can be achieved after a primary vaccination series with either wP or aP vaccine. There is substantial and consistent evidence both from observational and analytical studies that a single dose of pertussis vaccine in infancy has significant effectiveness (around 50%) in preventing severe disease and that 2 doses provide high protection ( $\geq 80\%$ ), although it is essential to complete a full routine series to obtain the full protective effects conferred by pertussis vaccination.

SAGE noted that recent evidence suggests that maternal immunization with aP during pregnancy is safe and highly effective in protecting infants from pertussis and that it may have a high impact on morbidity and mortality in infants too young to have been immunized. This conclusion does not extend to wP vaccines, given the absence of immunogenicity and efficacy data in pregnant women and concerns regarding potential higher reactogenicity in adults. The immunization of newborn infants was considered as a potential strategy worth pursuing but currently limited by insufficient data on impact and safety and lack of aP stand-alone vaccine. SAGE agreed that "cocooning"<sup>5</sup> may have an impact on disease prevention in some settings if high coverage can be achieved in a timely manner, and that health-care workers can be considered as the highest priority group for adult pertussis vaccination programmes.

Vaccination of pregnant women is considered likely to be the most cost-effective complementary strategy to prevent pertussis-associated infant mortality, more

Le risque de résurgence associé à l'utilisation des vaccins acellulaires pour la primovaccination, comportant l'augmentation du nombre de cas de maladie infantile par rapport aux vaccins à germes entiers, montre que les pays où le nombre de doses utilisées/à un prix abordable est limité doivent continuer à administrer les vaccins à germes entiers pour la primovaccination des nourrissons. Le passage des vaccins à germes entiers aux vaccins acellulaires dans cette indication ne sera donc envisagé que si l'on peut inclure un grand nombre de doses (y compris plusieurs rappels) dans les calendriers nationaux de vaccination, ce qui a des implications importantes au niveau du coût, compte tenu du prix beaucoup plus élevé des vaccins acellulaires et du plus grand nombre de doses requises. La surveillance et les données de la modélisation indiquent que l'utilisation des vaccins acellulaires pourrait entraîner une résurgence de la coqueluche après un certain nombre d'années et un risque accru de mortalité pour les nourrissons par rapport aux programmes administrant des vaccins à germes entiers. L'ampleur et le délai de cette résurgence sont difficiles à prévoir compte tenu des nombreux facteurs qui interviennent, tels que la couverture vaccinale, l'immunité naturelle, le type de vaccins, les calendriers, etc.

Un examen des stratégies pour réduire davantage la mortalité infantile a été présenté au SAGE. On peut protéger les nourrissons et les jeunes enfants contre la coqueluche sévère ou mortelle par la primovaccination avec le vaccin à germes entiers ou le vaccin acellulaire. De nombreuses données provenant d'études observationnelles et analytiques, et allant dans le même sens, indiquent qu'une seule dose de vaccin antioquelucheux administrée au nourrisson a une efficacité importante (environ 50%) pour éviter la maladie grave et que 2 doses confèrent une protection élevée ( $\geq 80\%$ ), bien qu'il soit essentiel d'administrer la série complète de la vaccination systématique pour obtenir un effet protecteur complet.

Le SAGE a pris note des données récentes laissant à penser que l'administration du vaccin acellulaire aux mères pendant la grossesse est sans danger et hautement efficace pour protéger les nourrissons de la coqueluche et qu'elle pourrait avoir un fort impact sur la morbidité et la mortalité chez les enfants encore trop jeunes pour avoir été vaccinés. Cette conclusion ne vaut pas pour les vaccins à germes entiers compte tenu de l'absence de données sur l'immunogénicité et l'efficacité chez la femme enceinte et des inquiétudes quant à une réactogénicité potentiellement plus élevée chez l'adulte. La vaccination des nouveau-nés a été considérée comme une stratégie potentielle à tenter, mais elle se heurte actuellement à l'insuffisance des données sur l'impact et l'innocuité et au fait qu'il n'existe pas de vaccin antioquelucheux acellulaire présenté seul. Le SAGE a convenu que la stratégie du «cocooning»<sup>5</sup> (vaccination de l'entourage proche) pourrait avoir un impact sur la prévention de la maladie dans certaines situations si elle est réalisée à temps et que les personnels soignants doivent être considérés comme le groupe le plus prioritaire pour les programmes de vaccination des adultes contre la coqueluche.

On considère que la vaccination des femmes enceintes est probablement la stratégie complémentaire ayant le meilleur rapport coût/efficacité pour éviter la mortalité infantile associée

<sup>5</sup> The definition of "cocooning" (immunization) is available at [http://en.wikipedia.org/wiki/Cocooning\\_\(immunization\)](http://en.wikipedia.org/wiki/Cocooning_(immunization))

<sup>5</sup> La définition de "cocooning" (vaccination de l'entourage proche) est disponible sur [http://en.wikipedia.org/wiki/Cocooning\\_\(immunization\)](http://en.wikipedia.org/wiki/Cocooning_(immunization))

effective and favourable than cocooning. Countries may thus consider the immunization of pregnant women with 1 dose of Tdap (in the 2nd or 3rd trimester) in addition to routine primary infant pertussis vaccination in countries or settings with high infant morbidity/mortality due to pertussis. The value of this strategy will need to be further assessed in women who have been primed with aP vaccines in childhood and in LMICs.

SAGE emphasized the importance of efforts to improve surveillance of disease burden particularly in LMICs, and assessment of impact of infant immunization, with particular focus on fatalities in infants <1 year of age and on hospital surveillance. SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.

The systematic review (including effectiveness and safety) of the optimal primary immunization schedules (in association with DT-containing vaccine) is ongoing and will be presented at the October 2014 SAGE meeting. The 2010 pertussis position paper will be updated after the results of this review become available. Meantime a short update to the position paper will be published to clarify that the statement in 2010 on the choice of vaccine is no longer valid.

### **Non-specific effects of vaccines on childhood mortality**

In 2012, SAGE requested that WHO review the evidence concerning the possible non-specific effects of routine infant vaccines on mortality. As a result, a working group was established in March 2013 to review data on non-specific mortality effects, with a charge to assess whether current evidence is sufficient to lead to adjustments in policy recommendations, or that further scientific investigation is warranted. If further research is warranted, the working group was asked to define the path towards obtaining unequivocal evidence on the issues that would support future robust, evidence-based adjustments in immunization policies.

In April 2013, SAGE reviewed protocols for 2 commissioned independent systematic reviews to assess (i) the epidemiological evidence regarding non-specific effects of vaccines on mortality, and (ii) evidence of non-specific immunological effects due to vaccination that might inform any evidence on mortality effects. In April 2014, the results of the reviews, which focused on *Bacillus Calmette-Guérin* (BCG), DPT and measles vaccines and their effects among children aged <5 years, were presented to SAGE.

SAGE was also updated on the use of different schedules, and the amount of time during which DTP was the last vaccine administered ("DTP weeks"), in countries worldwide using nationally representative data from Demographic and Health Surveys and Multiple Indicator Cluster surveys. There is a substantial degree

à la coqueluche et qu'elle est plus favorable et plus efficace que le «cocooning». Les pays pourront donc envisager d'administrer aux femmes enceintes 1 dose de vaccin Tdap (au deuxième ou au troisième trimestre de la grossesse) comme stratégie complémentaire à la primovaccination systématique des nourrissons dans les situations où l'on observe une forte morbidité ou mortalité due à la coqueluche. L'utilité de cette stratégie devra encore être évaluée chez les femmes ayant eu une primovaccination avec le vaccin acellulaire dans l'enfance et dans les pays à revenu faible ou intermédiaire.

Le SAGE a insisté sur l'importance des efforts pour améliorer la surveillance de la charge de morbidité, notamment dans les pays à revenu faible ou intermédiaire, et de l'évaluation de l'impact de la vaccination du nourrisson en s'intéressant plus particulièrement aux décès chez les enfants âgés de <1 an et sur la surveillance dans les hôpitaux. Il a déterminé que les conditions nécessaires pour la résurgence de la coqueluche ainsi que les stratégies efficaces pour la prévenir étaient des aspects importants pour les études de modélisation.

L'examen systématique (y compris sur l'innocuité et l'efficacité) des calendriers de primovaccination optimaux (en association avec le vaccin contenant les anatoxines diphtérique et tétanique) se poursuit et sera présenté à la réunion du SAGE en octobre 2014. La note de synthèse de 2010 sur les vaccins anti-coquelucheux sera actualisée après avoir pris connaissance des résultats de cet examen. En attendant, une brève mise à jour sera publiée précisant que la déclaration de 2010 sur le choix du vaccin n'est plus valable.

### **Effets non spécifiques des vaccins sur la mortalité de l'enfant**

En 2012, le SAGE a demandé à l'OMS de passer en revue, pour les vaccins figurant dans le calendrier des vaccinations systématiques du nourrisson, les données factuelles concernant les effets non spécifiques éventuels sur la mortalité. Un groupe de travail a par conséquent été créé en mars 2013 pour examiner les données sur ces effets, avec la tâche d'évaluer si, en l'état, elles suffisaient pour déboucher sur des ajustements dans les recommandations sur la politique vaccinale ou justifiaient des recherches scientifiques plus poussées. Dans ce cas, le groupe était chargé de définir les moyens d'obtenir des données incontestables sur ces questions susceptibles d'étayer des ajustements solides, fondés sur des données probantes, aux politiques de vaccination.

En avril 2013, le SAGE a revu les protocoles de 2 examens systématiques indépendants demandés pour évaluer i) les données épidémiologiques concernant les effets non spécifiques des vaccins sur la mortalité et ii) les données sur les effets immunologiques non spécifiques de la vaccination susceptibles d'apporter un éclairage sur d'éventuels effets, preuves à l'appui, sur la mortalité. En avril 2014, les résultats des examens axés sur le vaccin par le bacille Calmette-Guérin (BCG), le DTC et le vaccin antirougeoleux, et leurs effets sur les enfants âgés de <5 ans, ont été présentés au SAGE.

Le SAGE a été également informé de l'application au niveau mondial des différents calendriers, et du temps écoulé au cours duquel le DTC est le dernier vaccin administré («semaines DTC»), à l'aide de données représentatives à l'échelle nationale et provenant des enquêtes démographiques et sanitaires ou des enquêtes par grappes à indicateurs multiples. Le nombre

of variation in DTP weeks between countries driven by different vaccine schedules, coverage levels, timeliness of vaccination, and supplementary vaccination campaigns.

SAGE concluded that the findings from the immunological systematic review neither exclude nor confirm the possibility of beneficial or deleterious non-specific immunological effects of the vaccines under study on all-cause mortality. The published literature does not provide confidence in the quality, quantity, or kinetics of impact of any non-specific immunological effects in young children after vaccination. There was recognition that non-specific immunological effects following exposure to any antigen, vaccine or natural exposure, are plausible and common, but their biological effects are not fully understood.

Regarding the possible non-specific effect of BCG on all-cause mortality, the epidemiological review suggested possible beneficial effects on all-cause mortality. SAGE concluded that the evidence does not support a change in policy for BCG immunization as soon as possible after birth. The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality and this should be emphasized.

Regarding the possible non-specific effect of DTP on all-cause mortality, the available data neither exclude nor confirm the possibility of beneficial or deleterious non-specific effects of DTP vaccines on all-cause mortality. Randomized controlled trials did not contribute any evidence on non-specific effects of DTP. SAGE concluded that the evidence does not support a change in policy for DTP, and emphasized the benefit of DTP in preventing disease and the importance of the current recommendation.

Regarding the possible non-specific effect of measles-containing vaccines on all-cause mortality, the review suggested possible beneficial effects on all-cause mortality. SAGE concluded that the evidence does not support a change in policy for measles vaccine. The available data suggest that the current WHO recommended schedule for current standard titre measles-containing vaccine has a beneficial effect on all-cause mortality in children.

SAGE considered that the non-specific effects on all-cause mortality warrant further research. SAGE recommended that the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) be tasked with providing advice on which priority research questions need to be addressed in order to inform policy decisions, and what kinds of studies and study designs would provide answers to these questions. 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

des semaines DTC varie sensiblement entre les pays appliquant divers calendriers de vaccination, selon les niveaux de couverture, la ponctualité des vaccinations et les campagnes de vaccination supplémentaires.

Le SAGE a conclu que les résultats de l'examen systématique de l'immunologie ni n'infirmen ni ne confirment la possibilité d'effets immunologiques bénéfiques ou négatifs non spécifiques des vaccins sur la mortalité toutes causes confondues. La littérature publiée n'apporte aucune certitude quant à la qualité, la quantité, ou la cinétique de l'impact d'effets immunologiques non spécifiques chez le jeune enfant après la vaccination. Il a été reconnu que des effets immunologiques non spécifiques après exposition à tout antigène, qu'il s'agisse d'un vaccin ou d'une exposition naturelle, sont plausibles et courants, mais leurs effets biologiques ne sont pas totalement compris.

Concernant les effets non spécifiques éventuels du BCG sur la mortalité toutes causes confondues, l'examen de l'épidémiologie indique la possibilité d'effets bénéfiques. Le SAGE en conclut que les données factuelles n'accréditent pas un changement de la politique préconisant la vaccination par le BCG dès que possible après la naissance. Les informations à notre disposition donnent à penser que le calendrier recommandé actuellement par l'OMS pour le BCG a un effet bénéfique sur la mortalité toutes causes confondues et que ce point devrait être souligné.

Concernant les effets non spécifiques éventuels du DTC sur la mortalité toutes causes confondues, les données disponibles ni n'infirmen ni ne confirment la possibilité d'effets bénéfiques ou négatifs non spécifiques de ce vaccin sur la mortalité toutes causes confondues. Aucun essai contrôlé randomisé n'a apporté de contribution au corpus de données disponibles. Le SAGE en conclut que les faits connus n'accréditent pas un changement de politique pour le DTC. Il souligne les avantages de ce vaccin pour la prévention des maladies et l'importance de la recommandation actuelle.

Concernant les effets non spécifiques éventuels du vaccin anti-rougeoleux sur la mortalité toutes causes confondues, l'examen laisse entrevoir des effets bénéfiques possibles. Le SAGE en conclut que les faits connus n'accréditent pas un changement de politique pour la vaccination antirougeoleuse. Les données disponibles laissent à penser que le calendrier actuel recommandé par l'OMS pour le vaccin contenant un titre standard pour la valence rougeole a un effet bénéfique sur la mortalité de l'enfant toutes causes confondues.

Le SAGE a considéré que les effets non spécifiques sur la mortalité toutes causes confondues donnaient matière à de nouvelles études. Il a recommandé de demander au Comité consultatif sur la recherche pour la mise en œuvre de la vaccination et des vaccins (IVIR AC) d'apporter sa contribution pour définir les questions prioritaires devant être traitées afin d'orienter les décisions politiques, ainsi que les études, avec leur conception, pouvant être entreprises pour y répondre. Le SAGE a décrit certaines considérations à prendre en compte dans les débats du Comité – l'évaluation du recours à des essais contrôlés randomisés de grande qualité là où c'est faisable (tout en relevant les défis éthiques et méthodologiques importants que cela implique), avec une puissance suffisante pour se pencher sur les différences selon le sexe et des critères de jugement immunologiques définis et standar-



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. SAGE considered that additional observational studies with substantial risk of bias would be unlikely to contribute to policy decision-making and therefore should not be encouraged.

### **Integration of immunization and child health services**

For some time SAGE has been concerned that there is insufficient coordination and integration of vaccine initiatives with primary healthcare programmes. In response, provision was made at this meeting for SAGE to review current initiatives to improve coordination and integration of vaccination with other critical child health services, assess what additional measures may be needed to strengthen synergies, and to discuss how, and to what extent, immunization can be integrated with other maternal and child health services at the global, regional, national, district and service delivery levels.

As the starting point for this discussion, SAGE took the WHO working definition of integration as “the management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system”. SAGE also recalled their 2012 recommendation related to integration in the context of new vaccine introduction which stated that “opportunities for improving integration of delivery of services, commodities, and messages with other parts of the health system should be actively sought, with the recognition that integration is a bi-directional process”.

An orientation to the global landscape and initiatives for maternal and child health illustrated the imperative need for integration. Although substantial progress has been made towards achieving Millennium Development Goals #4 and #5, significant challenges and inequities remain. Effective interventions are known and multiple action plans exist, but much health sector work still occurs in isolation without sufficient consideration of the person-centred focus of the health system. However, progress on delivery strategies has created unique opportunities for integration at the point of service delivery. The concept of “EPI Plus” using immunization visits for pregnant women and children as a platform to deliver other interventions, e.g. vitamin A, anthelmintic treatment, malaria interventions, is well established for both campaigns and routine services. The Integrated Global Action Plan for Pneumonia and Diarrhoea includes immunization as part of a comprehensive “protect-prevent-treat” approach where elimination of these child killer diseases cannot be achieved by vaccination alone, but must be accompanied by improvements in water and sanitation, breastfeeding promotion, and access to oral rehydration salts and antibiotics. Engagement of all

disés à priori pour répondre à la question explicite des effets non spécifiques – en insistant sur le fait que la recherche future devait s’appuyer sur un large pool de chercheurs et une grande diversité de localisations géographiques appliquant un protocole standardisé. SAGE considère que des études d’observation supplémentaires, qui comportent un risque important de biais, auraient peu de chances d’apporter une contribution à la prise de décisions politiques et qu’il ne faudrait donc pas les encourager.

### **Intégration de la vaccination et des services de santé de l’enfant**

Depuis un certain temps, le SAGE est préoccupé par l’insuffisance de la coordination et de l’intégration des initiatives de vaccination avec les programmes de soins de santé primaires. En réponse, une disposition a été prise lors de cette réunion pour que le SAGE examine les initiatives actuelles visant à améliorer la coordination et l’intégration de la vaccination avec d’autres services essentiels de santé de l’enfant, évaluer les mesures additionnelles pouvant être nécessaires pour renforcer les synergies et discuter comment, et à quel point, la vaccination peut être intégrée à d’autres services de santé de la mère et de l’enfant aux niveaux mondial, régional, national et à celui de la prestation des services.

Comme point de départ pour cette discussion, le SAGE a pris la définition de travail de l’OMS concernant l’intégration, à savoir «la gestion et la prestation des services de santé de façon à ce que les clients bénéficient d’une continuité des services de prévention et de soins, selon leurs besoins, dans le temps et aux différents niveaux du système de santé». Il a par ailleurs rappelé sa recommandation de 2012 relative à l’intégration dans le contexte de l’introduction de nouveaux vaccins énonçant qu’«il convient de rechercher activement les occasions d’améliorer l’intégration de la délivrance des services, des biens et des messages avec d’autres composantes du système de santé, en reconnaissant que l’intégration est un processus bidirectionnel».

Une orientation sur la situation mondiale et les initiatives pour la santé de la mère et de l’enfant a illustré l’obligation de l’intégration. Bien que des progrès sensibles aient été faits pour atteindre les objectifs du Millénaire pour le développement 4 et 5, il subsiste des défis importants et des inégalités. On connaît les interventions efficaces et il existe de multiples plans d’action, mais une grande partie du travail dans le secteur de la santé continue de se dérouler de manière isolée, sans prendre suffisamment en considération que le système de santé doit être axé sur la personne. Toutefois, les progrès dans les stratégies de prestation ont créé des opportunités uniques d’intégration sur le lieu même où les services sont dispensés. Le concept de «PEV-plus» (c’est-à-dire de mettre à profit les consultations de vaccination des femmes enceintes et des enfants pour dispenser d’autres interventions, comme l’administration de vitamine A, les traitements contre les vers, les interventions antipaludiques, etc.) est bien établi, qu’il s’agisse des campagnes ou des services de routine. Le Plan d’action mondial intégré pour prévenir et combattre la pneumonie et la diarrhée inclut la vaccination dans une approche globale de «protection-prévention-traitement», dans le cadre de laquelle l’élimination de ces causes de mortalité de l’enfant ne peut pas être obtenue uniquement avec les vaccins mais doit s’accompagner d’améliorations au niveau de l’eau et de l’assainissement, de la promotion de l’allaitement

sectors, focus on country level, and strong links among initiatives is needed to accelerate action.

It was noted that integration has been studied intensively because of the longstanding debate between vertical and horizontal/health systems approaches to programme delivery, and because of the potential benefits integration, including greater efficiency and reduced redundancy, enhanced user satisfaction, and greater intervention coverage. However, the evidence base on integration remains limited. Although there is some evidence of improved use and delivery of services, care is needed to ensure that integration is not detrimental to some already successful programmes.

SAGE heard directly of Ethiopia's country level experience in improving child survival and early achievement of MDG #4 through integrated health service delivery at the community level. Central has been the creation of a salaried cadre of over 30 000 health extension workers who receive 10 months' training, and are charged with delivering an integrated package of prioritized health interventions including immunization, at the community level. Key factors in Ethiopia's success were high-level leadership from the late Prime Minister, a commitment from donors to pooled funding, development of an integrated medicines and supply chain, integrated monitoring, and guidelines and tools packages.

In conclusion, it was noted 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 DoV consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the GVAP. ■

au sein, et d'un meilleur accès aux sels de réhydratation orale et aux antibiotiques. Il faut l'engagement de tous les secteurs, un centrage sur les pays et des liens solides entre les initiatives pour accélérer l'action.

Il a été noté que l'intégration avait été étudiée de manière approfondie en raison du débat qui dure depuis longtemps sur les mérites comparés des approches verticales et horizontales pour l'exécution des programmes, ainsi que de ses avantages potentiels, notamment une plus grande efficacité, une diminution des doublons, une meilleure satisfaction des usagers et une plus grande couverture des interventions. Néanmoins, les bases factuelles de l'intégration demeurent limitées. Bien qu'il y ait certaines preuves d'une amélioration de l'utilisation et de la prestation des services, il faut veiller à ce que l'intégration ne se fasse pas au détriment de la réussite de certains programmes existant déjà.

Le SAGE a directement pris connaissance de l'expérience menée en Éthiopie pour l'amélioration de la survie de l'enfant et la réalisation de l'OMD4 par une prestation intégrée des services au niveau communautaire. La création d'un cadre salarié pour plus de 30 000 agents de santé de proximité qui ont eu une formation de 10 mois et qui étaient chargés de dispenser un ensemble intégré d'interventions sanitaires prioritaires au niveau communautaire, dont la vaccination, a joué un rôle central. Les clés de la réussite éthiopienne en matière d'intégration ont été le "leadership" assuré à un haut niveau par l'ancien Premier Ministre, l'engagement des donateurs sur un financement groupé, la mise en place d'une chaîne intégrée d'approvisionnement en médicaments et en fournitures, l'intégration du suivi, ainsi que des séries d'outils et de directives.

En conclusion, le SAGE a estimé que l'intégration nécessitait, de par sa nature même, un débat élargi au-delà du Groupe. À cet égard, il a été proposé que le groupe de travail du SAGE sur la Décennie de la vaccination étudie des options pour aller de l'avant (l'intégration se traduisant à la fois comme un principe directeur et un objectif stratégique pour le GVAP). ■

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- (1) WHO WWW SERVER: Use WWW navigation software to connect to the WER pages at the following address: <http://www.who.int/wer/>
- (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](mailto: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.

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

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## SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Action	Apr 2013	Ongoing	<p>A teleconference was held May 13 2013 with J. Abramson, P. Figueroa, and N. Arora and EPI (M. Zaffran and T. Goodman) to discuss 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 summarizing this area of work. It was agreed that an effort would be made to highlight this area of work in a few slides of the IVB Director's next presentation to SAGE. Discussions are ongoing.</p> <p>The topic of integration was on the agenda of the April meeting.</p> <p>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 DoV consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the GVAP.</p>
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Action	Nov 2008	Ongoing	<p>A workshop organized by WHO/AFRO was held in Grand Bassam (Cote d'Ivoire) from 13-17 May 2013, in collaboration with the MOH and other immunization partners (GAVI, UNICEF, USAID/MCHIP et NESI) to revise the 2006 EPI prototype curricula for medical &amp; nursing/midwifery teaching schools in the AFR. During the workshop, 4 drafts of EPI prototype curricula were produced and were to be harmonized, finalized and edited. That is 2 curricula for medical schools in French and 2 curricula French &amp; English for nursing/midwifery schools. The 4 curricula have been finalized and edited and will be ready for diffusion to countries by end 2014.</p>
General	SAGE encouraged the European region to document and share its experiences in country profiling, tailoring responses and using novel communication strategies to effect behaviour change.	Action	Nov 2010	Ongoing	<p>EURO is working to give countries tools to address vaccine hesitancy at the individual level. These include: 1. Development of the Tailoring Immunization Programs "TIP" toolkit, which allows a country or sub-national level authority to segment/profile a population based on behaviors rather than background characteristics. The resulting group profile can help inform programmatic responses that could be communication-oriented or inform improved service delivery. Best practices from other disease programs are included that can be adapted for country-specific issues. Pilot testing of the framework has been conducted in several European countries: TIP was implemented in Bulgaria and on three projects in Sweden (Somali immigrants, migrants, and anthroposophic communities) and Bulgaria. In 2013, TIP was implemented in France and the UK. Use of the tool in Germany is being discussed. TIP will be adapted for use on a global level and a second edition will be published later in 2014. In June 2014, TIP was pilot tested in South Africa 2. Strengthening the ability of member states to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication was published in 2013. 3. Advocacy for immunization and strengthening the use of new media led to involvement of well-ranked bloggers who write in Russian and English to better engage around vaccine confidence. 4. A vaccines social media strategy and a smart-phone immunization tracker/reminder 'app' for parents has been launched and is currently being modified by national immunization programs in 10 countries to be adapted to local schedules. 5. An online vaccines resource centre was launched in 2012 and has been strengthened and improved through 2012-2013, with a number of MS using or translating the caregiver and health-care worker tools presented.</p>

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General	SAGE encouraged the Regional Office in EMRO to pay special attention to countries affected by political turmoil and requested specific monitoring for any adverse impacts on immunization programmes in GAVI graduating countries.	Action	Apr 2011	Ongoing	There are no GAVI graduating countries in the EMR. EMRO is working closely with and is paying special attention to the countries affected by political turmoil. The following support was provided since the last SAGE meeting in April 2014: <ul style="list-style-type: none"> <li>• continuing implementation of routine vaccination in the provinces hosting the refugees camps in Jordan.</li> <li>• implementation of the national Measles campaign in Syria in June 2014.</li> <li>• provision of support to Tunisia for recruiting technical staff to support EPI.</li> <li>• provision of support to Tunisia for preparing for introduction of IPV vaccine. Provision of technical support to MOH and NITAG, Egypt for setting alternate vaccination schedule and procurement modalities to overcome the stock-out of different vaccines.</li> </ul>
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.	Action	Apr 2012	Ongoing	Advice being sought through the ECBS - added to agenda of next meeting, 15-19 October 2012. SAGE had previously requested that a paper be developed, highlighting the circumstances in which off-label use of any vaccine could be recommended, while clarifying the differences between regulatory decisions and public health recommendations. During the November 2012 SAGE meeting, SAGE further requested that ECBS prepare guidance for national regulatory authorities on studies needed to support evidence-based, off-label use of vaccines which benefit public health. It was noted that for regulators, product specific data are paramount. SAGE requested that an additional document be prepared to advise the national immunization technical advisory committees about the type of data that might support a policy recommendation to use a vaccine outside its licensed schedule in order to achieve public health benefits such as operational simplicity or cost savings. The ECBS guidance document has been delayed and will be prepared after its October 2014 meeting. The paper clarifying the differences between regulatory decisions and public health recommendations has been commissioned and is under development. A draft paper intended for publication in a peer review journal should be available around the time of the October 2014 SAGE meeting.
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.	Action	Apr 2014	Ongoing	A document on GACVS future is currently under preparation and will address this issue in particular.
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.	Action	Apr 2014	ongoing	A draft concept note on developing a 2nd year of life platform has been produced, and is being used as the basis to establish a discussion group of partners to move this area of work forward. Additionally, the 2nd year of life platform has been included in a WHO proposal for funding support which is currently being reviewed for consideration by the BMGF.



Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers	SAGE suggested to monitor gaps and opportunities and consecutively develop a systematic process to responds to these needs in collaboration with key partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines.	Pending	Nov 2010	Ongoing	WHO is actively contributing to increasing global access to vaccines through the following activities: 1) close collaboration (participation in annual meetings and bilateral meetings) with IFPMA and DCVMN as federations of manufacturers form developing and industrialized countries to ensure that they all have clarity on the needs of developing countries both in terms of types of vaccines but also in terms of their programmatic suitability; 2) Active participation in the annual DCVMN meeting to update them on new developments, concerns, and issues related to vaccine presentations, prequalification, regulation financing and priority country need. 3) WHO has resurrected and chaired the VPPAG (Vaccines Presentations and Packaging Advisory Committee) a forum for discussion between the public and private sectors on the characteristics of vaccines required for developing countries. The full participation of industry enables them to have more visibility of the needs and constraints of countries; 4) The DoV work stream on global access and vaccine price indicator which gets reported every years to the SAGE working group on the DoV. 5) General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster. 6) A new committee known as the Product Development for Vaccines Advisory Committee was established and met for the first time 8-10 Sep 2014. The group reviewed 19 pathogen specific global pipeline analyses (all available from the meeting website) and advised WHO on strategic prioritization for WHO activities related to early stage vaccine R&D (pre-licensure to Phase 2). The group will oversee the development of Vaccine Preferred Product Characteristics. 7) the Vaccine Product, Price and Procurement project (V3P) to support GAVI graduating and middle income countries through the provision of improved vaccine product and price information for decision-making. More information on V3P is provided under the topic of financing in the tracking sheet.
Childhood mortality	SAGE noted the recommendation by IVIR-AC that WHO would encourage countries to collect local data at country level and not only estimated age specific mortality rates by epidemiological modeling or expert elicitation.	Action	Nov 2010	Ongoing	All models reviewed by IVIR-AC are hampered by the lack of primary data, and more efforts should be made to make such data readily available. Specifically, for pertussis disease burden estimation IVIR-AC suggests validating the parameter estimates against data from Senegal and Europe as a first step, although primary data from developing countries that is currently not publicly available would provide a more compelling comparator for validation. For polio more primary data should be made available for all models. IVIR-AC recommends that polio related data should be made available for multiple modeling groups to encourage comparison of results using different approaches. Ongoing/standing issue for many other diseases.
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.	Action	Nov 2012	Ongoing	The SAGE report of progress with GVAP was presented to the WHO Executive Board on January 20, 2014. The concerns expressed by SAGE on lack of progress in some areas was noted by the EB. The EB Members also acknowledged the importance of data quality for monitoring programs and taking corrective actions. The WG met again in February 2014 where it specifically addressed the formulation of indicators that they found problematic in their review of progress and proposed reformulation.  The SAGE assessment report was further presented to the WHA. A record number of 54 interventions on the report were made. In general, the report was very positively received. Several issues were highlighted, the most prominent being the issues of vaccine prices and access to affordable vaccines.  The 2013 secretariat progress report was reviewed by the DoV WG. The WG assessment report will be presented to SAGE at their October 2014 meeting

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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.	Action	Nov 2012	Ongoing	IVIR-AC concluded that the DOVE study presented on the approximate cost and impact may be adequate for high level use such as tracking of the GVAP and justifying its funding to donors on return of investment but had observations with the regard to the state of the art of the individual modeling components. Furthermore, IVIR-AC identified the need for increased transparency and clarity in all methods used including refined sensitivity and uncertainty analysis.
Dengue Vaccine	SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy.	Action	Apr 2012	Ongoing	The dengue vaccine safety profile will be updated once an application for licensure has been filed.  A risk management plan will be discussed at the December 2014 GACVS meeting.
Global vaccine safety Blueprint	The Blueprint implementation should be led by WHO and its partners. It should be aligned with other related WHO capacity-building efforts. This includes in particular immunization programme and national regulatory authorities strengthening together with the development of national expert advisory bodies. SAGE suggested that a mechanism be developed to enable prioritization of both activities and countries in the implementation of the Blueprint. SAGE invited the GAVI Alliance and other partners to support this implementation.	Action	Nov 2011	Ongoing	The Global Vaccine Safety Initiative has been launched and hosted its second annual meeting in November 2013. The portfolio of activities is now publicly available covering all 8 strategic objectives with priorities endorsed by the Planning Group.  The GVSII has been operating with 2 annual Planning Group meetings. The third GVSII meeting will take place in October 2014 in China, jointly with national pharmacovigilance centres meeting.
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Action	Apr 2010	Ongoing	In 2010/2011, with an objective of addressing ethical and regulatory challenges for follow up activities after the announcement of the Thai RV144 trial, which demonstrated for the first time a moderate (31.2%) level of efficacy in preventing HIV infection. Following SAGE recommendation on these aspects WHO/IVR/HVI and UNAIDS implemented the following 2 activities:  1. Development of a new ethics guidance point on ethical involvement of populations with high risk for HIV infection (i.e. people who injecting drugs) through extensive regional consultations. In 2013-14, the focus of work in this area is on "standards of prevention", i.e. the development of a framework that provides guidance on the non-vaccine preventive interventions, e.g. pre-exposure prophylaxis, to be provided during HIV vaccine trials.  2. In support of regulatory frameworks, WHO/IVR/HVI and UNAIDS have initiated a project on the development of a policy/discussion paper to facilitate national decision making with regard to the novel strategies for testing HIV vaccines; namely, most recently HIV vaccine trials in adolescents, adaptive trial design, etc. Currently, i.e. in Q1 2014, guidance on the future use of adenoviral vectors in HIV vaccine research.  In October 2013, a written update was provided to SAGE on the progress of HIV-vaccine research, and will be provided ahead of the October 2014 SAGE meeting.

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Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Action	Apr 2012	Ongoing	Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in February 2014. There is still no identified breakthrough case among vaccinated children since the introduction of hepatitis A in the national immunization program in 2005. Hepatitis A cases have reached an all time low in 2013. Still occurring cases indicate that the risk persists in the population. As also requested by SAGE, an economic analysis of the impact of the single dose immunization strategy against hepatitis A in Argentina has been done. Estimated total vaccination cost for the 2006-2010 post vaccination period was ~US\$ 45 million. The total of medical and societal costs plus immunization cost decreased from ~US\$ 105 million for 2000-2004(pre vaccination) down to ~US\$ 56 million for the 2006-2010 post vaccination period i.e. a reduction rate of 46.5%. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentina surveillance data will continue.
Hepatitis B	All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals.	Action	Nov 2008	Ongoing	EMR has a Regional Committee goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. EMRO is working with Member States to ensure achievement of this goal. WPR established a Regional Committee goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017. SEARO has a drafted regional strategy. AFRO has convened a regional hepatitis TAG and plans to present a plan for comprehensive viral hepatitis control during the 2014 RC Meeting. EURO will consider a regional hepatitis B control goal. 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 ( <a href="http://www.who.int/csr/disease/hepatitis/Framework/en/index.html">http://www.who.int/csr/disease/hepatitis/Framework/en/index.html</a> ).
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.	Action	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. 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 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 GVS goals. In 2012, WPRO convened EPI and MCH managers from the five priority countries to jointly propose actions towards improving birth dose uptake.
Hepatitis E	SAGE approved draft ToRs for a Working Group on Hepatitis E and requested that WHO establishes this group in the summer 2013.	Action	Apr 2013	Completed	The SAGE Hepatitis E working group was established in 2013. The group met face-to-face in June 2014 and held multiple teleconferences. It will report to SAGE at the October 2014 meeting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Immunization Supply Chains	SAGE commended the IPAC "Call-to-Action" as a strong advocacy document and suggested the recommendations be distilled into key messages that could be used in the GVAP report to the WHA and in the context of the 40-year anniversary of EPI. SAGE endorsed the IPAC "Call-to-Action" and affirmed the importance of the WHO-UNICEF Joint Statement on EVM as tools for global policy advocacy. Both need to be packaged in an effective and complementary manner.	Action	Apr 2014	Closed	The IPAC "Call to Action" has been finalized in English and published as an official WHO document. It is currently being translated into French. The document was shared as part of the materials provided for the Ceremony around the WHA commemorating the 40 years of EPI. Both the IPAC "Call to Action" and the WHO/UNICEF Joint Statement have been finalized and have been packaged in a way that highlights their differences and complementarity.
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%.	Action	Apr 2014	Ongoing	This will be undertaken in 2015 as part of expanding the EVM assessment with additional modules covering Human Resources; LMIS; and System Design (among possible others). The EVM assessment has already be designed for supervisory purposes.

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

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Impact of the introduction of new vaccines on immunization and health systems	SAGE recommended that the ad-hoc working group work towards producing guidelines and tools for WHO to assist decision-makers and EPI managers contemplating the introduction of new vaccines, in order to take account of collateral effects inherent in introduction. The guidelines should provide a set of indicators that would enhance the potential positive effects, and reduce any potential negative effects, both on the immunization system and the health system. The guidelines should accommodate vaccines with different characteristics. SAGE noted the importance of the ad hoc working group continuing to include a broad range of partner agencies, and encouraged to seek endorsement of this work at senior levels of partner agencies.	Action	Apr 2010	Ongoing	Further information was collected through a search of the published, unpublished and grey literature (such as post-introduction evaluation reports), as well as through key informant interviews. An in-depth study in 7 countries was conducted by LSHTM in 2011-12 to gather further information. Final results were presented in a meeting in London in November 2013. The ad-hoc group has updated the framework based on the data obtained and has drafted a guideline (Vaccine Introduction Guidelines – Adding a vaccine to national immunization programme) to assist country decision makers and EPI managers to take account of the potential effects/impacts of new vaccine introduction on the immunization and health systems. The 'Principles for adding a vaccine to a national immunization programme while strengthening the immunization and health systems' were endorsed by SAGE in April 2012 and form part of this guideline document, to be published in 2014. The ad hoc working group included a broad range of partner agencies (WHO, UNICEF, WB, CDC, PATH, JSI, LSHTM, JHU) and has sought endorsement of this work at senior levels of partner agencies. The revised Vaccine Introduction Guidelines which were published in 2014 (Principles and Considerations for Adding a Vaccine to a National Immunization Programme) as a result of the proceedings of the ad hoc working group, have been vetted by the partner agencies and endorsed by their senior personnel.
Implementation Research	SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.	Action	Apr 2014	Ongoing	The September 2014 IVIR-AC meeting concluded that that the models presented by modeling groups from Australia, UK and US were appropriate in terms of structure to better understand both schedule optimization in various countries and different transmission settings. However, availability and quality of data in LMICs remains the key problem, thus IVIR-AC calls for better surveillance systems in LMICs. An IVIR-AC subgroup under the "WHO VPD burden and impact framework" will identify specific data needs for parameterization of various models by conjoining need with epidemiological expertise.
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.	Action	Apr 2014	Ongoing	During IVIR-AC September 2014 meeting it was suggested to develop standardized protocols and start implementing high quality RCTs where feasible. At least studies should mimic RCT situations with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints. With BMGF support a multi-disciplinary team with IVIR-AC participation will start reviewing the evidence and identify research questions.
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.	Action	Nov 2013	ongoing	This recommendation is now part of the new IVIR-AC agenda under research to minimize barriers and improve coverage of vaccines currently in use. During the September 2014 meeting IVIR-AC identified the need for standardization of research tools and protocols to examine the integration of immunization with other health interventions and non-vaccination to be applied locally, by antigen including on how to translate the evidence to community messaging. IVIR-AC recommended to establish a sub-group to propose elements of the menu of solutions on the integration of care with immunization programs and another sub-group on non-vaccination. A two year time line selective approach on integration was proposed at two levels i.e. service delivery and management. IVIR-AC recommended to use the project proposal on "Evaluation of GAPPD interventions: example for Mazabuka District in Zambia" as a case study.

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Influenza	SAGE requested that WHO report on epidemiology and surveillance of H7N9 as well as on the development of a potential vaccine candidate.	Action	Apr 2013	Ongoing	There has been no sustained human to human transmission of H7N9. As of 28 August 2014, 453 cases have been confirmed with 154 deaths in two waves ((1) Feb-May 2013, (2) Oct. 2013 – present). These cases were from China (Mainland, HK and Taiwan) including a Chinese case detected in Malaysia. WHO, through its global network GISRS, has been monitoring the evolution of the H7N9 and conducting continuous risk assessment. So far, although internal genes of the H7N9 virus are constantly reassorting with avian influenza A(H9N2) endemic in poultry locally, the HA and NA are less divergent. Antigenically the H7N9 virus remains closely related to the WHO recommended vaccine virus A/Anhui/1/2013-like virus. Clinical and epidemiological features of H7N9 remain unchanged: CFR: 34.6%; Mean age of cases in 2nd wave: 53yo, M:F=2.3:1. So far 8 reverse genetics engineered candidate vaccine viruses developed and available from the WHO GISRS. However classical reassortment has not yet succeeded.
Integration of vaccine services	SAGE requested a session during the April 2014 meeting on integrated approaches in immunization and other healthcare programs.	Action	Apr 2014	Completed	A session on integrated approaches in immunization and other healthcare programs took place at the SAGE meeting in April 2014. During the session in April 2014 it was noted 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 DoV consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the GVAP. Monitoring progress with integration of immunization with other primary health care programmes, as part of the GVAP monitoring, was discussed with the Chairs of SAGE and the SAGE DoV WG. It was agreed that the secretariat would put together data for a couple of indicators for review by the WG, on the basis of which they could choose one. While the quality of the data may not currently be sufficient to effectively monitor integration, it was felt that the report would serve to highlight the importance of integration and the fact that this was an important component of GVAP.
Japanese encephalitis	Interference with the immune response to other vaccinations, number of doses required and the duration of protection need to be assessed.	Action	Apr 2006	Ongoing	A comprehensive evidence review has been conducted by SAGE WG and findings will be presented at SAGE Oct 2014 meeting.
Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated.	Action	Apr 2006	Ongoing	Assessment using serum was carried out by PATH and published Am J Trop Med Hyg July 07. Field validation of serum and CSF in India and Bangladesh was assessed in a joint WHO/CDC meeting, SEARO, February 2008. Nepal and Cambodia field evaluation of JE assays is complete and paper has been submitted to JID. Assessment of kits using CSFs accepted for publication in Am J Trop Med Hyg. CDC Fort Collins will distribute the 3rd serum and CSF proficiency test panel to evaluate in-house and commercial JE ELISA assays to WPRO JE labs 4th quarter 2012. The three 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 CDC JE regional reference Lab was fully accredited by WPR and HQ Lab Coordinators. August 2012. A WPR JE labnet meeting took place on 15 March 2013 and a Regional JE workshop for WPR is planned the week of 17 June in Seoul. Submission for publication of a paper summarizing the development of the JE LabNet is pending. The Regional Reference Laboratory for JE in the Western Pacific Region at the Victorian Infectious Diseases Reference Laboratory, Melbourne, has been fully accredited in Oct 2013. The Global Specialized Reference Laboratory for JE at the National Institute of Infectious Diseases, Tokyo, has also been fully accredited in Oct 2013. The diagnostic assay produced by PanBio ceased production at the end of 2013. An alternative assay produced by InBios with similar performance will be used in the WHO laboratory network. The training workshop at the Korean CDC in June was intended to introduce the network to this kit. A biregional laboratory training workshop and laboratory network meeting is being planned for March 2015.

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Japanese encephalitis	SAGE looked forward to better assessment of the disease burden and identification of target populations for immunization and to reviewing the regional JE control goal currently under development and the activities to achieve this goal.	Action	Nov 2008	Ongoing	WHO is reviewing evidences in context of the SAGE working group on JE. This will be presented in the context of the JE session at SAGE Oct 2014.
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.	Action	Nov 2010	Ongoing	<p>Access to vaccines for Middle Income Countries (MICs) is important from a public health impact perspective and from an equity viewpoint. Also, MICs could provide a large demand volume for vaccine supply, promoting competition and a healthy vaccine market to the benefit of both recipient countries and suppliers. Various efforts are ongoing to support MICs including: GAVI Alliance support for about 40% of MICs, capacity building for market intelligence and procurement (UNICEF SD and WHO), efforts to promote price transparency (GVAP price report and Vaccine Product, Price Procurement initiative V3P), initiatives to explore access to affordable prices (Harvard Global Health Institute, GAVI Alliance preliminary studies), support to countries graduating out of GAVI support (graduation assessments and funded graduation plans), pool procurement efforts (UNICEF SD; PAHO; and regional efforts - EMRO, Baltic States), technical assistance efforts for setting up of CMYPs, strengthening of NRAs, NITAGs, initiatives to improve sustainable financing (SIVAC, SIF) and informed decision making (ProVac). Exceptional, catalytic support is also provided to non GAVI countries for introduction of IPV in accordance with the POlio Endgame timelines.</p> <p>However, in 2012 SAGE noted with concern that these efforts are fragmented and are failing to optimize synergies in the work being undertaken by each agency. SAGE noted that with a modest investment in technical assistance and capacity building could be significantly strengthened. SAGE requested that this issue and achievements be revisited in a subsequent meeting and that a task force is establish by WHO to coordinate policies and efforts of partners. 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 aim is to finalise a strategy and plan of action by April 2015. This will allow coordination of efforts for effective and efficient results and identification of gaps for further action.</p> <p>Strengthening of country procurement regulation and capacity has already been identified as a clear need in past consultations/analytical work. Different efforts are ongoing in this area: UNICEF SD MICs tender, PAHO revolving fund, EMRO and Baltic States pool procurement initiatives, different discussions on procurement planned or initiated by WHO regions (e.g. WPRO). The Vaccine Product, Price, Procurement initiative (V3P) provides a platform for countries to share and receive information on available procurement method and to convene countries for procurement discussions. The work of the MICs task force will allow to take stock of ongoing effort and shape future direction in this as well as related areas.</p>



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Malaria	SAGE requested that it be kept informed of developments in the ongoing multi-country Phase 3 trial and indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur.	Action	Oct 2009	Ongoing	<p>The timing for the Decision session depends on the timing of the regulatory decision. The European Medicines Agency is expected to make a regulatory decision between July and September 2015. The submission was made in July 2014. If the September 2015 timeline is met for EMA decision a SAGE/Malaria Policy Advisory Committee meeting joint session is expected in Oct 2015.</p> <p>The final results from the Phase 3 trial were reviewed by JTEG 25-26 September 2014, and SAGE will be sent the JTEG meeting report as soon as it is available.</p> <p>Any recommendation for use in the 5-17 month age range is likely to focus on the 5-9 month age period for the primary immunization series due to the age pattern of malaria. JTEG reviewed the data on a fourth booster dose given 18 months after the primary immunization series.</p> <p>The first wave of African national regulatory authorities will receive submissions for marketing authorization during early 2016.</p> <p>If EMA positive opinion, WHO recommendation for use, and PQ has occurred by 2016, the GAVI Board will meet to consider the full Phase 3 results and updated impact estimates to make a decision on the possible opening of a window for the malaria vaccine.</p>
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.	Action	Apr 2013	Ongoing	<p>Malaria Vaccine Preferred Product Characteristics were shared by email with SAGE committee members for their individual comment during July 2014. The document has passed external review with positive comments, and is now in the process for publication as a WHO document during 2014.</p> <p>A new committee known as the Product Development for Vaccines Advisory Committee met for the first time 8-10 Sep 2014. The group reviewed 19 pathogen specific global pipeline analyses (all available from the meeting website) and advised WHO on strategic prioritization for WHO activities related to early stage vaccine R&amp;D (pre-licensure to Phase 2).</p> <p>The meeting report will be shared with SAGE as soon as it is available.</p> <p>The criteria the committee used to prioritize WHO activities in early stage vaccine R&amp;D were the unmet public health need, the chances of a product emerging in 5-10 years, and the added value of WHO engagement to advance product development to meet the need in low income countries.</p> <p>WHO plans to engage in further PPC development and clinical trial design consensus-building in the chosen priority pathogen areas as resources and staffing.</p>
Maternal Immunization	SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulatory 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.	Action	Nov 2013	ongoing	<p>A review was conducted by the Essential Medicines group in July 2014 (report in preparation). Secretariat is working with a public health/regulatory consultant on an options paper that will be available in 2015. Recommendations from that work will also be considered in the implementation of the influenza maternal immunization project, that begun in 2014.</p>

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Pertussis	A systematic review of the optimal primary immunization schedules (in association with diphtheria, tetanus toxoid containing vaccine) is ongoing and will be presented at the October 2014 SAGE meeting. The 2010 pertussis position paper will be updated after the results of this review are available. In the meantime a short update to the position paper will be published to clarify that the previous statement on the choice of vaccine contained in the 2010 vaccine position paper no longer holds true.	Action	Apr 2014	Ongoing	An update of the pertussis position paper was published in the WER on Friday July 25. The systematic review was completed and a face-to-face meeting of the pertussis Working group took place at the end of August 2014. In view of the conclusions of the group that there was no evidence to recommend significant changes to the immunization schedules and in the context of the Ebola outbreak pressure, the decision was made to postpone the reporting to SAGE and related discussions to the April 2015 meeting. The publication of the full update to the pertussis position paper will then be initiated after the April 2015 SAGE meeting.
Polio	SAGE recommended working closely with countries on activities towards OPV2 withdrawal.	Action	Apr 2013	Ongoing	A joint letter to all OPV only using countries was sent by the WHO DG and UNICEF ED, and the GAVI CEO where applicable, highlighting the importance of IPV introduction and outlining the SAGE recommendation on IPV introduction schedules and planning timelines. All regions have held, or will have held by the end of this year, at least one meeting that included a substantive focus on IPV introduction. In addition, many regions have held Gavi application development workshops; this has led to 66 out of 73 eligible countries applying for support already. Joint WHO/UNICEF regional coordination mechanisms are established to ensure countries are suitably supported in the decision making process and in the development and implementation of introduction plans. A large number of countries (113 of 126, or 90%) have confirmed decision or intent to introduce IPV by end of 2015 in preparation for the withdrawal of type 2 OPV. Work is now ongoing to i) ensure that declared intent materializes into commitment and ii) countries with no plan developed for IPV introduction have one ready before the end of the year.
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.	Action	Apr 2013	Ongoing	The GPEI has constituted a Legacy Working Group (LWG), currently comprised of representatives from the spearheading partners (Rotary, WHO, CDC and UNICEF) and the Bill and Melinda Gates Foundation to take forward the legacy planning work. The LWG has finalized and is implementing its workplan. One of the major activities within the workplan is to hold broad consultations with relevant stakeholders to document the lessons learnt and knowledge of the programme, to guide the direction of the legacy work, and to establish what benefit the lessons and resources of the GPEI could be to other initiatives. These consultations began in early 2014 and are continuing through the rest of the year. The consultation will include plans for soliciting contributions from communities and front-line health workers' on their experiences of polio eradication. In addition, the GPEI has contracted a consultant group that will conduct in-country interviews that will include learning lessons of polio eradication.
Polio	SAGE encouraged a technical briefing on key OPV2 withdrawal issues at the WHA 2014, in advance of a potential WHA resolution in 2015 on a target date for the withdrawal of OPV2 from all routine immunization programmes globally.	Action	Apr 2013	Completed	A side-event on the IPV introduction and OPV2 withdrawal was organized during the WHA in 2014.

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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 OPV2 withdrawal and introduction of IPV.	Action	Apr 2013	Ongoing	The Immunization Systems management group, co-chaired by WHO and UNICEF, has been established to coordinate efforts towards the activities relating to OPV2 withdrawal and IPV 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 IMG (CDC, WHO, UNICEF, BMGF, Rotary and GAVI) since April 2013 has been impressive. WHO/EPI has filled an additional 3 professional staff positions at HQ to contribute to this effort. UNICEF HQ has filled two additional HQ positions. Significant numbers of staff and consultants have also been deployed at Regional levels of both organizations, and funding has been sent to all regional offices. 66 out of 73 Gavi eligible countries have applied for IPV introduction support. For non Gavi countries, a financing mechanism has been rolled out to support 16 countries in Tier 2 and Tier 3 or LMIC which are not GAVI eligible. This mechanism will enable partners to support some countries that need it with vaccine introduction grants and/or time limited procurement of IPV. As of September 26 2014, a total of 113 countries (90%) have indicated their intent to introduce IPV by the end of 2015.
Polio	SAGE reinforced the importance of conducting a technical briefing on IPV introduction for OPV-using countries during the WHA in May 2014.	Action	Apr 2014	Completed	An IPV Technical Briefing was held as a side-event of the May 2014 WHA.
Polio eradication	"To facilitate prioritization, planning and implementation of IPV introduction at country level, SAGE recommended that consideration be given to developing a resolution on accelerated IPV introduction for submission to the World Health Assembly (WHA) in 2014."	Action	Nov 2013	ongoing	The WHA noted the progress of IPV introduction in 2014, based on the report from Immunization systems management group (IMG). The resolution on OPV2 withdrawal, including accelerated introduction of IPV, is scheduled to be proposed and discussed during the WHA 2015, if persistent cVDPV in Nigeria and Pakistan are eliminated and major criteria for judging country readiness for OPV2 withdrawal are met by then. These criteria include a) status of introduction of IPV in OPV-only using countries, b) registered bivalent OPV for routine immunization, c) establishment of stockpile and outbreak response protocol for type 2 virus, d) completion of phase 1 containment activities under the Global Action Plan (GAP) and e) affirmation of wild poliovirus type 2 eradication by the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC).
Polio eradication	SAGE encouraged WHO to specifically assess how existing international mechanisms could be used to strengthen and implement vaccination recommendations for travellers entering and leaving polio-infected countries and areas and, for areas of uncontrolled transmission, to consider travel advisories.	Action	Nov 2011	Completed	This topic was extensively discussed during the SAGE polio WG meeting in February 2014, and subsequently presented to SAGE in April 2014. The Emergency Committee under IHR met in late April and the DG made a temporary recommendation for travelers from polio-exporting and infected countries.
Polio eradication	SAGE requested that the Polio working group draft the necessary protocols for the 5 major components of the proposed strategy for type 2 virus detection and response after OPV2 cessation, in the areas of virus notification, surveillance, vaccine stockpiles, response and management of travellers for presentation to the SAGE in 2014.	Action	Nov 2013	ongoing	It is ongoing in collaboration with HSE cluster. It is planned to be submitted for SAGE October 2014 for review.
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.	Action	Nov 2011	Ongoing	Since 2013 IVIR-AC includes two programmatic and implementation research members from AFR and SEAR. Since 2014 IVIR-AC includes a mathematical modeller/economist from SEAR and a medical anthropologist from AFR. Currently 3 seats are vacant for a mathematical modelers and two health economists with experience in vaccine implementation research.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Action	Nov 2006	Pending	A comprehensive review of the work of the ECBS is still pending. The review will include (but not be restricted to) consideration of communication of ECBS outcomes. This will be linked with an overriding review of Expert Committees by the department of Essential Medicines and Health Products. A paper on the process of the review will be discussed by ECBS during its October 2014 meeting. SAGE will be invited to participate as soon as the review is terminated.
Security of vaccine supply	SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Action	Apr 2012	Ongoing	Discussion with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Internal WHO discussions are in progress. Meeting on new vaccine technologies held in February 2014. The work on the supply of affordable vaccine is an on-going effort in which all immunization partners are engaged. Affordability of vaccine remains an on going challenge for a number of countries however recent accomplishments in the area of IPV supply and financing are a good indication that the trend is evolving positively through strong partnership between the public and the private sectors. Given the amount of work going on in this area under several other initiatives including those reflected under item "Lower middle-income countries: Sustainable adoption and financing for new vaccines", we have discussed internally and have decided that, for the time being the production of a report was not warranted. SAGE will be kept informed on an on-going basis of progress made and new developments. More information on the topic of financing can be found at under respective topic in the tracking sheet.
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.	Action	Nov 2013	ongoing	Negotiations have already started. An operational framework for vaccine donation has been developed with USA and Germany. After a meeting of the working group of GHSI on 17-18 March, 2014, the framework was finalized, including the legal considerations, terms and conditions. WHO and Japan are also working on material transfer agreement. It will be presented at the GHSI Senior Official meeting on 29th September 2014 in Washington and hopefully approved at the GSHI Ministerial meeting in December 2014. The agreement with Japan for vaccine donation is still under negotiation since there are still some regulatory issues to be solved before accepting the vaccine. The agreement with France for vaccine donation is with LEG, however before accepting the vaccine we may have to wait for an approval from PQT. WHO is now submitting a proposal to HHS/BARDA to finance the smallpox vaccine prequalification for WHO stockpile.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Action	Nov 2013	ongoing	During 2013, a strategic review of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus surveillance networks was undertaken by WHO and its informal Technical Advisory Group for new vaccines surveillance and presented to SAGE in November 2013. WHO has developed a sentinel surveillance management framework to prioritize and guide actions to implement all SAGE recommendations from the 2013 meeting. Actions already implemented including: quarterly sharing of case-based data for both IB-VPD and RV networks; quarterly assessment of sentinel site performance based on agreed process and performance indicators; piloting of a web-based, case-based data management system in PAHO and SEARO (the system will include realtime data entry, verification and analysis; Regional Office support has been enhanced to selected sentinel sites including site visits and training. WHO's informal Technical Advisory Group for these sentinel surveillance networks is being briefed quarterly on progress and will meet in Geneva the week of 27 October 2014 to discuss the network status and ability to measure vaccine impact. Priority next steps for implementation in 2015 will also be identified.
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.	Action	Nov 2011	Ongoing	Written update to SAGE was provided ahead of the November 2013 SAGE meeting. In December 2012, the first consultation of the TB TEG was held to review clinical trial plans for two advanced new TB vaccine candidates, VPM1002 (VPM, Germany) and M72 (GSK Biom, Belgium). Another meeting is planned for Q3 with the remaining (advanced) developers of new TB vaccines, and a report will be provided to SAGE together with the 2014 annual update on TB vaccines, in Oct. 2014.
Typhoid	Need for advocacy and prioritization at international level. To include prioritizing WHO's prequalification for new-generation typhoid vaccines and the need for international financing mechanisms.	Action	Nov 2007	Completed	The status on the specific recommendation from the 2007 SAGE meeting is now considered "completed" (with the last update for the April 2014 SAGE mtg in archive). A SAGE session on typhoid conjugate vaccines is expected to be scheduled after 2015. Currently, 2 typhoid conjugate vaccines have been licensed by NRAs, one vaccine is undergoing review for national licensure, and several others are in clinical trials. A WHO expert consultation in July 2014 reviewed the adequacy of the clinical data to inform the SAGE pathway and recommended further clinical data to be generated for a future SAGE review.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Action	Nov 2010	Ongoing	A set of one diagnostic tool and 6 in-depth tools had been envisaged. The basic tool (diagnostic tool) has been developed at HQ. The EURO, AMRO/PAHO and AFRO regional offices and HQ of WHO, UNICEF, and MCHIP are working on developing the 6 in-depth tools to address different facets of the problem. The in-depth tool "A Guide to Tailoring Immunization Programmes (TIP)" has already been developed by WHO-EURO and is available at <a href="http://www.euro.who.int/_data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf">http://www.euro.who.int/_data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf</a> . In June 2014 a meeting in South Africa took place to pilot test TIP in a low-income setting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Vaccination in humanitarian emergencies	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Action	Apr 2012	Ongoing	Due to lack of staff and three Level 3 emergencies in 3 months, The Emergency Risk Management and Humanitarian Response (ERM) Department lacked the capacities to complete this task. The relevance and applicability of this recommendation will be reviewed in the coming months, once the demands on ERM staff for field deployments to assist in emergencies have settled down.
Vaccine Hesitancy	SAGE suggested that the definition include "when uptake of a vaccine or immunization programme in a community is lower than would be expected in the context of information given and services available".	Action	Apr 2013	Completed	<p>The Working Group reworded the definition of vaccine hesitancy taking into account the proposed wording by SAGE:</p> <p>"Vaccine hesitancy is an emerging term in the discourse on determinants of vaccine acceptance where uptake of a vaccine or immunization program in a community is lower than would be expected in the context of information given and services available. Vaccine hesitancy recognizes that issues of complacency, convenience and/ or confidence in vaccine(s) or immunization programs may all contribute to the delay or refusal of one, some or almost all vaccines. These factors which influence vaccine acceptance vary by setting and responses need to be locally assessed."</p> <p>During the face to face meeting in December 2013, the working group revisited the definition to shorten and make it more comprehensive. The wording of new definition is: "Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services.</p> <p>Vaccine hesitancy is complex and context specific varying across time, place, and vaccines. It includes factors such as complacency, convenience, and confidence."</p>
Vaccine Hesitancy	SAGE recommended close linkages and interaction with key WHO and UNICEF initiatives to address the unvaccinated or under-vaccinated groups and relevant interventions.	Action	Apr 2013	Ongoing	Close collaboration with partners, initiatives, and key stakeholders in the field of vaccine hesitancy is sought. During the Working Group's monthly teleconferences, partners are invited to present their work (e.g. UNICEF on their polio-related work) and link with the Working Group directly. In addition, WHO colleagues from other departments such as Central Communications and the Vaccine Safety and Vigilance Team were attending the 3rd face-to-face meeting of the Working Group in December 2013. UNICEF staff is participating in the proceedings of the Working Group as part of the Secretariat.
Vaccine Supply	It was noted that SAGE needs to address the constraint experienced across Regions of repetitive shortfalls in vaccine supply, both for existing vaccination programmes (in particular for DTP-containing vaccines) as well as for new/emerging vaccines, and the impact on vaccine coverage in several countries.	Action	Nov 2012	Ongoing	Discussions have been initiated with UNICEF Supplies Division, and UNICEF Programme Division to work on global vaccine supply issues. A meeting was held in Copenhagen on 28 September 2013 to review the supply of traditional vaccines. Both DTP vaccine and to a lesser extent mono-HepB vaccine are increasingly of limited supply. Further intelligence is needed on countries plans to start DTP booster doses and Hep B birth doses, both of which require the vaccines without further combination.
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.	Action	Nov 2011	Ongoing	As the Bill & Melinda Gates Foundation is now accepting Letters of Inquiry for the development of an easy-to-use tool that rapidly assesses the immune status of children against select vaccine-preventable diseases. Inquiries will be welcome that focus on prototype development and detail plans for future commercialization possibilities.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Action	Nov 2011	Ongoing	<p>WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. A draft document which reviews, for a selected list of vaccine-preventable diseases, laboratory test available and associated requirements for specimen collection/transport, personal experience and training, and laboratory supplies and equipment has been prepared. The draft will be reviewed internally and following recommended changes will be submitted for review by external experts. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results were summarized in an accompanying document. Work in progress was presented to WHO and UNICEF Regional Focal Points for immunization during the Meeting on Monitoring National Immunization Systems, 9-11 October 2012 for their comments. Internal and external review of the document will continue and after incorporating the comments draft guidelines will be developed for use of sero-surveillance as an evaluation tool for immunization programmes.</p> <p>Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella and primarily to be applicable in a pre- and post-SIA (supplementary immunisation activity) setting. An expert working group has been assembled and based on the expertise in the various fields of each of the members, needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given subtasks in developing parts of these guidelines that pertain to their respective expertise. A working draft will be finished by the end of Q4/2014 and will be tested subsequently in pilot studies in two different settings, pre- and post-campaign, for its applicability. These pilot studies are expected to take start Q1 2015 and will run during the entire year of 2015. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by Q1 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.</p>
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.	Action	Nov 2011	Ongoing	<p>To improve the precision and usefulness of survey results and to reduce the cost of surveys, 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 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 ongoing in Bangladesh. The methods will be reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee.</p>

Topic	Recommendations/Action item	Category	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.	Action	Nov 2012	Ongoing	A sub-group of 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. The report is currently in publication.  A new work track was started with IVR in order to harmonize safety monitoring during pregnancy clinical trials.
Varicella	The recommendations by SAGE on the use of varicella and herpes zoster vaccines should be reflected in an update of the previous 1998 WHO position paper on varicella vaccines.	Action	Apr 2014	Completed	The updated varicella and herpes zoster position paper including the recommendations from the April 2014 SAGE meeting was published in the WER on the 20th of June 2014. ( <a href="http://www.who.int/wer/2014/wer8925.pdf?ua=1">http://www.who.int/wer/2014/wer8925.pdf?ua=1</a> )
Yellow Fever	SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against YF.	Action	Apr 2013	Ongoing	A proposed revision to the International Health Regulations (2005) (IHR) to extend the validity of a certificate of vaccination against yellow fever from 10 years to the extent of the life of the vaccinated person was endorsed by the WHO Executive Board in January 2014, and recommended for adoption to the World Health Assembly (WHA); any revision to the IHR must be adopted by the WHA, followed by an extended period prior to which the revised provisions enter into force for the 196 States Parties to the IHR (including all WHO Member States). In May 2014, the WHA adopted revised provisions on yellow fever vaccination under the IHR.





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## Update on the Regional Immunization Program of the Americas

The most recently available data on the situation of vaccine-preventable diseases (VPDs) and the immunization program of the Americas is presented under the framework of the Regional Immunization Vision and Strategy (RIVS).

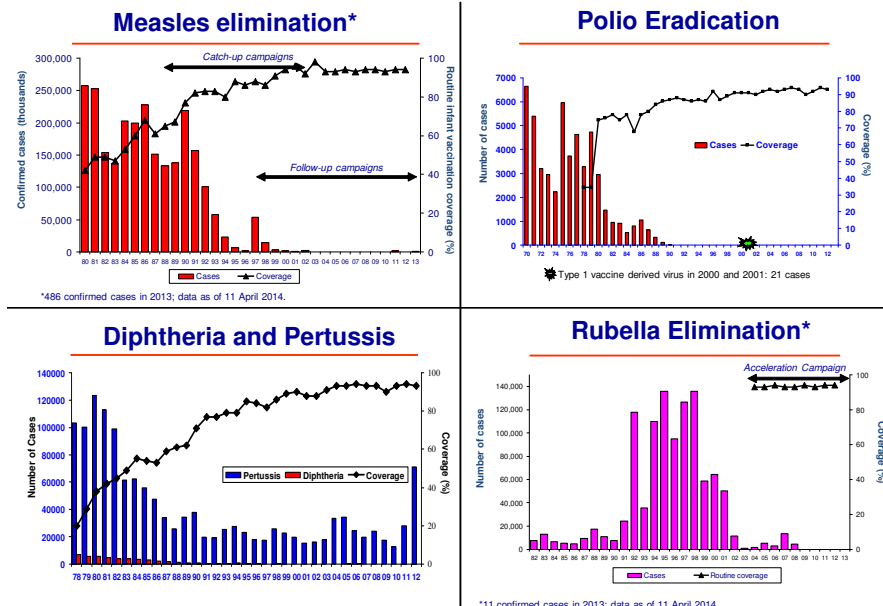
The RIVS is the Global Immunization Vision and Strategy (GIVS) restructured to accommodate immunization needs and objectives at the regional level. Its goals are to maintain coverage achievements, complete the unfinished agenda and meet new challenges.

The Region is working to present the regional adaptation of the Global Vaccine Action Plan (GVAP) to PAHO's Directing Council in 2015.

### **Maintaining the Achievements**

Coverage levels have remained over 90% throughout the Region and work is ongoing to maintain VPD control and elimination.

## Achievements in the Americas



Available preliminary data for 2013, however, suggests that regional DTP3 and Polio3 coverage may have declined compared to previous years. This situation is being examined.



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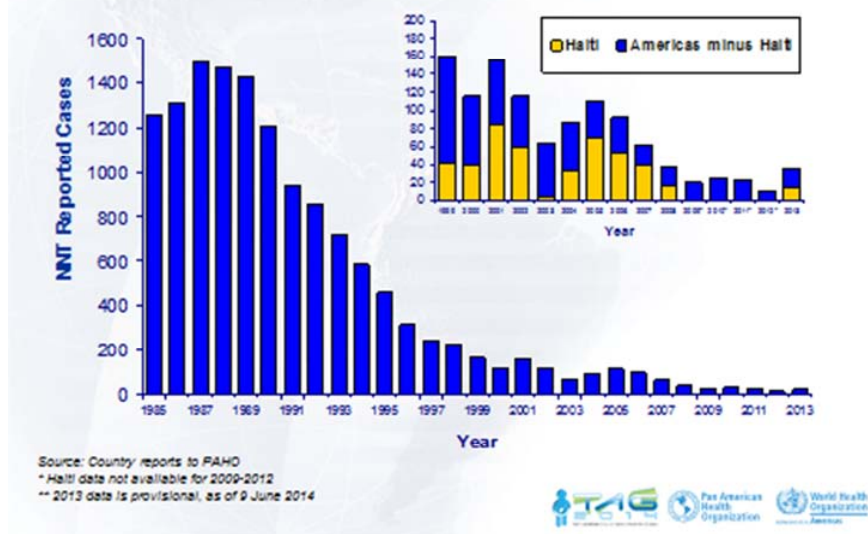


### Addressing the Unfinished Immunization Agenda

Work in this area has revolved around targeting underperforming municipalities and other areas within countries. Latin American countries have identified risk areas based on coverage, VPD surveillance performance, and other socio-demographic and contextual factors. It is of concern that only about half of the ~15,000 municipalities in Latin America and the Caribbean (LAC) reach coverage rates  $\geq 95\%$ . Furthermore, it is also concerning that there are several municipalities, concentrated in a few countries, reporting coverage levels  $< 50\%$ .

Since its creation in 2003, Vaccination Week in the Americas (VWA) has served as a platform to target vulnerable populations every year. In 2014, VWA's slogan was "Vaccination: Your best shot" in acknowledgment of the FIFA World Cup of Football (Soccer) taking place in Brazil. Finally, an important part of the unfinished agenda is the elimination of neonatal tetanus (NNT) as a public health problem<sup>1</sup> in Haiti. While cases have continued to decline over the years, elimination has proven challenging.

### Neonatal Tetanus Elimination, The Americas 1985-2013



### Meeting New Challenges

The introduction of new more expensive vaccines has been one of the main challenges immunization programs of the Americas have faced in recent years. About 90% of the birth cohort in the Region lives in countries that have introduced a pneumococcal conjugate vaccine in their regular program (~60% of the cohort of LAC); ~87% of cohort is living in countries that have introduced rotavirus vaccine (60% of

<sup>1</sup> NNT elimination is defined as  $< 1$  case of NNT per 1,000 live births in every municipality.



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the cohort of LAC), and ~75% of girls 10-14 years old live in countries that have introduced a human papilloma virus (HPV) vaccine.

### ***Operational Activities***

Of all the EPI components that the RIVS identifies as components requiring additional strengthening, cold chain and supply chain operations, syringe quality control program, economic evaluations (i.e. the ProVac Initiative), and vaccine effectiveness studies for rotavirus and conjugated pneumococcal vaccines were highlighted as a priority. The Revolving Fund for Vaccine Procurement is an important element of the program, as LAC countries finance >90% of national EPIs with national funds.

**Over the last 22 years, PAHO's Technical Advisory Group (TAG) on Vaccine-preventable Diseases has issued specific recommendations on the presented topics. Some key recommendations in the different topics discussed in this year's XXII TAG Meeting include the following:**

- ***Update on Implementation of TAG Recommendations on the Polio Eradication and Endgame Strategic Plan 2013-2018***
  - TAG reiterates the recommendations issued during the extraordinary TAG Meeting on Polio conducted in April 2014 (these recommendations can be found in the Polio section of the [2014 TAG report](#)).
- ***Update on Pertussis Vaccination***
  - Although both available pertussis vaccines (aP and wP) elicit a good immune response, evidence suggests aP has a short-lived duration of protection. As such, countries should give preference to the use of wP containing vaccines. Countries using current vaccination schedules with whole-cell pertussis vaccines should continue to do so and countries using aP should actively monitor the risk that waning immunity poses to the population.
  - Countries should ensure homogenous vaccination coverage  $\geq 95\%$  with 3 doses of pertussis-containing vaccines in children aged <1 year; and encourage timely initiation and completion of the schedule. Coverage attained with the 4th dose of the DPT vaccine should be the object of careful recording, monitoring, reporting and evaluation.
- ***Status of Human Papilloma Virus Vaccination***
  - TAG affirms the sound and robust evidence base that demonstrates the safety and efficacy of HPV vaccines among adolescent and young women. TAG also endorses the March 2014 and prior GACVS statements related to HPV vaccine safety. As such, TAG continues to encourage countries to adopt HPV vaccines in the routine national immunization schedule to prevent cervical cancer. To harmonize regional and global recommendations on HPV immunization schedules, TAG endorses the April 2014 SAGE recommendations:



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- A 2-dose schedule with an interval of at least six months between doses is recommended for girls aged <15 years of age. This also applies to girls aged ≥15 years at the time of the second dose. If for any reason the interval between the first and second dose is shorter than 5 full months, a third dose should then be given ≥6 months after the first dose.
- The 3-dose schedule (0, 1/2, 6 months) remains recommended for girls aged >15 years (when immunization is initiated) and for immunocompromised individuals of all ages, including those known to be HIV-positive;
- These schedule recommendations apply to both the bivalent and tetravalent vaccines.
- TAG reaffirms that it is important for countries that are considering the introduction of the HPV vaccine, to carefully plan information systems to collect and analyze coverage data at all levels. Countries that have already introduced an HPV vaccine should strengthen their efforts to characterize vaccination coverage at subnational and national levels.
- ***Vaccination with Pneumococcal Conjugate Vaccine in Adults***
  - TAG endorses the recommendations of the working group, including:
    - The introduction of pneumococcal conjugate vaccines in children continues to be the priority for reduction of pneumococcal disease.
    - Introduction of PCV13 vaccination for healthy adults into immunization programs will depend on the results of studies of efficacy, cost-effectiveness, and herd effect.
    - Countries that have already introduced the 23-valent polysaccharide vaccine for use in adults could use the sequential schedule (conjugate-polysaccharide) for high-risk adults\*.
    - Countries that do not use pneumococcus vaccine in high-risk adults\* and consider vaccination of this population a priority could include PCV13 in their vaccination schedules, based on immunogenicity studies.
    - Implementation or strengthening of epidemiological surveillance of pneumonias and IPD in adults is a priority for countries.
    - Countries that have already introduced PCV vaccines for children should spell out mechanisms to measure the impact of vaccination on other age groups (herd effect).
  - TAG encourages innovative surveillance and assessment approaches to better understand the preventable burden of pneumococcal disease in adults. Interaction with influenza surveillance networks should be further explored.
  - Countries should seek to improve PCV vaccination coverage rates in children.

\* Adults in high risk groups are adults ≥50 years of age, with the follow conditions: cerebrospinal fluid leak, cochlear implant, sickle cell disease/other hemoglobinopathy, congenital or acquired asplenia, immunocompromised persons, congenital or acquired immunodeficiency, human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia,



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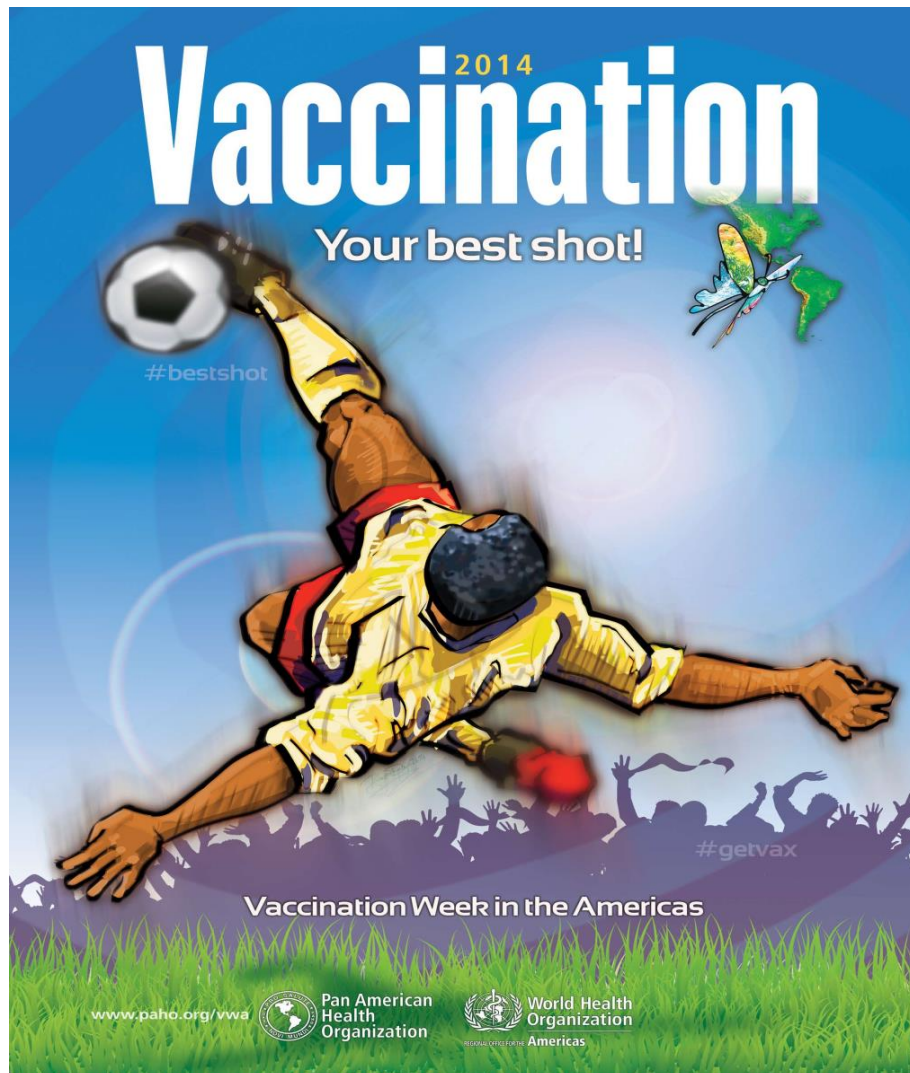


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lymphoma , Hodgkin's disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, and multiple myeloma. This is a special recommendation for individual clinical decision-making.



**Technical Advisory Group on Vaccine-preventable Diseases (TAG)  
XXII Meeting  
Washington DC, 1-2 July, 2014**



**Technical Advisory Group on Vaccine-preventable Diseases (TAG)  
XXII Meeting  
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## Acronyms

aP	Acellular Pertussis
AFP	Acute Flaccid Paralysis
CDC	Centers for Disease Control and Prevention of the United States
CRS	Congenital Rubella Syndrome
cVDPV	(Circulating) Vaccine-derived Poliovirus
DHS	Demographic and Health Surveys
DPT3	Third dose of the Diphtheria-Pertussis-Tetanus vaccine
DQS	Data Quality Self-assessment
DoV	Decade of Vaccines
EIR	Electronic Immunization Registry
EMRO	Eastern Mediterranean Region of the World Health Organization
EPI	Expanded Program on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
GNI	Gross National Income
GVAP	Global Vaccine Action Plan
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
IBD	Invasive Bacterial Disease
ICG	International Coordination Group
IDQi	Project for Improving Data Quality for Immunization
IHR	International Health Regulations
IPD	Invasive Pneumococcal Disease
IEC	International Expert Committee (for the documentation and verification of measles, rubella, and congenital rubella syndrome elimination in the Americas)
IPV	Inactivated Polio Vaccine
JRF	PAHO-WHO/UNICEF Joint Reporting Form on Immunization
LAC	Latin America and the Caribbean
MICS	Multiple Indicator Cluster Survey
MR	Measles-Rubella Vaccine
MMR	Measles-Mumps-Rubella Vaccine
MMR1	First dose of the Measles-Mumps-Rubella Vaccine
MMR2	Second dose of the Measles-Mumps-Rubella Vaccine
M&E	Monitoring and Evaluation
NIP	National Immunization Program
NNT	Neonatal tetanus
OCV	Oral Cholera Vaccine
OPV	Oral Polio Vaccine

bOPV	Bivalent Oral Polio Vaccine
mOPV	Monovalent Oral Polio Vaccine
tOPV	Trivalent Oral Polio Vaccine
PAHO	Pan American Health Organization
PEES	Polio Eradication and Endgame Strategic plan
PHEIC	Public Health Emergency of International Concern
Spn	<i>Streptococcus pneumoniae</i>
PCV	Pneumococcal Conjugate Vaccine
PCV13	Pneumococcal Conjugate Vaccine 13-Valent
PPV23	Pneumococcal Polysaccharide Vaccine 23-Valent
REVELAC-i	Influenza Vaccine Effectiveness Evaluation Network for Latin America and the Caribbean
RF	PAHO's Revolving Fund for the Purchase of Vaccines and Immunization Supplies
RIVS	Regional Immunization Vision and Strategy
SAGE	Strategic Advisory Group of Experts on Immunization (for the World Health Organization)
SARI	Severe Acute Respiratory Infection
TAG	Technical Advisory Group on Vaccine-preventable Diseases
Tdap	Tetanus Toxoid Acellular Pertussis Vaccine (for adolescents and adults)
TEPHINET	Training Programs in Epidemiology and Public Health Interventions Network
UNICEF	United Nations Children's Fund
VE	Vaccine Effectiveness
VWA	Vaccination Week in the Americas
WASH	A nonprofit, nonpartisan initiative dedicated to helping solve the global safe drinking Water, Sanitation, and Hygiene challenge
WHA	World Health Assembly
WHO	World Health Organization
wP	Whole-cell Pertussis
WPV	Wild Poliovirus
WPV1	Wild Poliovirus type 1
WPV2	Wild Poliovirus type 2
WUENIC	WHO/UNICEF Estimates of National Immunization Coverage

## Introduction

The XXII Meeting the Technical Advisory Group (TAG) on Vaccine-preventable Diseases of the Pan American Health Organization (PAHO) was held in Washington, DC, United States on 1-2 July 2014. The slogan for the meeting was “Vaccination: your best shot!”, chosen in the context of the FIFA Football (Soccer) World Cup taking place at the same time in Brazil. This meeting’s objective was to review progress on selected topics and issue recommendations to address pressing challenges faced by national immunizations programs in the Americas.

PAHO’s Assistant Director, Dr. Francisco Becerra, welcomed the participants and gave a brief introduction to the TAG’s charge as regional technical advisory group on vaccine-preventable diseases. This TAG meeting was marked by the recent passing of Dr. Ciro de Quadros, TAG President since 2004. Before starting the meeting, Dr. Peter Figueroa asked the audience for a minute of silence in memory of Dr. de Quadros. Dr. Jon Andrus, PAHO Deputy Director, shared reflections to honor Dr. Ciro de Quadros. Dr. de Quadros led the Immunization Program of the Americas at PAHO between 1977 and 2002, after having worked in a rural area of the Amazon in his native Brazil and for the World Health Organization in smallpox eradication in Ethiopia. During his tenure at PAHO, Dr. de Quadros oversaw the implementation of the regional Expanded Program on Immunization (EPI) and led the polio and measles elimination efforts. More recently, he actively contributed to global level policy development and promoted evidence-based decision-making worldwide in his role as Executive Vice-President of the Sabin Vaccine Institute. He was also instrumental in the development and endorsement of the Global Vaccine Action Plan (GVAP), the framework of the Decade of Vaccines (DoV) initiative that seeks to expand the benefits of vaccination to everybody regardless of where a person was born or lives.

Dr. de Quadros was a public health visionary and strategist, and he viewed vaccination as a human right. Through vision, diplomacy and persistence he not only helped the Region of the Americas pioneer disease elimination, but also forged partnerships that led to making the EPI of the Americas the most successful immunization program in the world. In 1995, he created PAHO’s TAG as an advisory body for polio elimination, and later expanded its mandate to provide guidance on vaccine-preventable diseases and the full immunization program. Dr. de Quadros received many awards during his life. One of the closest to his heart was the “Public Health Hero of the Americas” award presented to him by PAHO’s Director Dr. Carissa F. Etienne, in April 2014, roughly a month before his death.

Dr. de Quadros donated the money he received as part of the Prince Mahidol Award, an annual award given by the Thai Royal Family for outstanding achievements in medicine and public health worldwide, to create the Regional Immunization Award. This Award has been proposed to be renamed the “Ciro de Quadros Immunization Award”.

Dr. Peter Figueroa chaired the meeting *ad interim*. TAG members acknowledged the contributions of PAHO's Secretariat to the success of the meeting and issued this report in memory of Dr. Ciro de Quadros.

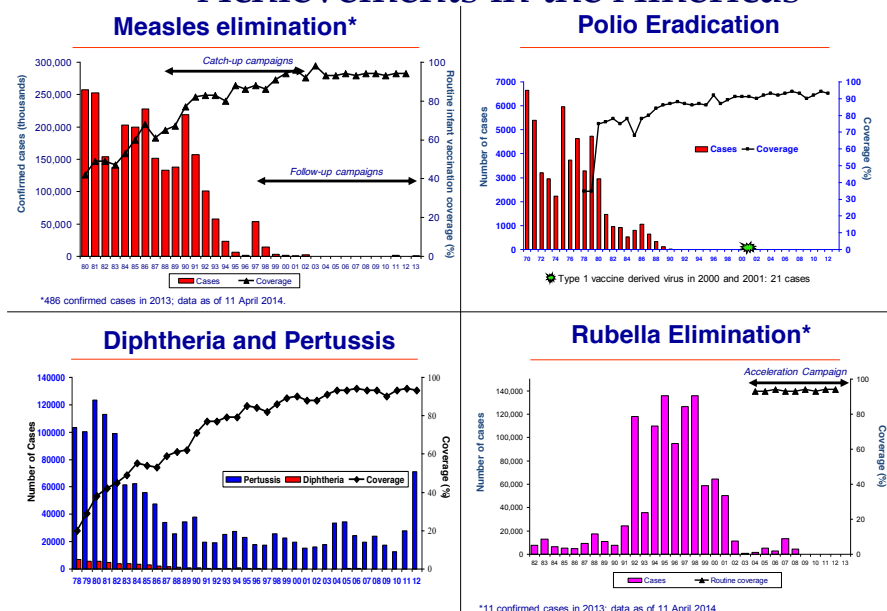
## Update on the Regional Immunization Program of the Americas

The most recently available data on the situation of vaccine-preventable diseases (VPDs) and the immunization program of the Americas were presented, under the framework of the Regional Immunization Vision and Strategy (RIVS). The Region is working to present the regional adaptation of the Global Vaccine Action Plan (GVAP) to PAHO's Directing Council in 2015. Data for topics discussed during the XXII meeting of the Technical Advisory Group (TAG) were not presented in detail in this overview.

### Maintaining the Achievements

Coverage levels have remained over 90% throughout the Region and work is ongoing to maintain VPD control and elimination.

## Achievements in the Americas

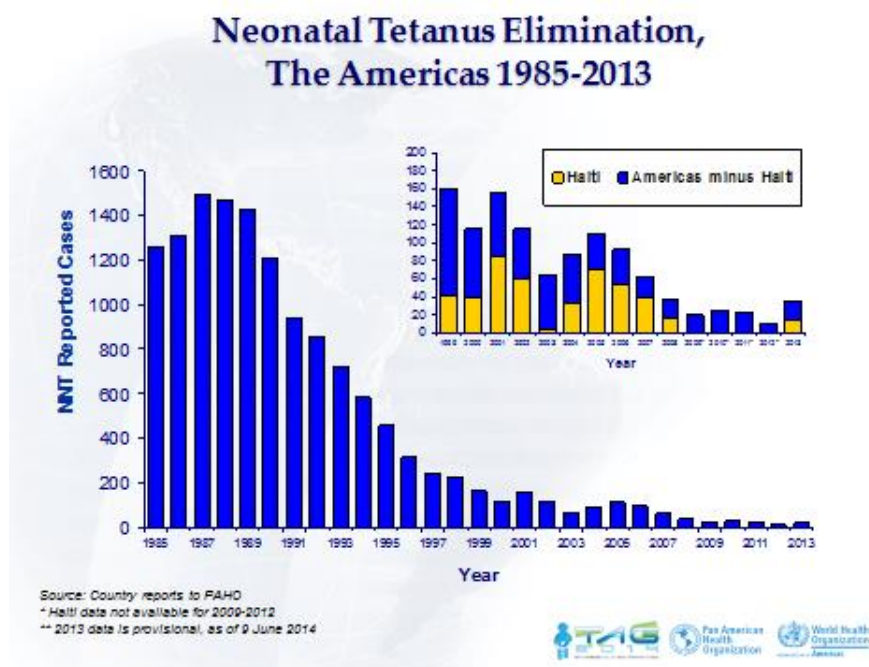


Available preliminary data for 2013, however, suggests that regional DTP3 and Polio3 coverage may have declined compared to previous years. This situation is being examined.

### Addressing the Unfinished Immunization Agenda

Work in this area has revolved around targeting underperforming municipalities and areas within countries. Latin American countries have identified risk areas based on coverage, VPD surveillance performance, and other socio-demographic and contextual factors. It is of concern that half of the ~15,000 municipalities in Latin America and the Caribbean (LAC) don't reach coverage rates  $\geq 95\%$ . Furthermore, it is also concerning that there are several municipalities, concentrated in a few countries, reporting coverage levels  $< 50\%$ .

Since its creation in 2003, Vaccination Week in the Americas (VWA) has served as a platform to target vulnerable populations every year. In 2014, VWA's slogan was "Vaccination: Your best shot!" in acknowledgment of the FIFA World Cup of Football (Soccer) taking place in Brazil. Finally, an important part of the unfinished agenda is the elimination of neonatal tetanus (NNT) as a public health problem<sup>1</sup> in Haiti. While cases have continued to decline over the years, elimination has proven challenging.



### **Meeting New Challenges**

The introduction of new more expensive vaccines has been one of the main challenges immunization programs of the Americas have faced in recent years. About 90% of the birth cohort in the Region lives in countries that have introduced a pneumococcal conjugate vaccine in their regular program (~60% of the cohort of LAC); ~87% of cohort is living in countries that have introduced rotavirus vaccine (60% of the cohort of LAC), and ~75% of girls 10-14 years old live in countries that have introduced a human papilloma virus (HPV) vaccine.

### **Operational Activities**

Of all the EPI components that the RIVS identifies as components requiring additional strengthening, cold chain and supply chain operations, syringe quality control program, economic evaluations (i.e. the ProVac Initiative), and vaccine effectiveness studies for rotavirus and conjugated pneumococcal vaccines were highlighted during this meeting. Finally, the Revolving Fund for Vaccine Procurement was mentioned in the context of sustainability, as LAC countries finance >90% of national EPIs with national funds.

<sup>1</sup> NNT elimination is defined as <1 case of NNT per 1,000 live births in every municipality.

## Update on Implementation of TAG Recommendations on the Polio Eradication and Endgame Strategic Plan 2013-2018

### **Background**

The Polio Eradication and Endgame Strategic plan (PEES), as approved by the Executive Committee of the WHO in January 2013, has 4 main objectives:

1. Detection and interruption of poliovirus transmission.
2. Strengthening of systematic immunization programs and withdrawal of the oral polio vaccine.
3. Containment and certification.
4. Delivery plan for the legacy of polio eradication.

The principal activities proposed by WHO for implementation of the Polio Eradication and Endgame Strategic Plan, 2013-2018 are:

- Strengthen epidemiological surveillance to rapidly detect any poliovirus importation. Acute flaccid paralysis (AFP) surveillance remains the primary mechanism for the detection of poliovirus. In addition, environmental surveillance can complement AFP surveillance for detecting the presence of poliovirus in selected areas and populations.
- Increase vaccination coverage. Reach and maintain vaccination coverage  $\geq 95\%$  in all districts and municipalities.
- Introduce at least one dose of the inactivated polio vaccine (IPV) in vaccination schedules for every country. The strategic plan establishes that the type 2 vaccine virus must be removed from the oral vaccine by mid-2016. Before its removal, all countries must introduce at least one additional dose of IPV by the end of 2015.
- Certify eradication and containment of all polioviruses by the end of 2018. Safe management and containment of infectious and potentially infectious materials in laboratories will be essential to minimize the risk of wild poliovirus reintroduction following interruption of global transmission.
- Contribute to reaching other health goals through the transfer of acquired knowledge and experiences gained through the polio eradication process.

In April 2014, an extraordinary meeting of the TAG was convened to review and discuss the adoption of this plan in the Americas. This report has been widely circulated in the Region.

### ***Current status of implementation of the Polio Eradication and Endgame Strategic Plan in the Americas***



The countries of the Region have given continuity to epidemiological surveillance of AFP cases in children under 15 years of age. Since 1986, the Region has met the target set for the AFP reporting rate indicator; however, the rate is not uniform among all countries. For example, the percentage of cases with adequate samples has ranged between 79% and 73% over the last 10 years, with the fewest number of adequate samples in 2013. Also, the percentage of cases investigated in the first 48 hours has not exceeded 80% in the last 2 years, reaching only 75% and 61% in 2012 and 2013, respectively.

Currently, routine environmental surveillance has been conducted only in the state of São Paulo in Brazil. Through this surveillance the country was able to detect an imported wild poliovirus in a sample collected in the residual waters of the Viracopos airport in March 2014. This type of complimentary surveillance is being evaluated for use in other select countries.

The countries of the Region continue working to reach and to maintain adequate vaccination coverage through different strategies, implemented both in the regular program and in supplementary vaccination campaigns. Countries are also taking advantage of the opportunity of Vaccination Week of the Americas to intensify vaccination in remote areas and vulnerable communities. Furthermore, the endorsed collaboration between Canada and PAHO has helped countries strengthen various components of the EPI in priority areas and municipalities, seeking to increase vaccination coverage.

The Region has made substantial progress in the introduction of at least one dose of IPV. To date, 14 countries in the Region are using IPV in their routine vaccination schedules during the first year of life, which corresponds to 65% coverage of the birth cohort in the Region. PAHO will continue to support countries in decision-making and in the process of introducing at least one dose of this vaccine to their basic vaccination schedules against polio.

The Regional Certification Commission is in the process of formalizing its formation and the first meeting of the commission should be held this year. In 2010, the Region completed the first phase in the process of containment of infectious or potentially infectious materials. WHO is reviewing the guidelines for the second phase of containment and should issue its recommendations in the coming months. The countries of the Americas have not created any special structure to achieve the polio eradication objective, but have instead strengthened the regular EPI. In 1995, PAHO formed a Commission to evaluate how the eradication process had affected country health systems. The final report "Taylor Commission," titled as such because it was chaired by Dr. Carl Taylor, emeritus professor at the School of Public Health at Johns Hopkins University in the United States, documents the lessons learned and the positive impact of the polio eradication program on health services in the Region.

On 5 May 2014, the Director-General of WHO declared the international spread of wild poliovirus in 2014 a Public Health Emergency of International Concern (PHEIC). The current situation of the international spread of wild polioviruses in 2014 to date is in contrast to the near-cessation of international spread of wild poliovirus from January 2012 through 2013, low transmission season for this disease (i.e. January to April). If not properly responded to, this situation could put the global eradication goal at risk.

The Director-General endorsed the following recommendations provided by the International Health Regulations Emergency Committee that was convened on 28-29 April 2014:

- All states that are currently exporting wild poliovirus (Pakistan, Cameroon, and the Syrian Arab Republic) pose the greatest risk of further exportations and should ensure that all residents and long-term visitors receive a dose of OPV or IPV between 4 weeks and 12 months prior to international travel.
- States Infected with Wild Poliovirus but Not Currently Exporting (Afghanistan, Equatorial Guinea\*, Ethiopia, Iraq, Israel, Somalia and particularly Nigeria) also pose a risk to exportation and should encourage residents and long-term visitors to also receive a dose of OPV or IPV 4 weeks to 12 months prior to travel.

\*At the time these recommendations were made, there were no reported exportations from Equatorial Guinea. Since then, on 18 June, an isolate of WPV1 was detected in Brazil that indicated a close match with a strain of WPV1 that was recently isolated from a case of polio in Equatorial Guinea. According to the International Health Regulations (IHR) temporary recommendations issued by the Director-General of WHO on 5 May 2014, Equatorial Guinea is considered a polio exporting country. The country should therefore ensure that all residents and long-term visitors (of more than 4 weeks) who travel internationally receive a supplementary dose of the polio vaccine between 4 weeks and 12 months prior to departure.

**Recommendations:**

- TAG expresses concern regarding the reported decline in Polio3 coverage at the national and sub-national levels in the Americas. As such, TAG strongly urges countries to ensure high, homogenous polio coverage to maintain the achievement of polio elimination in the Region.
- TAG notes the confirmed isolation of WPV1 in Brazil from environmental sampling in the state of Sao Paulo in March 2014 and commends Brazil for its response to this isolation. This finding confirms that the risk of WPV is real for the Region.
- In light of the newly confirmed risk of WPV importation in the Americas, TAG calls upon PAHO Member States to urgently take action to strengthen AFP active surveillance. The

reported decline in the proportion of laboratory specimens of quality collected and timeliness of case investigations jeopardizes the opportune detection of imported WPV (or VDPVs) and rapid deployment of response activities.

- Due to its high cost and involved methods, expansion of environmental surveillance networks in the Region needs further assessment. TAG recommends that PAHO assess the strengths and weaknesses of existing environmental sampling methods and based on this risk assessment and evaluation of existing methods, PAHO should propose potential options for environmental sampling in selected settings in the Region.
- PAHO should conduct a risk analysis to identify areas in the Region with a high concentration of WPV importation (and VDPV) risk (i.e. geographic areas with suboptimal polio3 coverage and a large number of international visitors from polio endemic or at risk areas).
- TAG reiterates the recommendations issued during the extraordinary TAG Meeting on Polio conducted in April 2014:
  - TAG agrees with the renewed efforts towards eradicating polio and the objectives of the polio endgame. These efforts include the ongoing removal of Sabin oral polio vaccine from the routine immunization schedule.
  - TAG reiterates its previous recommendations, emphasizing:
    - The importance of achieving and maintaining high and homogenous vaccination coverage rates to reduce risk of importations of WPV and cVDPV, and
    - The need for continued strengthening of epidemiological AFP surveillance.
  - TAG urges implementation of environmental surveillance towards validating the elimination of cVDPVs and WPV.
  - TAG agrees with the six prerequisites stated by SAGE to switch from tOPV to bOPV.\*
  - The countries of the Americas are already in the process of introducing IPV. At the end of 2015, approximately 80% of the birth cohort in the Americas will be covered with IPV. PAHO is providing technical cooperation to the countries on this process.
  - The remaining countries must decide when they will be able to introduce IPV, taking into consideration affordability (price for vaccines and operational costs), current opportunity costs, and sustainability. PAHO should continue working with the countries to help remove barriers for such introduction.
  - When introducing IPV, countries should consider sequential schedules. Ideally, countries should consider two IPV doses followed by two OPV doses. However, if a country is considering only one IPV dose, this should be with the first DTP dose and followed by three OPV doses.
  - Countries should not consider moving directly to an IPV only schedule at this time, unless they meet the criteria previously recommended by TAG and WHO

(low risk of transmission and importation, high homogeneous coverage, and good sanitation).

\*According to the SAGE's recommendations, prior to the withdrawal of OPV2 – by replacing tOPV with bOPV in all OPV-using countries, six prerequisites must be in place:

1. Validation of the elimination of persistent cVDPV type 2 and confirmation of WPV2 eradication;
2. A mOPV type 2 stockpile and response capacity;
3. Surveillance capacity and an international notification requirement for all Sabin, Sabin-like, and cVDPV type 2 viruses;
4. Sufficient bOPV products for all OPV-using countries;
5. Affordable IPV option(s) for all OPV-using countries;
6. Phase II bio-containment of all cVDPVs type 2 and WPV.

## Status of Human Papilloma Virus Vaccination

As of June 2014, 21 countries and territories in the Americas have introduced the vaccine against human papillomavirus (HPV) in their publicly funded immunization programs. Notably, Brazil introduced the HPV vaccine in March 2014 and 4.2 million Brazilian girls aged 11–13 years (85.3% of the target population) received the first vaccine dose by the end of June. Compared to the Sub regions of North America, the Southern Cone and the Andes, fewer countries in Central America and the Caribbean have introduced the HPV vaccine. Overall, an estimated 83% of a typical birth cohort of adolescent girls (6.3 million girls) has in principle access to HPV immunization in the Americas.

However, data on HPV vaccination coverage are limited. Only one country publishes coverage data each year, which are estimated through nation-wide surveys. For 2012—the sixth year of vaccination in this country – the estimated first-dose coverage in girls aged 13 years was 47%; drop-out between the first dose and the dose given after six months was 57%. For the same year, nine countries reported the number of administered HPV vaccine doses in their UNICEF/WHO Joint Reporting Forms (JRF); overall, 8.7 million doses were administered. For the four countries with adequate data for analysis (4.7 million doses administered), first-dose coverage ranged from 51% to 81%. Drop-out between the first dose and the dose given after six months ranged from 14% to 41% for the three countries with a classical 3-dose immunization schedule and was 48% for the country with an extended 3-dose immunization schedule. Although limited, these coverage data indicate that real access to and/or acceptability of the HPV vaccine and the monitoring of vaccinated cohorts remain deficient.

In July 2013, TAG recommended extended HPV immunization schedules for adolescents aged <14 years. TAG considered that these schedules could offer immunological, programmatic and financial advantages. In April 2014, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) discussed the same issue. Specifically, SAGE considered that vaccine-induced antibodies mediate HPV vaccine efficacy and that, as immunobridging studies show, adolescent women had similar or higher antibody titers than adult women. SAGE also considered a systematic review of randomized and non-randomized studies and a descriptive review of observational studies, as well as the findings of an ad-hoc expert consultation on HPV immunization schedules. SAGE concluded that, based on immunologic evidence, a 2-dose extended schedule with a minimum interval of six months administered to adolescent women was non-inferior to a 3-dose classical schedule administered to adolescent and adult women. SAGE recognized that the potential of reducing the dose schedule from 3 to 2 and the flexibility in intervals between doses may lead to improvement in vaccination coverage.

Despite concerns by the public and some health professionals, the HPV vaccine is safe. In 2013–2014, WHO's Global Advisory Committee on Vaccine Safety (GACVS) reviewed the occurrence of events supposedly attributed to HPV vaccine and immunization at three occasions, namely in June and December 2013, and March 2014. At the last occasion, GACVS stated that “it is

important to highlight and reiterate [these reviews] because a number of national immunization programs have been facing real and potential public losses of confidence in their programs as a result of increased negative publicity, even from safety issues that have been addressed.” The efforts made by immunization programs to guarantee safe vaccine development and administration, the characteristics of today’s HPV vaccines, the data generated in the controlled clinical trials, and the data emerging from post-marketing active surveillance and large and lengthy studies are the four elements that underpin HPV vaccine safety.

Emerging evidence shows the effectiveness of HPV immunization programs in reducing HPV infections and precancerous cervical lesions among young women. HPV immunization has a real potential to curb the burden of HPV-related cancers within a generation. However, the realization of this potential depends on a greater uptake and acceptability of the HPV vaccine by the public and health professionals alike.

#### **Recommendations:**

- TAG affirms the sound and robust evidence base that demonstrates the safety and efficacy of HPV vaccines among adolescent and young women. TAG also endorses the March 2014 and prior GACVS statements related to HPV vaccine safety. As such, TAG continues to encourage countries to adopt HPV vaccines in the routine national immunization schedule to prevent cervical cancer. To harmonize regional and global recommendations on HPV immunization schedules, TAG endorses the April 2014 SAGE recommendations. Specifically,
  - A 2-dose schedule with an interval of at least six months between doses is recommended for girls aged <15 years of age. This also applies to girls aged ≥15 years at the time of the second dose. If for any reason the interval between the first and second dose is shorter than 5 full months, a third dose should then be given ≥6 months after the first dose.
  - The 3-dose schedule (0, 1/2, 6 months) remains recommended for girls aged >15 years (when immunization is initiated) and for immunocompromised individuals of all ages, including those known to be HIV-positive;
  - These schedule recommendations apply to both the bivalent and tetravalent vaccines.
- Manufacturers and countries should work towards the harmonization of licensure information with recommended schedules at national level.
- TAG reaffirms that it is important for countries that are considering the introduction of the HPV vaccine, to carefully plan information systems to collect and analyze coverage data at all levels. Countries that have already introduced an HPV vaccine should strengthen their efforts to characterize vaccination coverage at subnational and national levels.
- TAG expresses concerns about the estimated low HPV vaccine coverage and high drop-out rate, which may indicate significant barriers, from parents and/or health workers, to access or lack of follow-up. TAG recommends that countries gather data to characterize these issues and to develop communication strategies to address them.

## Status of Influenza Vaccination in the Americas and Formation of the Network for Evaluation of Influenza Vaccine Effectiveness—REVELAC-i

The Region of the Americas has made considerable strides in the introduction of the seasonal influenza vaccine. By 2013, 40 of the 45 countries and territories of the Americas were using the seasonal influenza vaccine in the public sector to protect one or more risk groups. This includes 40 countries and territories that vaccinate the elderly, 39 that vaccinate health workers, 30 that vaccinate children (5 of them only children with chronic diseases), and 36 that vaccinate adults with chronic diseases. Great progress has been made in the vaccination of pregnant women, growing from 7 countries in 2008 to 26 countries in 2013.

To guide vaccine policy, especially during the last decade, countries located in tropical areas, especially in Central America, have worked to improve surveillance systems for the influenza virus in the sub-region. However, there are still uncertainties about the most appropriate timing and formulation for vaccination in this sub-region. A similar situation is observed in countries such as Peru with two influenza circulation patterns during the year.

In this context of successes and challenges in the Region, it is important to know the performance of this vaccine, yet there have been few effectiveness studies of the influenza vaccine in Latin America and the Caribbean (LAC). Given that effectiveness of the influenza vaccine varies depending on age, risk group, and a match between vaccine strains and strains circulating annually, it is necessary to systematically know the performance of the vaccine and to have evidence for adequate decision-making in public health.

In this context, during 2012, a pilot was carried out in four Central American countries to evaluate the effectiveness of the influenza vaccine, using the existing severe acute respiratory infection (SARI) surveillance platforms already in these countries. This was a collaborative project among the United States Centers for Disease Control and Prevention (CDC), Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET), and PAHO. The project took advantage of the lessons learned from the pilot and the official creation of the Network for Evaluation of Influenza Vaccine Effectiveness in Latin America and the Caribbean (REVELAC-i) in February 2013. That same year, the project was implemented in Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Honduras, Panama, and Paraguay during the 2013 influenza season.

The objective was to estimate effectiveness of the trivalent seasonal influenza vaccine in preventing SARI from influenza in the target vaccination groups (children and the elderly) that go to sentinel hospitals for SARI, using a test-negative case-control design. The nine countries participated with 71 sentinel hospitals.

The information on vaccination was completed using electronic immunization registries or paper records from the EPI, vaccination certificates, clinical files, and occasionally through

home visits. A patient was considered vaccinated if he or she had received at least one dose of vaccine more than two weeks before symptom onset.

As of 18 March 2014, 8 countries had reported a total of 2,395 SARI cases (627 influenza cases and 1,768 controls). The analysis included 1,865 patients: 144 influenza cases and 454 controls in children and 342 cases and 925 controls in the elderly. The greatest concentration of influenza cases was found in June and July [mainly influenza A (H1N1) pdm09 followed by A (H3N2) and influenza B], and circulation of the virus was recorded until December.

Crude vaccine effectiveness (VE) in children was 48% [22% to 66%], and 52% [36% to 72%] adjusted by week of symptom onset. In the elderly, crude VE was 57% [43% to 68%], 59% [45% to 79%] adjusted by week of symptom onset, and 57% [41% to 68%] adjusted by age group (60-69 years; 70-79 years, and ≥80 years). VE for influenza A (H1N1) pdm09 was 57% [14% to 79%] in children and 70% [53% to 80%] in the elderly. The moderate VE estimated in Latin America coincides with reported estimates from hospital-based studies in the Southern Hemisphere (Australia and New Zealand) and vaccination continues to be the best available prevention measure against complications and deaths due to influenza.

The REVELAC-i platform offers the opportunity to:

- Systematically evaluate VE using the existing sentinel hospital platform in countries.
- Continue integration of epidemiological surveillance, laboratory, and immunization programs to produce evidence for decision-making on influenza virus prevention and control.
- Explore the integration of sentinel surveillance for viral respiratory diseases with bacterial respiratory diseases using the REVELAC-i platform.
- Develop mechanisms to share experiences, lessons learned, and common methods among countries and research centers on influenza vaccine effectiveness, as well as for learning the impact of influenza vaccination.
- Conduct other evaluations, such as the effect of influenza vaccination on newborns in cohorts of pregnant women.
- Conduct knowledge, attitudes, and practices surveys on influenza vaccination, among others.

#### **Recommendations:**

- TAG notes the progress made in influenza vaccine use and urges countries to expand the use of this vaccine and achieve higher coverage rates, in line with previous TAG and SAGE recommendations with an emphasis on pregnant women and health care workers.
- The TAG applauds the formation and progress of the Network for Evaluation of Influenza Vaccine Effectiveness (REVELAC-i) and encourages Latin American and Caribbean countries to continue to produce evidence on the performance and impact of the influenza vaccine; and to strengthen the integration among immunization, epidemiology, and laboratory.



- PAHO should support the continued strengthening of influenza surveillance and should analyze and present the data by geographical areas within countries, particularly in larger countries where the influenza epidemiology and seasonality varies by region.
- PAHO should continue to provide guidance to countries on choosing the most adequate vaccine for their epidemiological and contextual situation.

## Cholera Vaccination in the Americas

In 2013, cholera transmission was reported in four countries of the Americas—Cuba, Haiti, Mexico, and the Dominican Republic. Although transmission in Haiti has declined significantly since cholera emerged in October 2010, the country is still reporting the greatest incidence in the Region. During the 12 months from June 2013 to May 2014, 44,867 cholera cases and 450 cholera-related deaths were recorded in Haiti. In contrast, during the 12 months from October 2010 to September 2011, 464,670 cases and 6,555 deaths were reported—10 and 15 times greater, respectively, than in the most-recent 12-month period.

Deployment of oral cholera vaccine (OCV) has been considered since October 2010. At that time, PAHO recommended focusing emergency efforts on time-tested measures for cholera outbreak response. An expert consultation convened by PAHO in December 2010 recommended that the limited vaccine supply be used for demonstration projects and that efforts be taken to increase OCV availability. Between April and June 2012 two non-governmental organizations, GHESKIO and Zanmi Lasante/Partners in Health, conducted separate but coordinated cholera vaccination of nearly 100,000 people in one urban and one rural area of Haiti. In July–August 2013, the Haitian Ministry of Health vaccinated an additional 120,000 people in two localities.

TAG discussed the use of the oral cholera vaccine (OCV) in October 2012 with a focus on the Island of Hispaniola. As part of a regional initiative for elimination of cholera transmission on the Island, TAG recommended deployment of OCV in Haiti to mitigate the cholera burden in the short and medium term, until significant and sustainable advances are achieved in infrastructure for drinking water supply and sanitation. TAG's recommendations were adopted in the "National Plan for the Elimination of Cholera in Haiti, 2013–2020," which the Haitian Government issued in February 2013.

In Haiti, approximately 200,000 people received at least one dose of OCV in 2012–2013. These experiences demonstrate the feasibility of vaccination against cholera; second-dose coverage, measured with surveys, ranged from 63% to 77%. There are plans to vaccinate an additional 200,000 people in July and August 2014. The results of a clinical trial in an endemic area of Calcutta, India, show that OCV can have an effectiveness of 65% in the five years after vaccination.

The occurrence of cholera in Cuba and Mexico not only underscores the risk of importations, but also that indigenous transmission can occur after an importation. Although the cholera epidemic of the 1990s, which affected 21 countries of the Region, finally caused improvements in access to drinking water and sanitation, conditions that enable cholera transmission persist to different extents in some areas of all of the countries of the Region. For example, in 2010 in Central America, an estimated 12.7 million people (6% of the population) were living without access to drinking water and 35.7 million people (17%) without improved sanitation.

The emergency of cholera in Haiti has renewed the global debate on the role of reactive vaccination. Since 2012, OCV has been deployed in several African countries that experienced a cholera outbreak. The effectiveness of two doses of OCV was 87% in an outbreak in Guinea. Simulations suggest that reactive vaccination of people at high risk of exposure would be the most effective use of a limited vaccine stock. As part of contingency plans for *Vibrio cholerae* importations, a tactical use of OCV should be considered as part of an integrated response in specific geographical areas that have a high proportion of people who live in vulnerable conditions, such as rural populations with difficult access to health services (including indigenous people) and urban and peri-urban populations with vulnerability in access to drinking water and sanitation.

Jointly with partners, WHO launched in the second semester of 2013 a global OCV stockpile. This mechanism is managed as a rotating fund by the International Coordinating Group, which already manages similar stockpiles of meningococcal meningitis and yellow fever vaccines for outbreak response. Until June 2014, the International Coordination Group (ICG) accepted 5 country requests for a total 1.4 million doses. The global stockpile thus promises to be a great contribution to the timely deployment of OCV in outbreak settings.

#### **Recommendations:**

- TAG supports PAHO's efforts towards cholera transmission elimination in the Region of the Americas through the integrated action and contingency plans, including the use of OCV where indicated. To this end, efforts to mobilize sufficient resources for maintaining the role of the PAHO Secretariat in the Regional Coalition for Water and Sanitation to Eliminate Cholera in Hispaniola should be pursued.
- TAG reinforces previous recommendations to maintain WASH Advocates as a fundamental pillar to the comprehensive approach towards an overarching goal to eliminate cholera transmission. TAG also reaffirms that vaccination is one of possible short-term actions toward the achievement of the long-term elimination goal.
- Countries should continue cholera surveillance and assess the impact of OCV where used.

## Status of the Documentation and Verification Process of the Elimination of Measles, Rubella, and Congenital Rubella Syndrome

PAHO/WHO defines measles and rubella elimination as the interruption of endemic transmission of these viruses for a period of at least 12 months, in the presence of high-quality surveillance. To confirm elimination of these diseases, countries have to document interruption for a period of at least three years from the last known endemic case. In order to implement the documentation process, an International Expert Committee (IEC) was created and 23 national commissions were established, including one for the French Overseas Departments of the Americas and one sub-regional commission for English-speaking and Dutch-speaking Caribbean countries and territories, including Suriname.

### Progress

In their reports on elimination, the national and sub-regional commissions presented evidence indicating the interruption of endemic transmission of the measles and rubella viruses in their countries and territories including the occurrence of the last endemic measles case in 2002 and the active case searches for the period 2006-2012. This evidence suggested a strong basis for measles elimination in the Region. The evidence—studied by the IEC at its fifth meeting, held in April 2014—is the following:

- a) Member States have documented the last case of endemic transmission of measles and rubella in their countries and territories. Subsequently reported cases were import-associated, according to epidemiological and molecular epidemiology data. The last endemic cases of measles and rubella in the Region occurred on 16 November 2002 and on 3 February 2009, respectively. The last endemic case of congenital rubella syndrome (CRS) was found in a child born on 26 August 2009.
- b) In the period 2009-2013, the Region, on average, met the targets for four of the five epidemiological surveillance indicators (>80%) on a continuous basis (83-91%). The adequate investigation indicator was achieved only in 2011, since in several countries there were difficulties in visiting homes in the 48 hours following reports of suspected cases.
- c) Given the differences among and within countries in terms of sustained achievement of surveillance indicators, 16 of 23 countries with national commissions carried out active institutional and community case-finding over the period 2010-2013, to document the absence of measles and rubella cases in their territories. These countries established criteria for identifying areas for active case-finding, such as municipalities not reporting suspected cases, areas with a heavy flow of tourists or migrants, areas experiencing population shifts, border regions, areas with low vaccination coverage, and the presence of at-risk ethnic groups, among others.
- d) Likewise, 16 of 23 countries with national commissions carried out retrospective searches for suspected cases, using several sources of information. Criteria for selecting the institutions where the searches would be made included level of care and services provided, as well as being located in areas with unreliable notification of suspected CRS cases. No case of CRS was confirmed.

- e) Since the presence of dengue cases in several countries could have masked measles and rubella cases, 15 of 23 countries with national commissions and the Caribbean sub-regional commission tested a percentage of samples from patients with exanthema for measles and rubella in areas where the dengue virus was circulating. The same was done with dengue-negative samples in areas where suspected cases of measles had been reported. None of the processed samples tested positive for measles or rubella.
- f) Genotype D9 was isolated in the last endemic outbreak of measles reported in Colombia and Venezuela in 2002. Since 2003, countries have documented importation of measles cases by identifying viral genotypes. Genotypes D4 and D8, which mainly circulate in Europe, have been found in 88% of outbreaks.
- g) Rubella virus genotype 1C has been identified as endemic in the Americas. From 2006 to 2009, genotype 2B was isolated in outbreaks reported in three countries and is also considered endemic in the Region. For the period 2009-2013, reported genotypes 1E, 1G, 1J, and 2B have been linked to imported cases.
- h) From 1994 to 2013, nearly 500 million people  $\leq 40$  years of age were vaccinated in catch-up, follow-up, and speed-up campaigns. To complement the cohort analysis, 18 of 23 countries with commissions estimated the accumulation of susceptible individuals, prior to defining the target population for follow-up and speed-up campaigns.

At the fifth meeting of the IEC, Brazil presented the current epidemiological situation of the sustained measles outbreak affecting the states of Ceará and Pernambuco. After updating the figures through the weekly measles bulletins, the number of cases reached 424 confirmed cases for the period 2013-2014.<sup>2</sup> The date of rash onset was 19 March 2013 for the first case and 10 June 2014 for the most recent confirmed case. In addition, 53 suspected cases remain under investigation; rash onset of the last suspected case is 1 July in Ceará. The cases are distributed in 24 of 185 municipalities in Pernambuco and 13 of 184 municipalities in Ceará. Children under 1 year of age is the group most affected by this outbreak (43%); however, 100 cases in adults (>15 years) have been confirmed. Genotype D8 has been identified. The country has conducted a vaccination campaign aimed at children under 5 years of age in the affected states and has strengthened epidemiological surveillance as part of the attempt to interrupt this outbreak. TAG expresses concern that the measles outbreak in Brazil has persisted for over 15 months and that cases are still under investigation. While all documentation previously presented to the IEC pointed towards interruption of endemic measles circulation, the current outbreak is not consistent with elimination and must be urgently stopped. To this end, TAG is aware that both PAHO and the IEC stand ready to assist the government of Brazil in successfully interrupting the measles virus transmission in the country.

Global circulation of measles and repeated outbreaks represents a continuous risk of virus reintroduction into the Americas. The recent large outbreaks in Ecuador, Quebec, Brazil and United States have illustrated this real risk. TAG has previously stated that there is no room for complacency in order to maintain the achievements of elimination.

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<sup>2</sup> Data as of epidemiological week 24, 2014 (29 June – 5 July).

**Recommendations:**

- TAG recommends that the PAHO Secretariat review, with the Brazilian authorities, the epidemiological data and the outbreak response in order to identify opportunities to halt the epidemic as soon as possible.
- To this end, TAG urges Brazilian authorities to present the most updated data and outbreak response to both the TAG and IEC members.
- TAG suggests the Brazilian government consider PAHO's availability and readiness to provide any type of assistance to interrupt the measles virus transmission in the country.
- PAHO Secretariat should lead a further in-depth examination of the epidemiology of and response to recent outbreaks to better understand transmission patterns and age-distribution of cases, use of MR vs. MMR vaccines in outbreak response, the usefulness of dose 0 at 6 months of age in addition MMR1 at 12 months of age and MMR2 at 18 months of age during outbreaks.
- All countries need to maintain their capacity to respond rapidly and decisively to outbreaks. In order to anticipate the spread of an outbreak, thorough outbreak investigation is critical in order to define geographical areas and age ranges to be targeted. Outbreak responses must be aggressive and timely to halt secondary transmission.
- All countries should also review their measles/rubella surveillance performance and vaccination coverage levels to identify areas of vulnerability. Specifically and within the context of the 2014 FIFA World Cup, countries should implement additional surveillance actions (i.e., active searches) to document the absence of measles and rubella cases.
- TAG reemphasizes previous recommendations that coverage of at least 95% with 2 doses of measles-containing vaccines in all districts and in all countries is needed to maintain elimination. If 95% coverage is not reached with two doses, countries should continue to conduct periodic follow-up campaigns.
- TAG reissues its 2013 recommendation to lower the age for the second MR-containing vaccine dose to 18 months and use school entry requirements as a platform to monitor MR-containing vaccine vaccination status.

## Update on Pertussis Vaccination

The TAG has made several recommendations regarding pertussis surveillance and vaccination in the last four years. One of these recommendations was that countries should not change the whole-cell vaccine from routine vaccination against pertussis to acellular vaccines, because of evidence suggesting the shorter duration of the immunity conferred by the acellular vaccine.

In November 2012, SAGE expressed concern about the apparent resurgence of pertussis in some industrialized countries despite high vaccine coverage with acellular pertussis (aP) vaccines, which in some settings was associated with an increase in infant pertussis deaths.

With the objective of reviewing the most recent evidence about aP vaccine effectiveness, SAGE established a working group that reviewed the data of 19 developing and industrialized countries from various regions around the world that showed high vaccination coverage with the whole-cell pertussis vaccine (wP) or the aP vaccine.

Given the natural periodicity of pertussis, disease resurgence was defined as a larger burden of disease than expected when compared to previous cycles in the same setting.

### ***Main conclusions of SAGE pertussis working group:***

- The vaccination against pertussis is highly effective in reducing disease caused by *Bordetella pertussis*, with a large decline in overall global incidence and mortality compared with the pre-vaccination era in both wP- and aP-using countries.
- To date, there is no evidence of a widespread global resurgence of pertussis. There is however evidence that resurgence has occurred in 5 of the 19 countries reviewed, 4 of which were exclusively using aP vaccines. The increased number of cases in 1 country using wP vaccine was considered to reflect factors other than the use of this vaccine, such as surveillance, laboratory methods, and low vaccine coverage in some areas.
- Recent modeling studies, as well as data from a baboon model, supported the hypothesis that wP to aP vaccine transition may be associated with disease resurgence.
- Although the reasons for the resurgence were found to be complex and varied by country, SAGE concluded that the shorter duration of protection and likely reduced impact on infection and transmission conferred by aP vaccines play critical roles.
- The influence of changes in circulating pertussis strains on the effectiveness of aP or wP vaccines was not found to contribute to observed country level resurgence.
- Licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines, as aP vaccines induce a different type of immune response, and are less effective in clearing mucosal infections.
- Surveillance and modeling data suggest that the use of aP vaccines may result in a resurgence of pertussis after a number of years and might lead to an increased risk of death in young infants compared with programs using wP. The magnitude and delay for

this resurgence to occur are difficult to predict, given the many factors that intervene such as vaccine coverage, natural immunity, vaccine type, schedules, etc.

- Recent evidence suggests that maternal immunization with aP during pregnancy is safe and highly effective in protecting infants from pertussis and that it may have a high impact on morbidity and mortality in infants too young to have been immunized. This conclusion does not extend to wP vaccines, given the absence of immunogenicity and efficacy data in pregnant women and concerns regarding potential higher reactogenicity in adults.
- Vaccination of pregnant women is considered likely to be the most cost-effective complementary strategy to prevent pertussis-associated infant mortality.

### ***SAGE Recommendations***

All children should be immunized against pertussis, with the goal of maintaining high coverage, as minor reductions can lead to an increase in incidence.

The risk of resurgence associated with the use of aP vaccines for primary immunization, including increased disease in infants, compared with use of wP, indicates that countries where only a limited number of pertussis doses are used/affordable should continue to use wP vaccines for primary pertussis early infant vaccination. Thus the switch from wP to aP vaccines for primary infant immunization should only be considered if large numbers of doses (including several boosters) can be included in the national immunization schedules; this has substantial cost implications given the much higher cost of aP vaccines and higher number of doses required.

Countries may consider the immunization of pregnant women with 1 dose of Tdap (in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester) in addition to routine primary infant pertussis vaccination in countries or settings with high infant morbidity/mortality due to pertussis.

SAGE emphasized the importance of efforts to improve surveillance of disease burden particularly in developing countries, and assessment of impact of infant immunization, with particular focus on fatalities in infants <1 year of age.

### **Recommendations:**

- Although both available pertussis vaccines (aP and wP) elicit a good immune response, evidence suggests aP has a short-lived duration of protection. As such, countries should give preference to the use of wP containing vaccines. Countries using current vaccination schedules with whole-cell pertussis vaccines should continue to do so and countries using aP should actively monitor the risk that waning immunity poses to the population.
- PAHO should engage with partners, including WHO, in discussions with industry to advocate for the research and development of improved pertussis containing vaccines.



- Countries should ensure homogenous vaccination coverage  $\geq 95\%$  with 3 doses of pertussis-containing vaccines in children aged  $<1$  year; and encourage timely initiation and completion of the schedule. Coverage attained with the 4<sup>th</sup> dose of the DPT vaccine should be the object of careful recording, monitoring, reporting and evaluation.
- All countries should continue strengthening pertussis surveillance to better monitor the epidemiology of the disease. Also, countries should continue assessing the quality of their laboratory diagnostics and surveillance systems in order to evaluate the reliability of their data on incidence, case-fatality, age distribution, proportion of cases confirmed by different methods, and vaccine effectiveness.
- Every pertussis outbreak should be thoroughly investigated to improve the understanding of the current epidemiology of the disease in the Region of the Americas.
- The response to outbreaks of whooping cough should include lowering the age for initiating vaccination to 6 weeks and vaccinating pregnant women only in areas affected by the outbreaks. Currently, there is no evidence for TAG to recommend routine vaccination of pregnant women.

## Update on the PAHO Revolving Fund

For 35 years, the PAHO Revolving Fund (RF) has been one of the cornerstones of success of the immunization programs in the Region, in terms of the elimination and control of vaccine-preventable diseases and the rapid and sustainable introduction of new vaccines. In 2013, on behalf of 41 countries and territories, the RF acquired 46 different vaccine presentations, as well as syringes and cold chain equipment. A total of 1,335 purchase orders, with a consolidated value of \$495 million, were also placed, with more than 95% of funds from coming national budgets.

The countries and territories that participate in the RF have strongly expressed that it is critical to strengthen the management of the Fund and to safeguard its principles, including solidarity, Pan Americanism and equal access, in order to protect the achievements, progress and financial sustainability of immunization programs. However, the RF faces significant challenges with respect to the context of the vaccine market, in terms of the price and supply of some biologicals.

In order to strengthen the management of the RF, during the 52<sup>nd</sup> Directing Council in October 2013, Member States recognized the strategic importance of the RF and approved increasing their contribution from 3.5% to 4.25% (while maintaining the 3% RF capitalization rate) in order to increase the financial sustainability of this mechanism, while also ensuring greater efficiency and service in favor of countries and territories.

Similarly, during the same Directing Council, a resolution was passed that endorsed the principles of the RF and requested that PAHO continues administering this mechanism, without exception, in a way that respects its principles, terms and conditions, which that have contributed to the successes of the immunization programs in the Region. In particular, offering all countries vaccines at a single price and ensuring that is the lowest available. Since the principles of the RF were ratified however, some partners and vaccine producers have promoted- with even greater intensity- a differential pricing policy; in other words, they have promoted that countries, within the Revolving Fund and in other regions, pay vaccine prices according to their per capita income (Gross National Income – GNI per capita).

Regarding vaccine supply, the RF is faced with situations of limited or sensitive supply for four vaccines: yellow fever, Tdap, varicella and MMR. The global production capacity of the yellow fever vaccine continues to be insufficient. Because of this, a WHO/UNICEF/PAHO working group was established to prioritize the allocation of the limited supply.

The global demand for Tdap and varicella vaccines is increasing faster than production capacity, creating conditions of scarcity. In addition, reducing inventories in progress and long production cycles for these vaccines affect the availability to meet demands from countries that are not planned in advance.

With regard to measles-containing vaccines (MR and MMR), the global supply is inconsistent. Of the four prequalified producers, one has 80% of global production capacity, two have production difficulties and high prices, and one is stopping. The growing global demand for these vaccines can affect the timely supply, if countries in the Region do not plan their needs precisely and in advance.

To address these challenges, the RF has made improvements to its tools for supporting countries in their timely, long-term demand planning, as well as in their plans for vaccine introduction.

**Recommendations:**

- TAG reaffirms its recognition of the RF as a pillar in the progress and success of country immunization programs in the Americas. In turn, the TAG acknowledges the support that countries and territories provide to the RF.
- The TAG continues to recommend that countries ensure the development of increasingly accurate demand forecasts and with greater long-term visibility. The PAHO RF should support countries in the process of planning and monitoring.
- TAG continues to support other regional pooled procurement initiatives, such as the ongoing discussion in the Eastern Mediterranean Region of the World Health Organization.

## Update on Immunization Data Quality and Electronic Immunization Registries

Evidence supports the fact that more effective immunization coverage monitoring leads to better coverage. Latin America is a global leader in regional and country-led initiatives in the area of immunization data use and quality. Many countries in Latin America are rapidly advancing in the development and implementation of national electronic immunization registries (EIRs).

Immunization data quality, defined in practical terms as data that effectively reflects the reality it is meant to describe, is considered a priority for countries of the Americas and PAHO. The issue of immunization data quality was first discussed formally by Ministers of Health in 2002, in the context of a regional Resolution approved by PAHO's Sanitary Conference (CSP26.R9). That same year, PAHO's TAG on Vaccine-preventable Diseases put forward recommendations on data quality urging countries to regularly and systematically assess the quality of immunization data, within the context of regular ongoing supervisory activities. TAG also urged countries to strengthen data analysis capabilities including the identification of high-risk municipalities and the causes of low coverage, leading to the development of micro-plans to correct identified problems. Moreover, it called for the dissemination of assessment tools, for local adaptation and use.

TAG has since reinstated its original data quality recommendations, adding recommendations not only to assess data quality, but also to develop and implement work plans to follow-up on the monitoring system weaknesses detected. In 2009, TAG added a recommendation regarding the importance of having the EPI be actively involved in health surveys collecting vaccination coverage data. Also in 2009, TAG first issued a recommendation on EIRs, in the context of improving data quality, urging countries using EIRs to share experiences and lessons learned. Additional EIR recommendations were added in 2011 and in 2013, as more and more countries began developing and implementing EIRs. These recommendations call for coordination with other actors, system interoperability, EIRs that take into account the needs of the vaccinators, more monitoring and evaluation, and exploring using innovative mHealth technologies.

In the global context, since the inception of the DoV initiative and the implementation of the GVAP, endorsed by all WHO Member States in 2012, monitoring and evaluation have been at the forefront of the global immunization agenda. The progress report on GVAP presented to the World Health Assembly in 2014, highlighted issues related to the availability and quality of the data needed to monitor the achievement of GVAP goals and strategic objectives. During the 2014 World Health Assembly (WHA), several countries expressed their concern about immunization data. Countries from the Americas also expressed their awareness of the issues related to immunization data quality, and at the same time were able to share the steps they are taking to improve data quality and immunization monitoring.

SAGE discussed data issues with a focus on the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) in 2011. More recently, SAGE has emphasized the importance of improving data quality in order to better monitor the GVAP, but always stressing the importance that data has for managerial decisions at all levels, starting with health facilities.

Developing and maintaining good practices on data collection, aggregation and reporting, form archiving and analysis for decision-making is increasingly challenging. Primarily because more and more vaccines are added to vaccination schedules, the same personnel often has to deal with the delivery of more and more health interventions to more users in health facilities, and data collection needs multiply. In spite of these challenges, progress on improving immunization data quality and using that data for decision-making at all levels has been remarkable in Latin America over the last twelve years.

In this TAG session, the progress report on data quality and EIRs focused on activities done to improve data quality and use at the local level, data quality assessments, vaccination coverage surveys, and the implementation and development of EIRs. It presented work done on data quality assessment tools as part of a toolkit for coverage monitoring of integrated interventions targeting children and introduced the recently launched project “Improving Data Quality on Immunization” (IDQi). Finally, some important open questions were shared and PAHO’s vision and next steps on data quality and EIRs were presented.

Some details on the work on data quality and use, and EIRs in Latin America are provided herewith:

#### ***Data quality and use at the local level***

An important aspect of the work in immunization data quality has focused on where the data are generated: the local level. Recommendations have revolved around encouraging health care workers, the vaccinators, to use the data they collect to monitor the achievement of coverage goals and their drop-out rates, and to track and contact defaulters. Supervisory visits that include reviewing data on doses given, monitoring proper data recording practices, using paper registries or ticker-files to track defaulters, in addition to field verification of the vaccination status of the community, are strongly promoted. Work has also been done to promote the quality and proper use of vaccination cards.

#### ***Data quality assessments and follow-up***

Formal immunization data quality assessments, implemented by PAHO hand-in-hand with countries, using an adaptation of the WHO’s Data Quality Self-assessment (DQS), have been very useful in making immunization data quality and use an important component of the EPI. The first DQS in Latin America was conducted in Costa Rica with PAHO support in 2005. To date, over twenty countries have conducted a data quality assessment. Measurable improvements have been seen in countries that have repeated such assessment. Furthermore, the inclusion of concrete recommended activities following these assessments into annual or multiyear

immunization plans of action have resulted in increased visibility and heightened likelihood of implementing the recommendations.

### ***Coverage surveys***

Most surveys assessing immunization coverage rates in Latin America and the Caribbean are the Demographic and Health Surveys (DHS) and UNICEF's Multiple Cluster Indicator Surveys (MICS). To ensure that the data resulting from these and other similar surveys are useful to EPI managers, in 2009, TAG issued a recommendation urging immunization programs to be aware of the conduction of such surveys in order to ensure that questionnaires are adequate and interviewers are properly trained to assess vaccination status, and that the results are internally consistent between biologicals. EPI managers have been engaged with survey planning teams and PAHO, in collaboration with the US CDC, has been collaborating with countries to conduct secondary analyses focusing on vaccination timeliness, simultaneity, potential missed opportunities and related factors. PAHO has also recently supported surveys that seek to answer specific questions, in addition to coverage rates: Haiti (2009 and 2012), Paraguay and Venezuela (2011), El Salvador (2011-2012) and Bolivia (2013). The latter also included an operational study component to assess validity of maternal recall and to assess card quality (from pictures taken in the field) and data reliability between sources; analysis is ongoing.

### ***Electronic Immunization Registries***

With the increased availability of information and communication technologies, as well as connectivity in all countries over the last few years, countries have been developing and implementing EIRs. If well implemented, EIRs can facilitate monitoring coverage and implement tailored strategies aimed at increasing coverage. They can also help optimize the workflow and facilitate defaulter tracking, not only improving data quality and use, but also making immunization programs more efficient.

PAHO has facilitated experience exchanges between countries mainly through visits, virtual seminars, and face-to-face meetings. A landmark workshop to discuss issues related to the development and implementation of EIRs was held in Colombia in 2011 and a follow-up Immunization Registry workshop, with Latin American countries and selected GAVI-eligible countries from other regions, took place in Brasilia in November 2013. From this work, best practices and lessons learned on EIR development, implementation and use are being compiled. Much remains to be done in terms of EIR Monitoring and Evaluation (M&E). In May 2014, a DQS conducted in Panama included a module on EIR. This EIR evaluation module was recently developed by PAHO with support from partners. It includes questions to describe the registry's scope, the software's architecture, the EIR functionalities, the regulatory and legal context, issues of maintenance and sustainability; human resources; level of implementation and future plans. Questions on availability of adequate hardware (i.e. computers), Internet access, infrastructure, human resources and technical support, adequate use of the EIR and perceptions of EIR users (EPI and data entry clerks) were added to the DQS quality tools. The tool was useful and it will continue to be used and improved.

Finally, in order to move forward with technical cooperation on data quality and EIR development, implementation and M&E, PAHO has started implementation of project IDQi, which seeks to raise awareness of, interest in and commitment to select strategies in order to better track facility performance via immunization coverage monitoring. The IDQi project also seeks to improve follow-up of un/under-immunized individuals and foster linkages between coverage and supply chain data. Its expected outcomes include launching a virtual library of data quality best practices drawn from at least 3 case studies, launching a live toolkit that helps countries effectively initiate and/or improve embedded monitoring, and another toolkit that helps countries decide whether, when and how to introduce and/or expand EIRs. It also aims to raise awareness in 50 countries of all IDQi tools by 2016, 60% of which should be outside of PAHO. A TAG Member has been invited to be part of the IDQi project Advisory Group to help ensure that the project implementation is aligned with TAG recommendations.

**Recommendations:**

- TAG endorses the work being done in the Region in the area of immunization data quality and electronic immunization registries, as these efforts are in line with the GVAP, and reiterates all of its recommendations from previous years.
- TAG agrees that immunization data quality should be approached from several fronts, while always keeping the local level as the foundation for any efforts.
- TAG encourages the continued exchange of experiences between countries.

## Vaccination with Pneumococcal Conjugate Vaccine in Adults

Pneumococcal pneumonia and other diseases caused by *Streptococcus pneumoniae* (*Spn*) continue to be a substantial cause of morbidity and mortality worldwide. Pneumonia is the most common manifestation in adults, and bacterial pneumonia is the most common form of invasive bacterial disease (IBD), accounting for 90% of the total number of cases. Mortality associated with pneumococcal pneumonia has hovered around 25% globally in recent decades.

The epidemiology of pneumococcal disease in adults in developing countries is not well described, but it is acknowledged that the burden of disease globally is significantly underestimated. The burden of pneumonia disease in adults is greater in adults  $\geq 65$  years of age as has been seen in the United States, Argentina, and Brazil. In addition, the burden of this disease has increased due to the number of individuals with chronic diseases or infected with human immunodeficiency virus (HIV), and the increased age of the population in many countries. Drug resistance, which is the greatest obstacle to the successful treatment of infections, has also been on the rise. In industrialized countries, fatality from pneumococcal bacteremia can reach 15-20% among adults and 30-40% in older adults, even when patients receive appropriate antibiotic therapy and intensive care.

The 13-valent pneumococcal conjugate vaccine (PCV) is prequalified by the WHO and licensed for ages  $\geq 50$  years in several countries. Preliminary results of placebo-controlled double-blind clinical trials of PCV13 vaccine, carried out in over 85,000 people aged  $\geq 65$  years, showed efficacy in pneumonia reduction (CAPiTA study). However, to date, the final results have not been published.

As demonstrated with PCV7 vaccine, recently published studies demonstrate a reduction in invasive pneumococcal disease (IPD) and pneumonias in adults in the United States with the introduction of PCV13 in the vaccination schedule for children. In other industrialized countries, the incidence of IPD has decreased sharply with the introduction of pneumococcal conjugate vaccines, including other age groups that are not the primary vaccination target group, due to the herd immunity effect these vaccines provide.

Given that data on the herd effect is limited in low and medium income countries, it is difficult to predict the impact of pneumococcal conjugate vaccines introduced into the childhood vaccination schedule on the reduction of pneumonia, IPD, and serotype replacement in LAC. However, a study in Brazil demonstrates the effect of PCV10 on the reduction of child carriers. Several issues need to be considered in evaluation of the herd effect:

- Availability of surveillance data in the adult population (most LAC countries do not have this information).
- At least three years since the introduction of PCV in children.
- Data on colonization rates in children. In LAC, rates are around 45%.



- Strength of pneumococcal infection transmission. Socio-demographic factors such as overcrowding may facilitate pneumococcus transmission from a colonized person to others.
- Individual immunological response to the vaccine may be influenced by factors such as malnutrition, immunological status, and others.
- PCV vaccination coverage in children. PCV vaccine coverage in LAC is high in general.
- Vaccination schedules adopted by the countries (3+1; 3+0; 2+1).

To date, 27 countries and territories in the Region have introduced pneumococcal conjugate vaccines (PCV10 or PCV13); however, there is still no evidence of herd effect in LAC countries.

More recently, PCV13 immunogenicity studies have been conducted in adults. These studies have demonstrated good immunogenicity, especially for the serogroups included in the vaccine, both in healthy adults and in high-risk patients. The available data indicate that the high-risk population has a greater probability of developing pneumococcal disease and death.

In regard to cost-effectiveness, there are few studies on the cost-effectiveness of PCV13 vaccine in adults in LAC. Cost-effectiveness analyses in LAC will depend on future studies based on data on the adult disease burden, direct local medical costs, vaccine costs, herd effect, and data on efficacy of PCV13 in adults.

Countries should consider programming and logistical aspects of the introduction of a new vaccine in the immunization program, considering recent prior experiences with the introduction of other new vaccines.

PAHO organized a working group in WDC, on 2-3 June 2014 in order to discuss the topic of adult vaccination with the 13-valent pneumococcal conjugate vaccine (PCV13) as a public health policy in Latin American and Caribbean countries (LAC). The conclusions of the group discussion were presented to the TAG.

#### **Recommendations:**

- TAG endorses the recommendations of the working group, including:
  - The introduction of pneumococcal conjugate vaccines in children continues to be the priority for reduction of pneumococcal disease.
  - Introduction of PCV13 vaccination for healthy adults into immunization programs will depend on the results of studies of efficacy, cost-effectiveness, and herd effect.
  - Countries that have already introduced the 23-valent polysaccharide vaccine for use in adults could use the sequential schedule (conjugate-polysaccharide) for high-risk adults\*.
  - Countries that do not use pneumococcus vaccine in high-risk adults\* and consider vaccination of this population a priority could include PCV13 in their vaccination schedules, based on immunogenicity studies.
  - Implementation or strengthening of epidemiological surveillance of pneumonias and IPD in adults is a priority for countries.

- Countries that have already introduced PCV vaccines for children should spell out mechanisms to measure the impact of vaccination on other age groups (herd effect).
- TAG encourages innovative surveillance and assessment approaches to better understand the preventable burden of pneumococcal disease in adults. Interaction with influenza surveillance networks should be further explored.
- Countries should seek to improve PCV vaccination coverage rates in children.

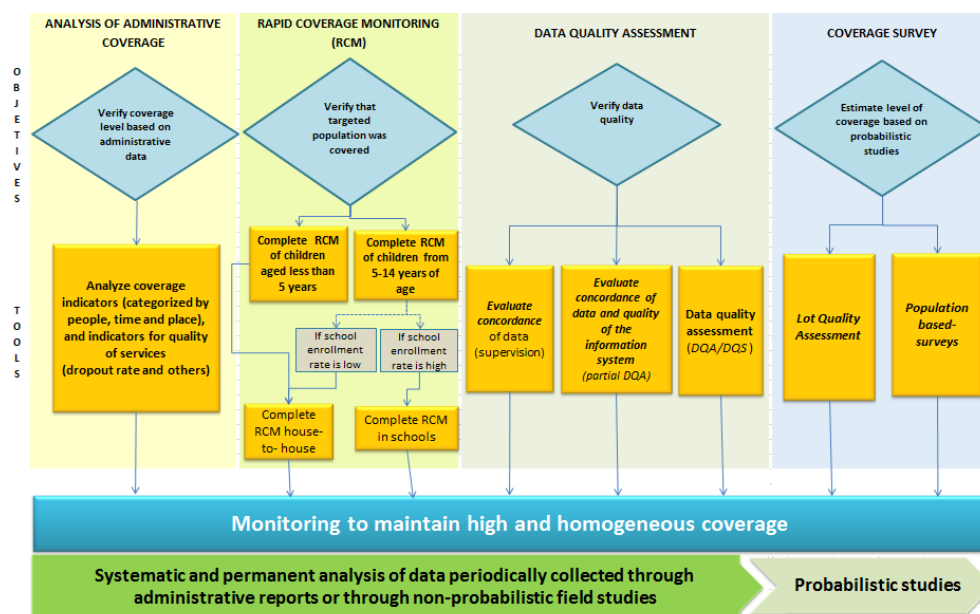
\* Adults in high risk groups are adults  $\geq 50$  years of age, with the follow conditions: cerebrospinal fluid leak, cochlear implant, sickle cell disease/other hemoglobinopathy, congenital or acquired asplenia, immunocompromised persons, congenital or acquired immunodeficiency, human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma , Hodgkin's disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, and multiple myeloma. This is a special recommendation for individual clinical decision-making.

## Tools for Improving the Effective Management of Immunization Programs at all Levels

In the context of high national vaccination coverage, reaching unvaccinated people requires a good understanding of the profile and location of vulnerable populations as well as the reasons they give for not initiating or completing the vaccination schedule. Thus, in 2002, TAG recommended that countries build data analysis capacity, including identification of high-risk municipalities and the causes of low coverage, and that the Organization develop and disseminate tools for their local adaptation and use. These recommendations were revisited in 2010 and 2013, and the Directing Council of the Pan American Health Organization recommended that the Director provide technical support to the Member States for evidence-based decision-making and for strengthening immunization programmatic and operational capacity.

In order to respond to the challenge of promoting systematic data analysis for immunization decision-making and programmatic strategy development, PAHO has created tools to 1) identify missed opportunities for vaccination that could make it easier to increase immunization service coverage; 2) systematize and facilitate monitoring of immunization data (and other interventions administered concomitantly with immunization) from the local level (figure below); and 3) integrate cost analysis into the planning and budgeting process.

Among the next steps, PAHO will continue to systematize the tools that countries have been using to provide local levels with guidance on data analysis to identify the characteristics of unvaccinated people and develop efficient strategies to reaching these populations. In an upcoming EPI evaluation, PAHO will integrate these three management and operational tools to help identify the most efficient strategies to employ in the micro planning and strategic planning processes for reaching the unvaccinated.



### Recommendations:

- TAG recognizes these tools for EPI are of great value for making informed decisions at the local, intermediate and national level.
- TAG encourages countries to test and adopt the tools proposed by PAHO, as well as document how these tools contribute to improved management of the program.

**5th South-East Asia Regional Technical Advisory Group on Immunization (SEAR-ITAG)  
Meeting Recommendations  
(August 2014)**

Progress has been made in immunization activities in the South-East Asia Region since the last ITAG Meeting held in April 2013. Two notable milestones include the RC resolution to eliminate measles and control rubella/CRS by 2020 which was endorsed in September 2013, and the certification of the region as polio-free in March 2014. The countries in the Region are well positioned to take the lessons learned and apply best practices to their respective national immunization programmes. Given these, the SEAR 2014 ITAG makes the following recommendations.

**1. Quality of Immunization Data**

The ITAG takes note of the emphasis placed by SAGE on the importance of accurate data on immunization system performance and the prevalence or incidence of vaccine preventable diseases for evidence-informed policy and operational support and for monitoring progress towards national, regional and global goals.

ITAG reiterates the position of SAGE that improvement of data quality should be one of the highest priorities for all stakeholders in the early part of the Decade of Vaccines.

The ITAG took note of several issues related to the quality of immunization data, including but not limited to: (1) the inadequate recording and reporting of immunization data; (2) the low availability of home-based records for immunization and variable quality of institutional (retrievable) records; (3) uncertainties on the size and distribution of the populations targeted for immunization; and (4) the discrepancies between house-hold surveys and administrative data.

The ITAG considers data to be of high quality if it is fit for purpose at all administrative levels for making policy and/or operational decisions, and monitoring performance, in terms of delivering services (coverage, supply, temperature monitoring) as well as in controlling the targeted diseases. This would require that data are complete, have internal and external consistency, and are available in a timely fashion at all levels of the systems with sufficient detail to allow informed decision-making and effective planning and monitoring.

*ITAG recommends that:*

- a. The SEAR Member States:
  - i. Improve data quality through making appropriate financial and human resource investments. Introduce measures to improve data quality, specifically: (1) conduct annual desk reviews to assess data quality; (2) conduct periodic in-depth data quality assessments; and (3) periodic household surveys to validate coverage in addition to collection of data on determinants of immunization coverage.
  - ii. Share national and sub-national level immunization coverage data and surveillance data with SEARO according to the agreed timelines and processes.
  - iii. Use in-country independent resources (e.g. academia, professional associations) to ensure the quality and independence of the data quality assessments.
  - iv. Develop, implement and monitor data quality improvement plans in response to the results of the assessments.
  - v. Engage National Immunization Technical Advisory Groups to participate in monitoring the progress on implementing the strategies for improving data quality.
- b. WHO SEAR supports the Member States to improve data quality by:

- i. Developing and publishing guidelines for assessing data quality and preparing data quality improvement plans.
- ii. Facilitating technical support to Member States for analysing and interpreting immunization data and translating the results to develop relevant policies and data quality improvement plans.
- iii. Organizing a Data Quality Meeting including a review of the JRF, just before 2015 ITAG meeting.

## 2. **Polio**

The SEAR ITAG congratulates Member Country EPI teams and their national governments for achieving polio-free certification and maintaining polio-free status. The ITAG recognizes the hard work done by the front-line health workers, vaccinators, supervisors, and managers for polio eradication and immunization programmes. The ITAG also recognizes the generous support and guidance by the donors and partners, and the important contributions of the National Certification Committees for Polio Eradication (NCCPE) and the Regional Certification Commission for Polio Eradication (RCCPE).

Despite this enormous achievement, the ITAG is concerned about the persistently low OPV3 coverage through routine immunization in Indonesia and Myanmar with resulting immunity gaps in children less than 5 years, and the persistent sub-optimal non-polio AFP rate in Sri Lanka and all AFP surveillance indicators in Timor-Leste. The ITAG notes that India, Indonesia, Myanmar and Timor-Leste are considered high risk, and Nepal and Thailand medium risk for polio outbreaks following importation based on the current regional risk assessment. The ITAG urges all countries in the Region to avoid complacency and re-commit to implementing certification-level polio eradication programmes including strong routine immunization delivery.

The ITAG commends the Government of India for implementing polio vaccination of travelers to/from polio infected countries to mitigate the risk of transmission following importation, and notes that other Member Countries are considering similar risk mitigation policies.

The ITAG notes the growing recognition of the importance of environmental surveillance to supplement AFP surveillance through early detection of imported WPVs and emerging VDPVs, and as a tool to monitor Sabin virus circulation after cessation of OPV. The ITAG also notes the Region's progress towards achieving the four objectives of Polio Endgame Strategic Plan 2013-2018 including plans for IPV introduction, tOPV to bOPV switch, and ensuring the legacy of polio eradication by utilizing polio-related resources for eliminating measles and controlling rubella/CRS, strengthening routine immunization, and improving epidemiologic and laboratory surveillance for other vaccine-preventable diseases.

The SEAR ITAG supports the recommendations of the SAGE, SEA RCCPE and the Global Polio Laboratory Networks.

*ITAG recommends that for the Member Countries:*

- a. All NCCPEs should remain active until global certification. Certification activities should continue as per recommendations by the Regional Certification Commission (SEA-RCCPE). All member countries should continue their efforts to sustain certification-level AFP surveillance and polio immunization performance.
- b. Indonesia, Myanmar, and Timor-Leste should urgently address the issue of persistent low polio immunization coverage through routine immunization. These countries should conduct at least two rounds of sub-national polio SIAs in 2015 targeting high risk populations and areas. Nepal and Thailand, as medium risk countries, should seriously consider conducting polio SIAs in 2015. Bangladesh, though low risk, should consider conducting appropriate supplemental polio immunization activities in high risk populations/areas. India and other countries should follow guidance from their respective national level expert advisory bodies.

- c. In view of the persistent sub-optimal non-polio AFP rate in Sri Lanka and all AFP surveillance indicators in Timor-Leste, both countries should conduct EPI and VPD surveillance reviews in 2015.
- d. In view of the continued transmission of polio in Nigeria, Pakistan, and Afghanistan, and the consequent potential for polio importation to the Region, all countries should conduct regular risk assessments and risk mitigation activities.
- e. To reduce the risk of importations, all countries should carefully consider introducing polio vaccination for travelers to/from polio infected countries in line with recommendations by the Polio Emergency Committee under IHR and WHO's International Travel and Health Guidelines.
- f. Initiate environmental surveillance in Bangladesh, and expand in Indonesia in 2014. Initiate environmental surveillance in Myanmar, Nepal, Thailand, and Timor-Leste in 2015.

*Recommendations for WHO- SEARO:*

- a. WHO SEARO to support countries to register IPV, bOPV and other EPI WHO prequalified vaccines, using the "WHO Guidelines on Expedited Approval of WHO PQ Vaccines" by September 2015.
- b. WHO-SEARO should continue to regularly share regional risk assessments with countries, assist countries with sub-national risk assessments, and monitor country risk mitigation activities.

*Recommendations for Partners:*

- a. Partners should work with countries to review IPV introduction plans and ensure vaccine availability in line with recommendations for polio vaccination in 2015 and the tOPV – bOPV switch.

### **3. IPV Introduction**

The ITAG applauds the continued commitment of Member States to initiate the Polio Endgame Strategies including the introduction of inactivated polio vaccines (IPV) during 2015. ITAG recognizes that ten countries already have introduction plans. Thailand is currently in the process of finalizing their plans. ITAG notes that in order to synchronize with the April 2016 expected timing of the global switch from tOPV to bOPV, all the countries will be required to introduce IPV by September 2015.

*ITAG recommends that:*

- a. WHO SEARO should provide countries with technical assistance for the timely introduction of IPV.
- b. WHO SEARO to provide additional support and guidance on the issue of IPV and bOPV registration and licensing.

### **4. Measles and rubella surveillance and immunization**

The ITAG is encouraged by the countries' commitment to the Regional goal of Measles Elimination and Rubella/CRS Control by 2020. The ITAG concludes that all countries are making efforts to put in place the necessary programme components leading to this goal, including building laboratory capacity, putting in place systems to conduct case-based reporting, and implementing data feedback mechanisms. ITAG clearly recognizes that with the integrated measles and rubella strategy, and the use of a combination vaccine (MR or MMR) that rubella/CRS will also be eliminated.

The ITAG will monitor a number of milestones that must be met to ensure that the Region remains firmly on track for measles elimination and rubella/CRS control by 2020.

*ITAG recommends, and will monitor, the following operational milestones:*

- (1) By the end of 2014:
  - a. Regional surveillance guidelines and national action plans will be in place.
  - b. All countries will have initiated case-based reporting of measles/ rubella.
  - c. Finalize plans to achieve, maintain and verify at least 95% population immunity against both measles and rubella in all age cohorts.
  - d. Individual case-based data should be reported monthly to the WHO country office and WHO SEARO in line with reporting requirements.
- (2) By the end of 2015:
  - a. Case-based surveillance for measles and rubella will be fully operational in all countries except for India and Indonesia which will be expanding case-based surveillance (see 3.c.).
  - b. All countries will have initiated sentinel surveillance for CRS.
  - c. Susceptibility profile of populations to measles and rubella in all countries will have been described.
  - d. A Regional Verification Commission will have been established and a National Verification Committee established in every country.
  - e. All countries will have adequate access to an accredited national and reference laboratory (ies).
- (3) By the end of 2016:
  - a. All countries in the Region will have an optimal two-dose measles-rubella containing vaccine schedule.
  - b. All countries will have conducted high quality wide age-range immunization campaigns against both measles and rubella.
  - c. India and Indonesia will have fully operational nationwide case-based, laboratory supported measles/rubella surveillance with strong links to outbreak investigations and inclusion of line-listed cases from confirmed outbreaks in the case-based system.
  - d. All countries to plan for evaluations of the impact of the nationwide wide age-range MR campaigns and plan for follow-up narrower age-range MR campaigns.

In addition, the ITAG urges **Thailand** to conduct a nationwide wide age-range serosurvey for measles and rubella at the provincial level or lower and report back to the ITAG at its next meeting the results of the serosurvey and its national plan to achieve the 2020 goals. Thailand should specify their plans to close any immunity gaps found and report back to the ITAG in 2015.

The ITAG understands that **Indonesia** has made significant progress decreasing measles and rubella cases through immunization, but significant challenges remain in achieving the 2020 measles elimination and rubella/CRS control goal. ITAG recommends Indonesia to determine the population immunity profile, develop plans for a nationwide wide age-range MR campaign by ITAG 2015, and conduct the SIA by 2016. Indonesia and the partnership should explore options to secure MR vaccine supply and operational costs.

The ITAG encourages **Myanmar** to implement a high-quality MR campaign as planned in early 2015, followed by MR vaccine introduction in routine, and a national coverage survey and to report back on EPI coverage at the 2015 ITAG meeting.

The ITAG is very pleased to note that **India** conducted a post introduction evaluation (PIE) of measles second dose (MSD) and is planning for MR introduction, with a campaign targeting children 9 months to <15yrs of age. The ITAG recommends that by the next ITAG in 2015, the country incorporate the recommendations of the PIE into their health plans and into the planning for MR introduction into routine. ITAG strongly recommends all that states give rubella vaccine



with both doses of measles vaccine. The ITAG would like to review at the 2015 meeting the plans for an expansion of the laboratory network as case-based surveillance is initiated in 2015.

The ITAG recommends that **Timor-Leste** introduce two doses of MR containing vaccine by 2015.

The ITAG recognizes the progress that **Nepal** has made and the high coverage reached by the MR campaign, and recommends the country introduce a second dose of MR vaccine into the routine vaccination schedule and expands the case-based surveillance system to cover all health facilities in the country.

The ITAG recognizes that **DPR Korea** has controlled measles well, perhaps already having eliminated measles. ITAG recommends DPRK conduct a nationwide serosurvey for rubella (across a wide age-range) and for measles, and to introduce a two dose schedule with a measles and rubella containing vaccine. Based on the results of the serosurvey, ITAG recommends DPRK conduct an MR campaign to close any immunity gaps. ITAG requests DPRK to complete the serosurvey and plans for MR introduction and campaign before the ITAG 2015 and report on these at the meeting.

The ITAG notes that **Bhutan, DPR Korea, Maldives, and Sri Lanka** may possibly have eliminated measles. These Member States should begin the process of verifying measles elimination and report back at the next meeting in 2015 on their progress to date.

Specifically related to the MR laboratory network, the ITAG recommends that:

- a. Laboratories should be scaled up to be fully functional to meet the demands of greater number of tests and with a turnaround time within 4 days.
- b. **Timor-Leste** should enhance its current laboratory to “proficient” status in order to support case-based surveillance.
- c. Laboratory capacity should be enhanced to provide the genotype data for measles and rubella required to identify indigenous transmission, sources of infection and imported and import-related cases.
- d. By 2016, for verifying interruption of indigenous transmission and to identify imported and import-related cases, measles virus genotypes should be characterized in at least 80% of chains of transmission.
- e. By the end of 2015, all member states should share genotype information in timely fashion.
- f. WHO SEAR should provide a training workshop on laboratory aspects of CRS in 2015.

The ITAG requests WHO-SEARO to provide an annual report on the progress towards reaching these milestones. The report will be provided to all ITAG members at least once a year prior to the annual ITAG meeting.

#### **5. Assessing population immunity and defining susceptible populations for action**

The ITAG recognizes that countries have the capacity and will need to commit to activities related to assessing population immunity, to identify susceptible populations (geographic, age groups, etc) and develop plans for MR vaccination activities. These vaccination activities, routine and campaign, are required between now and 2016 to ensure that the Region remains firmly on track for measles elimination and rubella/CRS control by 2020.

*ITAG recommends that:*

#### **By 2015:**

- a. All countries should describe population susceptibility with the purpose of preventing outbreaks of measles and rubella and report back to ITAG 2015.

- b. All countries should produce annual population immunity profiles and report to ITAG annually.

**By 2016:**

- a. Countries should identify their remaining susceptible populations following their nationwide wide age-range MR catch-up campaigns should conduct MR follow-up campaigns to achieve 95% immunity.

## **6. CRS Sentinel Surveillance**

ITAG recognizes the countries' commitment to the Regional goal of Measles Elimination and Rubella/CRS Control target by 2020. The ITAG acknowledges that Sri Lanka and Bangladesh already have CRS sentinel surveillance systems in place and have demonstrated that this is feasible. The ITAG concluded that all countries are making efforts to put in place the necessary components towards this goal, including building laboratory capacity, putting in place systems to conduct case-based reporting, and data feedback mechanisms.

ITAG acknowledges that the countries will need to commit to several actions between now and 2016 in order to ensure that the Region remains firmly on track for measles elimination and rubella/CRS control by 2020:

*ITAG recommends that:*

**By 2014:**

- a) For countries that have established CRS sentinel surveillance, a plan should be in place to conduct an evaluation of the surveillance system (may include retrospective review of data from the reporting sites).

**By 2015:**

- a) All countries should have initiated sentinel surveillance for CRS.
- b) For countries with established CRS sentinel surveillance, they should use CRS data in conjunction with case-based rubella data to monitor the progress of the rubella control programme.
- c) All countries with CRS sentinel surveillance should report data to the Regional office.

## **7. Japanese Encephalitis**

ITAG recognizes that there has been significant progress in JE control and prevention in the last few years in the ten countries that have JE. Surveillance has been established or strengthened in several countries; vaccine introduction with campaigns in select high risk areas (India, Nepal) or nationwide vaccination (Sri Lanka, Thailand); countries with well-established vaccination programmes are piloting or switching to newer vaccines and are evaluating vaccine impact through surveillance or case-control studies; operational research has been carried out in the Region. New opportunities, including two WHO-prequalified JE vaccines, GAVI financing for eligible countries and a renewed support from partners, now exist to achieve even greater control of the disease.

ITAG also recognizes that the surveillance data are not yet sufficient (in volume, breadth, quality, and/or laboratory confirmation) in some countries; data on JE sequelae are not available. Guidance and tools to use country level data for designing policies and strategies including JE vaccine introduction are still required. While mosquito control can be part of JE control programme, vaccination against JE is essential.

*ITAG recommends that:*

- a. Countries without adequate JE/AES surveillance data should establish or strengthen sentinel surveillance;
- b. Of the ten countries that have JE, those that are not vaccinating should establish disease burden to guide the development of a national policy for vaccination;
- c. Countries should analyse available JE/AES data to inform national policies on vaccine use and to track progress with disease control;
- d. Where it is not feasible to conduct vaccination in all affected areas at once, countries may consider a phased introduction;
- e. All countries that have introduced JE vaccine should have mechanisms to monitor JE immunization coverage, to verify immunization status and to conduct surveillance or special studies to evaluate vaccine effectiveness/impact;
- f. SEARO should develop Regional policy guidelines for JE control and prevention.

#### **8. Maternal and Neonatal Tetanus Elimination**

ITAG recognizes that the South-East Asia Region has achieved impressive results in validating MNT elimination in all countries except India and Indonesia, and that the Region has a strong chance of achieving MNT elimination goal by 2015.

ITAG acknowledges that after the validation of MNT elimination, countries will need to assess the status through an annual review in order to sustain MNT elimination.

*ITAG recommends that:*

- a. India and Indonesia should verify elimination status by the end of 2015.
- b. In order for countries to maintain elimination status, to conduct annual data reviews to assess MNT Risk status and to take action as appropriate.

#### **9. Influenza Prevention and Control**

The ITAG recognizes that there is evidence of significant year round seasonal influenza burden in this Region, and that Thailand is the only country in the Region that offers influenza vaccination through EPI. Furthermore, the ITAG recognizes the importance of delivering seasonal influenza vaccination to high-risk groups, in particular pregnant women and health care workers, to mitigate its health and economic impact in the Region. Furthermore, the ITAG notes the significance of the influenza vaccine for effectively responding to future influenza pandemics, as well as sustaining the Regional influenza vaccine manufacturing capacity. Predictable demand in the countries is required to sustain the flu vaccine manufacturing capacity in the Region.

*ITAG recommends that:*

- a. The countries in the Region should develop national policies on seasonal influenza vaccines for high-risk groups: pregnant women, children aged 6 – 59 months, the elderly, individuals with specific chronic medical conditions and health care workers;
- b. All countries in the Region should develop a plan for generating evidence or collating existing evidence for decision-making by the 2016 ITAG;
- c. All countries should strengthen influenza surveillance, establish disease burden and share data with WHO SEARO.

#### **10. Effective Vaccine Management**

ITAG recognizes that high quality vaccine supply chain management can only be achieved if all of the components in the supply chain comply with recommended storage and distribution practices,

and that the Effective Vaccine Management( EVM) initiative provides the guidelines and materials to support countries to improve their supply chain performance.

*ITAG recommends that:*

- a. Countries conduct Effective Vaccine Management (EVM) assessments and prepare EVM Improvement Plans with clearly defined roles and responsibilities which address gaps identified and the plan for how monitoring will occur regularly, and report to ITAG annually.
- b. Countries use 30-Day Temperature Recorders at national and sub-national levels with properly trained personnel.
- c. Countries establish real-time monitoring systems using innovative tools for the availability of data (e.g. temperature, cold chain equipment functionality, vaccine stock level).

#### **11. Adverse Events Following Immunization**

ITAG recognizes that the South-East Asia countries have made significant progress to implement post-marketing vaccine safety surveillance. However, in order to increase detection and investigation capacity, countries need to further develop a training strategy to reach out to frontline healthcare workers and to enhance capacity at district and regional levels to detect and report AEFIs.

*ITAG recommends that:*

- a. Countries develop guidelines to plan and to conduct field investigation of serious AEFI and report back to 2015 ITAG.
- b. WHO-SEARO to explore the role of autopsies in detecting AEFIs and to bring in guidelines as to how to more effectively capture AEFI deaths.

#### **12. Pooled procurement mechanisms**

ITAG recognizes that the smaller countries (Bhutan, Maldives and Timor Leste) may need to review vaccine procurement policies to continue with UNICEF supplied vaccine (procurement service mechanisms) or procure vaccine directly in compliance with Good Procurement practices principles. In the meantime,

*ITAG recommends that:*

- a. Countries share procurement models to both enhance vaccine product and market knowledge, as well as guide policy makers in making informed decisions on their procurement policies.
- b. WHO-SEAR should provide guidelines and lessons learned from other pooled procurement experiences to share with relevant countries.

*(The full report of SEAR-ITAG will be placed on IVD/SEAR website)*

**23<sup>RD</sup> MEETING OF THE TECHNICAL ADVISORY GROUP (TAG) ON  
IMMUNIZATION AND VACCINE-PREVENTABLE DISEASES  
IN THE WESTERN PACIFIC REGION**

**Manila, 17–20 June 2014**

**I. MEASLES ELIMINATION**

Preamble

In the light of the global burden of rubella and congenital rubella syndrome (CRS), the 2011 WHO rubella position paper recommends that countries take the opportunity offered by measles elimination activities to increase coverage with rubella-containing vaccines (RCVs). These measles vaccine delivery strategies provide an opportunity for synergy and a platform for advancing rubella and CRS elimination through the use of combined measles-rubella (MR) or measles-mumps-rubella (MMR) vaccines. In addition, surveillance for rubella can be integrated with measles surveillance through an integrated fever and rash surveillance system supported by the global measles and rubella laboratory network.

TAG notes the benefits of fully integrating rubella/CRS prevention with measles elimination and encourages all countries in the Region to plan, implement and evaluate both control efforts together. The 23rd TAG meeting included separate sessions for measles elimination and rubella/CRS prevention, hence this report will summarize these sessions under separate headings. Future TAG meetings will consider both diseases together in a single session.

Conclusions

The TAG notes the progress towards the 2012 regional measles elimination goal. The establishment of national verification committees (NVCs) and submission of annual progress reports documenting progress towards or achievement of measles elimination is a significant achievement. The TAG congratulates the four countries and areas (Australia, Macao [China], Mongolia, and the Republic of Korea) that were verified as having achieved the interruption of endemic measles virus transmission for a period of at least 36 months from the last known endemic case.<sup>1</sup> At the same time, these countries will need to be vigilant and sustain their achievements including an annual review and report of their status.

The TAG notes the resurgence of measles virus transmission in the Region that started in 2013 primarily in countries that had conducted nationwide measles containing vaccine supplementary immunization activities (SIAs) in 2010 and 2011. Increased burden of measles disease in 2013 and the first half of 2014 has been related to imported, import-related and endemic measles virus transmission.

The TAG notes the change in the age distribution of measles in some countries with cases among infants (including measles-related deaths) and adults. This age pattern has been observed in other countries and should be expected when vaccination has prevented most measles cases among age groups eligible for vaccination. However, in all countries experiencing outbreaks, the majority of measles cases in vaccine-eligible children are not fully vaccinated or have unknown vaccination status suggesting failure of the programme to vaccinate these children on schedule.

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<sup>1</sup> WHO. Guidelines on Verification of Measles Elimination in the Western Pacific Region. 2013: [http://www.wpro.who.int/immunization/documents/measles\\_elimination\\_verification\\_guidelines\\_2013/en/](http://www.wpro.who.int/immunization/documents/measles_elimination_verification_guidelines_2013/en/)

There is inadequate evidence to support the use of measles vaccine among infants younger than six months of age. Therefore, measles vaccine is not recommended among infants younger than six months of age. The strategy to prevent cases among infants younger than six months of age is to increase population immunity to stop the spread of measles (i.e. achieve herd immunity).

Priority activities to prevent future large scale measles outbreaks include: (1) maintenance and strengthening of current strategies (achievement of  $\geq 95\%$  coverage with two-doses of measles-rubella vaccine in the routine immunization programme, and MR catch-up and follow up SIAs as needed); and (2) proactive implementation of additional strategies including developing and implementing post-SIA activities to sustain the gains in population immunity obtained by the SIAs.

### Recommendations

1. All countries should maintain and strengthen routine immunization to achieve  $\geq 95\%$  coverage with two doses of MR-containing vaccine (MRCV) in the routine immunization programme in a schedule according to published WHO recommendations.<sup>2,3,4,5</sup> The TAG considers the use of single-antigen rubella vaccine as a missed opportunity to prevent measles.
2. Because of the importance of international spread among travellers, countries should take steps to encourage persons to be fully vaccinated prior to international travel to measles-endemic or -infected countries and areas.
3. Immunization programme managers should regularly review measles vaccination coverage (down to the lowest administrative unit), measles surveillance data (including age by vaccination status of cases), and programme capacity (vaccine supply, human resources) to identify communities at risk. This risk assessment should be used to mobilize additional resources to reinforce immunization services in high risk areas/marginalized groups. The U.S. Centers for Disease Control and Prevention and WHO are developing a measles risk assessment tool that should be available by 2015.
4. All countries and areas should have an outbreak response plan and maintain a sensitive epidemiological surveillance system supported by accredited laboratories to support timely detection of importations and outbreaks with prompt implementation of outbreak response measures. All outbreaks should be investigated, appropriate specimens collected and submitted to the laboratory, and chains of transmission documented. The age distribution of cases should be carefully examined to appropriately target outbreak response measures.
5. All WHO Western Pacific Region network laboratories should identify and share measles genotype information from all chains of transmission in collaboration with the Regional Office.
6. All countries and areas should continue to review and evaluate their progress toward or maintenance of measles elimination and NVCs should submit annual reports to the Regional Verification Commission (RVC) that document progress toward, achievement or maintenance of measles elimination.
7. Appropriate infection control measures and health care facility practices should be implemented to prevent transmission of measles and rubella in the health care setting, especially

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<sup>2</sup> Measles vaccine: WHO position paper. WER. No. 35, 2009, 84, 349–360; <http://www.who.int/wer>.

<sup>3</sup> Rubella vaccines: WHO position paper. WER No. 29, 2011, 86, 301–316; <http://www.who.int/wer>

<sup>4</sup> Meeting of the Strategic Advisory Group of Experts on immunization, November 2012 – conclusions and recommendations. WER. No. 1, 2013, 88, 11–13. <http://www.who.int/wer>

<sup>5</sup> Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. WER. No. 1, 2014, 89, 11–14. <http://www.who.int/wer>

in hospitals. These plans should include strategies to ensure that all health workers are immune to measles and rubella.

8. Appropriate measles case management protocols including vitamin A administration and antibiotics to treat secondary bacterial infections should be implemented to reduce morbidity and mortality associated with measles disease.<sup>6,7</sup>

9. Countries experiencing measles outbreaks should:

- To prevent measles virus transmission among pre school-aged children who are at highest risk of dying from measles, the second routine dose should ideally be given in the second year of life. Supplementary vaccine doses should be considered for unvaccinated children six months and older who are not yet age eligible for the first dose of measles-containing vaccine (MCV1) in the national immunization programme and who are at high risk of exposure to measles virus such as in outbreak settings or expected travel to measles affected areas. Children who receive supplementary measles vaccine doses prior to the country's recommended age for MCV1, should continue to receive the two doses of MR vaccine according to the national immunization schedule. School entry should be used as an opportunity to ensure that all children have two documented doses of MR vaccine prior to school entry.
- Analyse why measles outbreaks are occurring by conducting thorough outbreak investigations and conducting operational research to identify persons and groups at increased risk for acquiring measles, characteristics of unvaccinated persons and barriers to vaccination. Considerations include language or cultural barriers among minority populations, access for immigrant or mobile populations or other marginalized or socio-economically disadvantaged groups, vaccine refusal/hesitation, etc.
- Ensure high quality SIAs are conducted based on detailed analysis of and lessons learned from the past SIAs, for example, developing a mechanism to obtain better and reliable vaccination coverage estimates at subnational levels and to monitor identification and vaccination of unvaccinated children in previous immunization sessions.
- Conduct statistically valid post-SIA coverage surveys to document the coverage achieved.
- Review contents and implementation of the national surveillance guidelines and enhance surveillance activities including aggressive case detection or outbreak investigation after the SIA.
- Regularly (for example, annually) review and identify immunity gaps by geographic area (for example, district) and by birth cohort.
- Proactively take corrective actions to fill the immunity gaps, for example, selective immunization activities, smaller-scale (region-wide or province-wide) SIAs or more frequent follow-up SIAs targeting birth cohorts born after the last SIA in specific regions or provinces.

10. Countries with endemic measles virus transmission should update their national plans and develop or update subnational plans and strategies with special focus on high-risk groups and areas and on population immunity gaps.

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<sup>6</sup> Managing measles: Integrated case management reduces disease severity. BMJ. Vol 314, 1 Feb 1997:316-7.

<sup>7</sup> WHO. Pocketbook of Hospital care for children: Guidelines for the management of common illnesses with limited resources. 2013:174-178.

11. WHO should work with other international partners in supporting countries to plan and conduct the above-recommended actions.

## **II. POLIOMYELITIS (POLIO) ERADICATION**

### Conclusions

1. The TAG welcomes the conclusion of the 19<sup>th</sup> Meeting of the Regional Commission for the Certification of Poliomyelitis Eradication (RCC) regarding the polio-free status of the Region.
2. The TAG notes the draft plan, Polio Endgame in the Western Pacific Region, and acknowledges the progress made at the country and regional level in implementation of the global Polio Eradication and Endgame Strategic Plan. The progress includes identification of inactivated polio vaccine (IPV) introduction dates by most countries, registration of IPV in nearly all necessary countries, and initiation of funding requirements discussions.
3. The TAG notes that acute flaccid paralysis (AFP) surveillance indicators in some countries do not meet recommended standards in the first half of 2014.
4. The TAG raises concern that based on current progress, some countries are at risk of missing the global deadlines for IPV introduction by the end of 2015.

### Recommendations

1. The TAG recommends that all countries:
  - (a) improve AFP surveillance at the subnational level as outlined by the 19<sup>th</sup> RCC;
  - (b) analyze polio vaccination coverage among non-polio AFP cases to identify immunity gaps and undertake activities to maximize population immunity, particularly in preparation for the withdrawal of type 2-containing OPV;
  - (c) ensure that any wild or vaccine-derived poliovirus is detected in a timely manner and that a rapid response is initiated following detection; and
  - (d) begin planning for the containment of wild and vaccine-related type 2 polioviruses as per the endgame strategy by reviewing their inventories and destroying unnecessary stool specimens, thereby reducing the number of facilities with potentially infectious poliovirus-containing material.
2. Countries conducting environmental surveillance (Australia, China, Japan and Malaysia) should identify and characterize polioviruses using WHO-recommended methods and results should be shared with the WHO Regional Office for the Western Pacific at least on a monthly basis. Any wild or vaccine-derived poliovirus detected should be reported to WHO within 24 hours of assessment.
3. China provincial polio laboratories should work toward achieving the global timeline of 14 days for virus isolation.
4. All countries should develop national polio endgame plans. Exclusively oral polio vaccine (OPV)-using countries should finalize plans according to the timeline recommended by the Polio Oversight Board and reaffirmed by the Strategic Advisory Group of Experts on Immunization (SAGE):



- (a) by mid-2014 for countries in Tier 1 (China) and Tier 2 (Cambodia, Lao People's Democratic Republic, Papua New Guinea and Philippines); and
- (b) by end-2014 for countries in Tier 4 (Cook Islands, Fiji, Kiribati, Mongolia, Nauru, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, and Viet Nam).

These plans should include plans for IPV introduction and related communications and operational requirements. Since the temperature requirements of IPV are different from that of OPV, appropriate cold chain modifications should be made. Exclusively OPV-using countries that have not yet initiated development of this plan (Cambodia, Mongolia, Nauru, Samoa, Solomon Islands, Tonga, Tuvalu, Viet Nam) should do so urgently and should update the WHO Regional Office for the Western Pacific quarterly on progress. The TAG requests the Regional Office to provide technical support to countries in preparing these plans.

5. All exclusively OPV-using countries and areas that have not already done so should communicate a formal decision and date for IPV introduction to the WHO Regional Office for the Western Pacific. Countries are expected to introduce IPV by November 2015 as recommended by the Polio Oversight Board to ensure preparedness for the global switch from trivalent OPV to bivalent OPV tentatively planned for April 2016.
6. Countries should assess the financial requirements to implement all components of the polio endgame, including surveillance, containment, and IPV introduction, at the national level, and should identify funding sources as soon as possible. GAVI-eligible countries that have not yet submitted an application to GAVI for IPV support (Cambodia, Mongolia, Solomon Islands and Viet Nam) should apply in September 2014, or identify an alternative funding source before then.
7. The TAG notes that a communications plan for the polio endgame is being developed by WHO and encourages countries to use the document as a reference for the development of national communications plans for the polio endgame.

### III. RUBELLA ELIMINATION

#### Conclusions

The TAG notes that rubella infection affects a significant number of women of reproductive age in the Region. Some of these infections result in the babies being born with congenital rubella syndrome. Data from mathematical models suggests that there is a significant burden of CRS, miscarriages, and fetal deaths due to congenital rubella infection (CRI) in countries not implementing rubella control strategies. Therefore, the TAG reaffirms its 2013 recommendation that the Western Pacific Region should establish a regional goal for rubella elimination.

Most Member States in the Western Pacific Region are already implementing the immunization strategies needed to achieve measles elimination and most countries are now using measles and rubella combination vaccines to achieve measles elimination. Recognizing that rubella is less contagious than measles<sup>8</sup> and that full implementation of measles elimination strategies provides an opportunity to achieve rubella elimination, the TAG reaffirms that the

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<sup>8</sup> Basic reproduction rate ( $R_0$ ) (in developed countries) and implied crude herd immunity threshold ( $H$ ) of measles are 12-18 and 92-94, respectively, while  $R_0$  and  $H$  of rubella are 6-7 and 83-86, respectively

Region should utilize the measles elimination platform and strategies to achieve rubella elimination.<sup>9</sup>

### Recommendations

1. The TAG requests the Regional Director to seek endorsement of a regional rubella elimination goal (target date to be determined) by Member States in the Regional Committee Meeting in 2014.
2. The TAG encourages Member States to utilize the momentum for achieving measles elimination to develop a national policy, plans and strategies to eliminate rubella and prevent CRS in the context of their national policy and strategies for measles elimination and to utilize and enhance the synergy between the elimination initiatives. The TAG recommends the WHO Regional Office for the Western Pacific to provide support to Member States in developing national policies, plans and strategies to eliminate rubella.
3. The TAG encourages all Member States to investigate suspected rubella cases in an integrated measles-rubella case-based surveillance system. Investigation should include collecting appropriate specimens for laboratory confirmation and genotyping. Member States should submit rubella case-based data (including final classification of suspected cases as laboratory confirmed, epidemiologically linked, clinically compatible or discarded; and source of infection as endemic, imported, import-related, or unknown) on a monthly basis to the WHO Regional Office for the Western Pacific beginning in January 2015. The TAG requests the Regional Office to continue providing technical support to countries and areas to analyze data and describe the country-specific epidemiology of rubella including immunity gaps by sex and age.
4. The TAG encourages all Member States to conduct surveillance for CRS by strengthening the routine reporting of clinically confirmed CRS cases using the WHO clinical case definitions and/or establishing sentinel site surveillance for CRS. WHO is developing guidelines for CRS surveillance which should be available by the end of 2014.
5. TAG endorses the recent SAGE recommendations and encourages countries to give the first dose of RCV with the first dose of MCV as MR or MMR, because coverage with the first dose of MCV is usually higher than for the second dose and immunogenicity is equally high. Although vaccine manufacturers may restrict indications to children  $\geq 12$  months of age, the safety and immunogenicity of rubella and mumps combination vaccines among children 6 to 12 months of age are well-established. Combination MR and MMR vaccines can be safely used for MCV1 among children 8 to 12 months of age according to the national immunization schedules for MCV1 and for supplementary doses among children 6 months and older in outbreak settings.
6. The TAG considers the use of single antigen measles vaccine as a missed opportunity to prevent rubella and CRS. The TAG endorses the recent SAGE recommendations and encourages countries using different MCVs (that is, measles (M), MR or MMR) for the first and second routine doses to use the same vaccine (either MR or MMR) for both routine doses to simplify vaccine procurement, logistics, recording, and reporting, and to increase coverage and decrease vaccine wastage. These programmatic advantages likely outweigh the marginal increase in vaccine cost. Combination vaccines (MR or MMR) should be used when providing supplementary doses.

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<sup>9</sup>Rubella vaccines: WHO position paper. WER No. 29, 2011, 86, 301–316; <http://www.who.int/wer>

7. For countries that have not yet introduced rubella containing vaccine into the national immunization schedule (Viet Nam, Papua New Guinea, Vanuatu), to quickly increase population immunity, rubella-containing vaccine should be introduced following the implementation of wide age-range catch-up campaigns targeting children up to at least 15 years of age and based on rubella epidemiology. For countries that have recently introduced rubella-containing vaccine without first conducting a wide age-range catch-up campaign (China, Philippines, Solomon Islands), additional strategies should be considered to target both males and females to comprehensively fill immunity gaps. These strategies may include offering measles-rubella containing vaccine in schools, in colleges or universities, to health workers, to military and police, at other work sites, etc.
8. The TAG recommends the WHO Regional Office for the Western Pacific to continue to dialogue with countries to develop a consensus on the appropriate target year for rubella elimination in the Region.

#### **IV. HEPATITIS B CONTROL**

##### Conclusions

The TAG is pleased with the progress towards achieving the regional hepatitis B control goal of reducing hepatitis B chronic infection among 5 year-old children to less than 1% by 2017. The progress is due to the commitment and actions of Member States and is a true public health success story. The TAG recognizes that additional efforts are needed to achieve the 1% goal in all countries and areas, and to sustain the progress made. The TAG recognizes that World Health Assembly Resolution 67.6, which promotes comprehensive viral hepatitis prevention and control, provides a broader context for the prevention of hepatitis B through vaccination.

##### Recommendations

1. The TAG reaffirms the importance of providing a birth dose of hepatitis B vaccine to all newborns within the first 24 hours of life. Newborns that have not received hepatitis B vaccine within 24 hours should receive it as soon as possible thereafter.
2. The TAG recommends convening a consultation on strategies for increasing and sustaining hepatitis B vaccine birth dose coverage. The consultation would focus on developing action plans to implement strategies for improving birth dose vaccination coverage.
3. Because of the high risk of infection of health workers in the work setting, the TAG requests the Regional Director to advocate for the endorsement of a goal to introduce health worker hepatitis B vaccination policies in all countries and areas.
4. The TAG endorses the updated Western Pacific Region Strategic Action Plan for Hepatitis B Control Through Immunization, 2014-2019.
5. The TAG requests countries that require programme improvements to achieve the regional hepatitis B control goal to develop action plans to meet the regional goal by 2017.
6. The TAG endorses the 2013 Western Pacific Region Hepatitis B Expert Resource Panel recommendations.

7. The TAG endorses the development of a regional hepatitis B laboratory network in order to support the achievement of the regional hepatitis B goal. The TAG recognizes that resources will need to be secured under the leadership of WHO and Member States.

## **V. ACCELERATED CONTROL OF JAPANESE ENCEPHALITIS (JE)**

### Conclusions

JE virus is maintained in the environment in a zoonotic cycle among mosquitoes, birds and pigs. Human vaccination is the single most important control measure for JE disease. The TAG notes several important advances in JE control during the past year. There are several high quality JE vaccines available and two are now WHO-prequalified, facilitating procurement through United Nations agencies and with GAVI support. GAVI included JE vaccine among its supported vaccines in 2014 and the Lao People's Democratic Republic was the first country to apply for this support. Also, there were modest increases in donor support for JE surveillance and related activities. These advances support the establishment of a regional goal for accelerated control of JE as recommended by the TAG in 2013 and submitted for consideration and endorsement by the Regional Committee in October 2014.

As previously noted, expert consultation is needed to determine the appropriate targets and timeframe for the goal, and to identify strategies for achieving it. The SAGE review of JE vaccines and revision of the WHO position paper on JE vaccines in 2014 will provide supportive guidance on these strategies. JE surveillance is not systematic in some areas and is fragmented into multiple systems, hindering data analysis and interpretation. These weaknesses in surveillance limit efforts to estimate disease burden, define target populations for vaccination, and measure impact of vaccination in some countries. Synthesis of JE data from surveillance, outbreak reports, research studies and other sources has helped to fill this gap and provide evidence for decision-making in some countries.

### Recommendations

1. The TAG requests the WHO Regional Office for the Western Pacific to develop the targets, timelines and strategies to achieve a JE accelerated control goal through consultation with experts and Member States during the coming year.
2. The TAG reiterates the recommendation of the 22<sup>nd</sup> TAG that JE surveillance with laboratory confirmation should be further strengthened in endemic areas of the Western Pacific Region, and sentinel surveillance should be strengthened and made more systematic to facilitate reporting at the regional level.

## **VI. MATERNAL AND NEONATAL TETANUS (MNT) ELIMINATION**

### Conclusions

The TAG congratulates the Lao People's Democratic Republic on the 2013 achievement of validation of MNT elimination. The TAG also commends the progress made in Cambodia, Papua New Guinea, and the Philippines towards the 2015 MNT elimination goal and is pleased to note that all three countries have plans for validating MNT elimination in 2015. The TAG notes that vaccination is only one of multiple strategies that can be used to achieve MNT elimination including promoting health facility-based or clean deliveries, presence of skilled birth attendants, and safe cord care practices.

### Recommendations

1. The TAG urges the three remaining countries in the Western Pacific Region to implement their planned activities, to conduct pre-validation assessments and to complete validation surveys by end of 2015 in order to meet the 2015 global goal for MNT elimination.
2. The TAG further recommends that all countries and areas that have achieved elimination should annually review the WHO/UNICEF district data spreadsheet to identify low performing areas and implement appropriate corrective actions.

## **VII. EVIDENCE-BASED INTRODUCTION OF NEW VACCINES**

### Conclusions

The TAG notes that low-income and middle-income countries in the Western Pacific Region have made significant progress in introducing new and underutilized vaccines in the past year, yet still lag far behind high-income countries in including new vaccines in their national immunization programmes. An increasing number of Member States are gaining experience in collecting and evaluating evidence for vaccine introduction decision-making. Development of national plans for evidence-based introduction of new vaccines would facilitate a systematic approach to this process. WHO plays an important role in providing technical support and capacity building for the development and implementation of these plans, including the collection and evaluation of relevant evidence. Surveillance supported by laboratory confirmation is a key source of such evidence and the quality of surveillance requires consistent attention.

### Recommendations

1. Before making a decision on new vaccine introduction, countries should evaluate evidence on disease burden including surveillance, cost, the role of other disease prevention and control measures, vaccine characteristics, vaccine supply, and immunization programme and health system strength, as further detailed in the recently published WHO guidance, Principles and Considerations for Adding a Vaccine to a National Immunization Programme.
2. The TAG reiterates its advice that each Member State develops a national plan for evidence-based introduction of new vaccines in coordination with NITAGs or similar groups. This plan could be part of the comprehensive multi-year plan for immunization or other health plans. The TAG urges countries in which surveillance includes laboratory confirmation for diseases targeted by new vaccines to monitor and improve the quality of surveillance implementation.
3. The TAG requests WHO to provide guidance, technical support and capacity-building for development and implementation of national plans for evidence-based introduction of new vaccines.
4. The TAG requests countries introducing new vaccines to use the opportunity to strengthen health systems and to scale-up implementation of complementary interventions against the targeted diseases, as exemplified by guidance in the Global Action Plan for Pneumonia and Diarrhoea and Comprehensive Cervical Cancer Prevention and Control.

## **VIII. MEETING REGIONAL VACCINATION COVERAGE TARGETS**

### Conclusions

1. The TAG acknowledges the efforts countries are making to find innovative approaches to reach underserved populations, though the TAG also notes the uneven progress at subnational levels towards achieving vaccination coverage targets.
2. The TAG takes note of the need to improve the quality of the data countries are collecting and reporting, including coverage and financing-related data.

### Recommendations

1. Countries with either stagnant or declining vaccination coverage or prolonged vaccine-preventable disease outbreaks should consider conducting comprehensive programme reviews to identify crucial underlying factors that prevent achieving acceptable levels of population immunity and to define approaches to address them. This should include efforts to increase community demand and improve service delivery. Cambodia and Mongolia are two promising examples.
2. Countries are encouraged to review the quality of immunization data at all administrative levels annually and to use the data to improve programme performance and periodically perform in-depth data quality assessments, including surveys.
3. Countries are encouraged to analyze coverage data at all levels regularly and take action in low-performing areas. Countries are requested to share subnational coverage data annually with the WHO Regional Office for the Western Pacific according to a format to be provided.
4. The WHO Regional Office for the Western Pacific is requested to support countries by providing guidance on new information and communication technologies to improve the recording and reporting of data.

## **IX. REGIONAL FRAMEWORK FOR IMPLEMENTATION OF THE GLOBAL VACCINE ACTION PLAN IN THE WESTERN PACIFIC 2013-2020**

### Conclusions

1. The TAG welcomes the final draft of the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific 2013-2020, appreciates the broad consultation made in this process and supports the WHO Regional Office for the Western Pacific to seek endorsement for this framework from the Regional Committee.
2. Ensuring vaccine safety is an essential component of immunization programmes. The TAG appreciates that the WHO Regional Office for the Western Pacific and Member States have taken initiative to strengthen the adverse events following immunization (AEFI) surveillance system and the responses to vaccine safety incidents in some countries. The TAG noted that the Region's AEFI surveillance systems still require strengthening in many countries and areas.
3. The TAG notes that national regulatory authority (NRA) systems and functions for vaccines require strengthening in many countries and areas. The TAG appreciates that the WHO Regional Office for the Western Pacific and Member States have taken initiative to

formulate and operationalize a regional alliance to coordinate and support countries in developing or strengthening NRA systems.

4. Communication and social mobilization are essential components of an immunization programme. Immunization Week is a mechanism to promote immunization as a crucial public health programme to protect individuals and communities from vaccine-preventable diseases.
5. The TAG notes country concerns about vaccine prices that limit vaccine introduction and vaccine stock-outs that affect programme operations.

#### Recommendations

1. The TAG supports the WHO Regional Office for the Western Pacific in seeking Regional Committee endorsement of the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific and advocates that countries utilize the framework.
2. TAG encourages existing national technical advisory groups on immunization to discuss the immunization goals proposed in the Regional Framework for Implementation of GVAP in the Western Pacific and to formulate evidenced-based national policies to achieve these goals.
3. The TAG reiterates the recommendation made during the 20th TAG meeting that all Member States should emphasize strengthening the AEFI surveillance system.
  - The TAG encourages all countries to emphasize the importance of immunization safety practices for maintaining high quality immunization services.
  - The TAG advises all countries to strengthen the AEFI surveillance system, especially when vaccines are administered to large populations (such as during supplementary immunization activities) or with new vaccine introduction.
4. The TAG notes the important role of the Regional Alliance for NRAs for Vaccine in the Western Pacific as a platform to establish or strengthen vaccine regulatory system in countries and asks the WHO Regional Office for the Western Pacific to support the Alliance in implementing its workplans.
5. The TAG continues to endorse the implementation of Immunization Week and encourages all Member States in the Region to participate in this important event. The TAG requests the WHO Regional Office for the Western Pacific to explore establishing a theme for the 2015 Immunization Week in consultation with countries. In addition, Member States should use other opportunities as appropriate to promote the benefits of vaccination.
6. The TAG urges countries to strengthen their vaccine management systems to avoid vaccine stock-outs.
7. Given the substantial concern among low-income and middle-income countries about pricing of newer vaccines, the TAG requests the WHO Regional Office for the Western Pacific to explore interest among Member States to establish a regional pooled procurement mechanism to facilitate access to new vaccines and increase vaccine security for all vaccines.

## **WHO Media centre: Ebola situation assessment - 1 October 2014<sup>1</sup>**

### **Experimental Ebola vaccines- WHO consultation on Ebola vaccines**

From 29–30 September, WHO organized an expert consultation to assess the status of work to test and eventually license two candidate Ebola vaccines. More than 70 experts, including many from affected and neighbouring countries in West Africa, attended the event.

The expertise represented among participants ranged from the virology of emerging infections, to regulatory requirements that must be met, to medical ethics, public health, and infectious diseases. Heads of clinical research and other executives from the pharmaceutical industry also presented their views.

Some participants came with more than 3 decades of experience working in Africa on other infectious diseases.

Experts on the use of innovative, cutting-edge trial designs also shared their most recent work.

The overarching objective was to take stock of the many efforts currently under way to rapidly evaluate Ebola vaccines for safety and efficacy. The next step is to make these vaccines available as soon as possible – and in sufficient quantities – to protect critical frontline workers and to make a difference in the epidemic's future evolution.

All agreed on the ultimate goal: to have a fully tested and licensed product that can be scaled up for use in mass vaccination campaigns.

### **Two promising candidate vaccines**

Given the public health need for safe and effective Ebola interventions, WHO regards the expedited evaluation of all Ebola vaccines with clinical grade material as a high priority.

Two candidate vaccines have clinical-grade vials available for phase 1 pre-licensure clinical trials.

One (cAd3-ZEBOV) has been developed by GlaxoSmithKline in collaboration with the US National Institute of Allergy and Infectious Diseases. It uses a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted.

The second (rVSV-ZEBOV) was developed by the Public Health Agency of Canada in Winnipeg. The license for commercialization of the Canadian vaccine is held by an American company, the NewLink Genetics company, located in Ames, Iowa. The vaccine uses an attenuated or weakened vesicular stomatitis virus, a pathogen found in livestock; one of its genes has been replaced by an Ebola virus gene.

### **Phase 1 clinical trials**

WHO and other partners have helped facilitate expedited evaluation of these two vaccines in order to generate phase 1 safety and immunogenicity data for decision-making. A series of coordinated phase 1 trials is currently under way or will soon be initiated with international consortia at more than 10 sites in Africa, Europe and North America.

These studies aim to ensure good communication and harmonization of key design elements to allow for merging of data from different trials of the same candidate products.

The trials, which are being conducted in healthy human volunteers, are designed to test safety and immunogenicity and select the appropriate dose. Two phase 1 trials of the cAd3-ZEBOV started in September 2014 in USA and UK, and the first Phase 1 trial of VSV-ZEBOV is due to start early in October in USA.

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<sup>1</sup> <http://www.who.int/mediacentre/news/ebola/01-october-2014/en/>, accessed 2<sup>nd</sup> October 2014



The government of Canada has donated 800 vials of rVSV-ZEBOV to WHO. Once data on dosing from phase 1 trials become available, this donation could translate into about 1500 to 2000 doses of vaccine.

Both companies are working to augment their manufacturing capacity. The goal is a very significant increase in scale during the first half of 2015.

## **No delays**

One shared mindset was readily apparent during the two-day discussions. Nothing must be allowed to slow down the goal of making vaccines accessible to people in affected West African countries. The phrase, “Nothing can be allowed to delay this work”, was heard over and over again.

The ambition: to accomplish, within a matter of months, work that normally takes from two to four years, without compromising international standards for safety and efficacy.

In other words: to give the African people and their health authorities the best product that the world’s scientists, working collectively, have to offer.

## **What the experts considered**

Against this background, the meeting looked specifically at the objectives and key design elements for moving in an expedited manner to conduct additional clinical trials (phase 2 trial designs) that will generate additional safety data and evidence that the vaccine confers protection.

Parallel pathways for emergency use of experimental candidate vaccines with data collection, among frontline health care workers and other critical personnel, were also explored.

Apart from the great sense of urgency, the overall spirit of the discussions was characterized by a strong sense of solidarity with the people of West Africa, their governments, and their medical, scientific, and public health communities.

Equally strong was the insistence on ensuring that evidence on safety, immunogenicity, and efficacy of the vaccines is collected properly.

## **Multiple challenges**

Multiple potential challenges and uncertainties were put forward and assessed. Issues ranging from barriers to rapid implementation of R&D, to the design of trials and their use to guide eventual widespread vaccination, were discussed together with proposed ways to overcome them.

Some of the practical issues discussed included how to address communities’ perceptions regarding vaccines in general, and vaccine studies more specifically, public expectations for vaccine availability for widespread use, and whether there is an adequate infrastructure in place to rapidly and safely evaluate and distribute vaccines.

One important technical challenge is the fact that the candidate vaccines must be stored at a temperature of -80°C.

Further issues that need to be urgently addressed include identifying staff who can conduct trials meeting international standards, logistical issues (such as cold chain needs for the vaccines), and the resources needed to start the studies quickly.

Some of the scientific challenges include how to conduct studies as safely and rapidly as possible to inform decisions about mass production of vaccines and their administration.

Key questions

Discussions focused on the main questions that studies should help address, which part of the research should be conducted in non-affected areas and which part in affected areas, and how such decisions could either help expedite or delay the availability of robust evidence. One overarching conclusion was that the international community, joining the affected countries as a whole, has a responsibility and a role to play in accelerating the evaluation, licensing, and availability of the candidate vaccines – if proven safe and effective. For all these reasons, the actions emerging from the consultation clearly identify a role for each of the main stakeholders.

### **Randomized controlled trials**

Regarding the issue of how to accelerate the assessment and licensure of the vaccines, experts reiterated that, if feasible, randomized controlled trials are the design of choice because they provide the most robust data, in the shortest amount of time, to judge whether a vaccine is safe and induces protection.

Trials must be expedited, while preserving ethical and safety standards. Efficacy data of high quality must be gathered. Trials need to be carefully designed so that they concomitantly address the most important questions regarding safety, immunogenicity, and efficacy. While individually randomized controlled trials provide the most robust data, alternative designs should be considered when these trials are not judged feasible. These include cluster-randomized and stepped-wedge designs. As long as the amount of vaccine remains limited, units – such as health or treatment facilities – can be randomized. Regardless of the design chosen, trials should move forward as quickly as possible.

### **Alternative study designs**

Alternative study designs will not delay deployment of vaccine to those who need it. Instead, they will influence the choice of people who receive the vaccine. For some months to come, the critical limiting factor is extremely restricted vaccine supply, and not the need to conduct studies using alternative designs.

Descriptions of the so-called “randomized stepped wedge” design attracted lively interest and much discussion. In this design, a “wedge” (like a slice of a pie or a cake) of the study population is selected for step-wise inclusion in the trials.

As each “wedge” receives the vaccine, all lessons learned or needed to adjust the study design are then applied to the next group to be included in the study. The selection of study populations can be randomized by units, as described above; the entire study population eventually receives the vaccine if trials demonstrate sufficient efficacy.

Such a design makes it possible to roll out vaccinations and evaluate efficacy at the same time. It further has features that meet the explicit objective of fairness.

Other designs will be more relevant when large numbers of vaccine doses are available.

### **Involving countries**

Decisions on study designs and target populations must be made with the active participation of experts from the three hardest-hit countries. Consultations with frontline health workers should be undertaken as a matter of urgency to identify the most feasible approaches to evaluate vaccine efficacy and identify factors influencing acceptability of randomized trials. The experts discussed the importance of making sure that the trials are appropriately designed to inform the use of these vaccines in all populations, including children, pregnant women, and immunocompromised populations, including people who are HIV positive.

The group also discussed how best to use the doses of experimental vaccine donated by Canada and additional doses that may be available later this year and in 2015. If vaccine doses are used in the short term, vaccines should be deployed to consenting frontline health workers. The decision to initiate such deployment should be informed by data emerging from the phase 1 studies, and will occur with data collection on the deployment itself. Equity is important and therefore vaccine should be made available in an equitable and consensual manner to the affected countries. Maximizing the information gained from the use of these vaccines during this phase is critical.

## **Information sharing**

A cross-cutting issue is the need for data sharing – in real time – among the research, medical, and public health communities, coordinated by WHO. This was considered of paramount importance to inform decisions on future studies and scaling up the production of those experimental vaccines that look most promising.

Vaccine development normally takes a long time and is notoriously costly. Even under the best conditions and with the massive efforts of many partners, a significant number of doses will not be available until late in the first quarter of 2015.

One important factor for the completion of all the above steps is to secure the funding to ensure the production of the vaccine and to support priority studies. Major international funding partners should promptly pledge or commit the necessary funding so that this critical research is completed without further delay.

## **The African perspective**

The presence of West African researchers, scientists, clinicians, and health officials vastly enriched the discussions, especially concerning the practical dimensions of trial design. These experts further underscored the importance of communicating with communities and engaging their views, and called for qualitative studies to begin immediately. For example, some cultures are deeply distrustful of “Western” medicine and foreign medical staff in general, and of vaccines in particular.

Interventions from the three hardest-hit countries, Guinea, Liberia, and Sierra Leone, clearly stated that international assistance is both greatly needed and fully welcomed.

Families and entire villages have been shattered. Some communities are on the verge of hopelessness and helplessness. Many do not comprehend what hit them and why, especially as this is the first time that the Ebola virus and Ebola virus disease have been seen in West Africa.

Governments are on board. Clinicians are on board. Researchers and their institutes are on board.

Statements made by West Africans reminded all participants of what life is really like in these countries. Children do not play in school yards, play pens, fenced back yards, or terraced gardens. They play in the bush.

These realities of daily African life need to be kept in mind when high-risk exposures are considered and defined.

## **Health workers**

Participants were further reminded that the definition of “health care workers” in these African countries includes doctors, nurses, and laboratory technicians but also hospital

cleaners, ambulance drivers, burial teams, mortuary attendants, and in some instances, traditional healers.

As hospitals in many areas are overflowing or closed, the number of treatment beds in all three countries is woefully inadequate, and people frequently do not trust the health care system, more and more patients are being cared for by their loved ones in homes or within the community.

These people are also at very high risk of infection and should be considered when priorities for support – in all its forms – are being set. The importance of community engagement cannot be overstated.

Operational changes made since the unprecedented resolutions on Ebola virus disease were adopted by an emergency session of the UN Security Council (on 18 September) and by a UN General Assembly high-level session on Ebola (on 25 September) involve a vast groundswell scaling-up of international support to affected countries. This support includes a much larger number of medical staff working in countries, thanks to generous support from the governments of China, Cuba, and many others.

## **Lessons learned**

Participants also drew heavily on lessons learned, in the African setting, during trials for candidate malaria, HIV/AIDS, cholera, epidemic meningitis, hepatitis B, and other vaccines. As some experts noted, never again can the international community allow what boils down to “market failure” to create such catastrophic suffering for humanity in any country, in any region of the world.

The sense of urgency and need for speed, without compromising the integrity of studies or the quality of their data, are fully justified by the dire situation in affected countries and the risk that other countries may soon experience their first imported cases.

The Ebola outbreak currently ravaging parts of West Africa is the most severe acute public health emergency in modern times. Never before in recent history has a biosafety level 4 pathogen infected so many people so quickly, over such a wide geographical area, for so long.

## **Key expected milestones**

### **October 2014:**

Mechanisms for evaluating and sharing data in real time must be prepared and agreed upon and the remainder of the phase 1 trials must be started

### **October–November 2014:**

Agreed common protocols (including for phase 2 studies) across different sites must be developed

### **October–November 2014:**

Preparation of sites in affected countries for phase 2 b should start as soon as possible

### **November–December 2014:**

Initial safety data from phase 1 trials will be available

### **January 2015:**

GMP (Good Manufacturing Practices) grade vaccine doses will be available for phase 2 as soon as possible

### **January–February 2015:**

Phase 2 studies to be approved and initiated in affected and non-affected countries (as appropriate)

### **As soon as possible after data on efficacy become available:**

Planning for large-scale vaccination, including systems for vaccine financing, allocation, and use.

#### **Executive summary of the 18-19 June 2013 GAVI Alliance Board Meeting, Geneva, Switzerland**

The main decisions include the extension of the Board Chair's term through to December 2015 and agreement on the proposed process for appointment of the next Board Chair; approval of a supply chain strategy for the Alliance including approved additional funding to WHO through the business plan of US\$1M for 2014; and approval of the 2016-2020 Alliance Strategy framework including a continued focus on low income countries, improving coverage and access, equity and ensuring successful graduation of countries from GAVI support. On the new strategy framework, immediately following the Board meeting, work will commence on developing the corresponding key performance indicators (KPIs), reviewing the roles and responsibilities of partners, coordination and enhanced leveraging of partner contributions at global and country levels. In alignment with the GVAP vision and the new GAVI strategy, it was noted that SAGE will continue to have a central role in reviewing suggested indicators for measuring immunization outcomes beyond the current DTP3 coverage indicator.

The projected needs for implementing the new strategy for the period 2016-2020 is US\$9.5bn, excluding malaria and polio. The replenishment ask is US\$7.5 bn excluding assured resources. Germany confirmed their hosting of the replenishment in early 2015.

# Annex 1: Proposed strategic framework for the GAVI Alliance in 2016-2020

## GAVI Alliance strategy 2016-2020

Mission	To save children's lives and protect people's health by increasing equitable use of vaccines in lower income countries	Aspiration 2020	TBD	Disease dashboard	Empirical measurements (TBD) of health impact to which GAVI Alliance contributed in pneumonia, diarrhoea, HepatitisB and measles
Principles	<ul style="list-style-type: none"> <li><b>Country-led:</b> Respond to and align with country demand, supporting national priorities, budget processes and decision-making</li> <li><b>Community-owned:</b> Ensure engagement of communities to increase accountability and sustain demand and impact</li> <li><b>Globally engaged:</b> Contribute to the Global Vaccine Action plan, align with the post 2015 global development priorities and implement the aid effectiveness principles</li> <li><b>Catalytic &amp; sustainable:</b> Provide support to generate long term sustainable results including country self-financing of vaccines through the graduation process</li> </ul>	<ul style="list-style-type: none"> <li>&lt; 5 mortality rate</li> <li>Future deaths averted</li> <li>Future DALYs averted</li> <li># of children vaccinated with GAVI support</li> </ul>	<ul style="list-style-type: none"> <li>TBD</li> <li>5-6 million</li> <li>&gt;250 million</li> <li>&gt;300 million</li> </ul>	<ul style="list-style-type: none"> <li>Integrated: Foster integration of immunisation with other health interventions, harmonising support by the GAVI Alliance with other partners</li> <li>Innovative: Foster and take to scale innovation in development models, financing instruments, public health approaches, immunisation-related technologies and delivery science</li> <li>Collaborative: As a public private partnership, convene immunisation stakeholders and leverage the strengths of all Alliance partners through shared responsibility at both global and national level</li> <li>Accountable: Maximise Alliance cooperation and performance through transparent accountability mechanisms</li> </ul>	
Goals	1 Accelerate equitable uptake and coverage of vaccines	2 Increase effectiveness and efficiency of immunisation delivery as an integrated part of strengthened health systems	3 Improve sustainability of national immunisation programmes	4 Shape markets for vaccines and other immunisation products	
Objectives	<ul style="list-style-type: none"> <li><b>a</b> Increase coverage and equity of immunisation</li> <li><b>b</b> Support countries to introduce and scale up new vaccines</li> <li><b>c</b> Respond flexibly to the special needs of children in fragile countries</li> </ul>	<ul style="list-style-type: none"> <li><b>a</b> Contribute to improving integrated and comprehensive immunisation programmes, including fixed, outreach and supplementary components</li> <li><b>b</b> Support improvements in supply chains, health information systems, demand generation and gender sensitive approaches</li> <li><b>c</b> Strengthen engagement of civil society, private sector and other partners in immunisation</li> </ul>	<ul style="list-style-type: none"> <li><b>a</b> Enhance national and sub-national political commitment to immunisation</li> <li><b>b</b> Ensure appropriate allocation and management of national human and financial resources to immunisation through legislative and budgetary means</li> <li><b>c</b> Prepare countries to sustain performance in immunisation after graduation</li> </ul>	<ul style="list-style-type: none"> <li><b>a</b> Ensure adequate and secure supply of quality vaccines</li> <li><b>b</b> Reduce prices of vaccines and other immunisation products to an appropriate and sustainable level</li> <li><b>c</b> Incentivise development of suitable and quality vaccines and other immunisation products</li> </ul>	
Goal-level indicators	<ul style="list-style-type: none"> <li><b>% Fully immunised children</b> [to be further developed]</li> <li><b>Coverage by antigen:</b> Pneumo3, Rota last, Penta3, HPV last, Measles, MenA</li> <li><b>Equity of coverage</b> <ul style="list-style-type: none"> <li>Wealth equity</li> <li>Geographic equity (within and across countries)</li> <li>Gender equity</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li><b>Supply chain</b> : e.g., vaccine utilisation, % of immunisation sessions with adequate stocks of vaccines</li> <li><b>Data quality:</b> e.g., completeness &amp; timeliness of reporting, consistency among different sources</li> <li><b>Service delivery</b> : e.g., % of immunisation sessions conducted; Gender related barriers addressed in immunisation plans</li> <li><b>Demand:</b> Increase in demand for immunisation, e.g., as measured by survey</li> <li><b>Integration:</b> Indicator TBD</li> </ul>	<ul style="list-style-type: none"> <li><b>Fulfillment of co-financing commitments</b> (e.g., % countries meeting commitments in a timely manner)</li> <li><b>Country investments in vaccines and immunisation per child</b> (Split eligible/graduating/graduated countries)</li> <li><b>Immunisation coverage after graduation: GAVI vaccines maintained in EPI schedule</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Indicator on healthy market dynamics</b> (e.g., # of suppliers, # countries obtaining first choice, vaccines and other products)</li> <li><b>Reduction in price</b> (vaccines and other products) for GAVI countries, access to appropriate prices for graduated countries and LMICs</li> <li><b>Reduction in the delivery cost of immunisation</b></li> <li><b>Indicator on innovation</b> (e.g., thermo-stable vaccines; delivery technologies)</li> </ul>	
Strategic enablers	<p><b>A) Country leadership management &amp; coordination</b> (1) Strengthen institutional capacity for national decision-making, programme management and monitoring</p> <p><b>B) Resource mobilisation</b> (1) Secure long-term predictable funding for GAVI Alliance programmes as a prerequisite for continued success</p> <p>(2) Harness the capacity of the private sector, including through innovative finance mechanisms and contributions from vaccine manufacturers</p> <p><b>C) Advocacy</b> (1) Strengthen national political and subnational commitment for immunisation</p> <p>(2) Strengthen global political commitment for immunisation, health and development</p> <p><b>D) Monitoring &amp; Evaluation</b> Support GAVI as a learning Alliance through (i) Effective routine surveillance, programme monitoring and management (ii) Regular evaluation of the relevance, effectiveness, impact, and efficiency of the GAVI Alliance's investments to inform evidence-based policy development</p>				

The evaluation team prepares a comprehensive report of their findings and recommendations, addressing the core questions:

1. Is it proven beyond reasonable doubt that there is no longer any mosquito-borne malaria transmission in the country, and if so, what evidence is this based on?
2. Can it be stated with full confidence that the national health system, as it is, will be able to prevent re-establishment of malaria transmission in the country, and if so, what evidence is this based on?

This report is reviewed by a wider group of external and WHO experts, including invited topic experts if specific technical issues arise on specialized aspects of malaria control and elimination that have been highlighted by the evaluation team. The country will be asked to respond to questions that arise during this review. The collected reports and information are then reviewed by the WHO Expert Committee on Malaria. After any further clarifications from the country or provision of supplementary information that may be needed, the WHO Expert Committee submits a recommendation to the WHO Director-General regarding inclusion of the country in the WHO official register of countries where malaria elimination has been achieved. The certification process is summarized in *Box 1*. ■

L'équipe d'évaluation rédige ensuite un rapport complet qui présente ses observations et ses recommandations et répond aux questions centrales:

1. Est-il prouvé au-delà de tout doute raisonnable qu'il n'y a plus, dans le pays, aucune transmission du paludisme véhiculée par les moustiques et, le cas échéant, sur quelles données factuelles s'est-on fondé?
2. Peut-on affirmer sans crainte de se tromper que le système de santé national, dans sa forme actuelle, permettra d'empêcher la reprise de la transmission dans le pays et, le cas échéant, sur quelles données factuelles s'est-on fondé?

Ce rapport est examiné par un groupe plus large d'experts externes et d'experts de l'OMS, y compris, éventuellement, des spécialistes invités à s'exprimer sur des questions techniques spécifiques relevant d'aspects spécialisés de la lutte ou de l'élimination qui ont été mis en lumière par l'équipe d'évaluation. Il est demandé au pays de répondre aux questions qui se posent au cours de l'examen. Les rapports et les informations collectés sont ensuite passés en revue par le Comité OMS d'experts du Paludisme. Après que le pays a apporté d'éventuelles clarifications ou que les informations éventuellement nécessaires ont été fournies, le Comité d'experts de l'OMS soumet une recommandation au Directeur général de l'OMS concernant l'inscription du pays au Registre officiel de l'OMS des pays où l'élimination du paludisme a été réalisée. Le processus de certification est résumé dans l'*Encadré 1*. ■

## Global Advisory Committee on Vaccine Safety, 11–12 June 2014

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO to provide independent, scientifically rigorous advice on vaccine safety issues of potential global importance.<sup>1</sup> GACVS held its 30th meeting in Geneva, Switzerland, on 11–12 June 2014.<sup>2</sup> The committee reviewed 4 specific issues: the safety profiles of 2 novel vaccines – a live attenuated rotavirus vaccine and a recombinant hepatitis E vaccine; a study of the safety of meningococcal A conjugate vaccine among pregnant women in Ghana; and issues related to the monitoring of the safety of future anti-malarial vaccines. During the meeting, the committee also reflected on the accomplishments and opportunities after 15 years since the establishment of GACVS.

## Comité consultatif mondial de la Sécurité vaccinale, 11–12 juin 2014

Le Comité consultatif mondial de la Sécurité vaccinale (GACVS), composé d'experts cliniques et scientifiques, a été créé par l'OMS pour la conseiller, en toute indépendance et avec la rigueur scientifique voulue, sur des problèmes de sécurité vaccinale pouvant avoir une importance mondiale.<sup>1</sup> Le GACVS a tenu sa trentième réunion à Genève (Suisse), les 11 et 12 juin 2014.<sup>2</sup> Le Comité a examiné 4 questions spécifiques: les profils d'innocuité de 2 nouveaux vaccins – un vaccin antirotavirus vivant atténué et un vaccin recombinant contre l'hépatite E; une étude sur l'innocuité du vaccin antiméningococcique A conjugué chez les femmes enceintes au Ghana; et les questions relatives au suivi de l'innocuité des futurs vaccins contre le paludisme. Au cours de la réunion, le Comité a également réfléchi aux réalisations et aux opportunités en 15 ans de fonctionnement depuis sa création.

<sup>1</sup> See No. 41, 1999, pp. 337–338.

<sup>2</sup> GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: Bahrat Biotech, Hyderabad, India; Cincinnati Children's Hospital Medical Centre, Cincinnati OH, USA; Dalhousie University, Halifax, Canada; Food and Drugs Administration, Manila, Philippines; Inovax Biotech, Xiamen, China; London School of Hygiene and Tropical Medicine, London, United Kingdom; Navrongo Health Research centre, Navrongo, Ghana; Postgraduate Institute of Medical Sciences, Lucknow, India; University of Colorado, Aurora CO, USA; University of Ghana, Accra, Ghana.

<sup>1</sup> Voir N° 41, 1999, pp. 337–338.

<sup>2</sup> Le GACVS a invité d'autres experts pour présenter et discuter les données relatives à des sujets particuliers. Il s'agissait notamment de personnes affiliées aux organismes suivants: Bahrat Biotech, Hyderabad (Inde); Cincinnati Children's Hospital Medical Centre, Cincinnati OH (États-Unis d'Amérique); Dalhousie University, Halifax (Canada); Food and Drugs Administration, Manille (Philippines); Inovax Biotech, Xiamen (Chine); London School of Hygiene and Tropical Medicine, Londres (Royaume Uni); Navrongo Health Research centre, Navrongo, Ghana; Postgraduate Institute of Medical Sciences, Lucknow (Inde); Université du Colorado, Aurora CO (États-Unis d'Amérique); Université du Ghana, Accra (Ghana).

## Safety profile of a novel live attenuated rotavirus vaccine

Rotavirus gastroenteritis remains a major cause of morbidity and mortality among young children. Two rotavirus vaccines are currently widely used in national immunization programmes. A new rotavirus vaccine, Rotavac, was licensed in India in January 2014. The vaccine is derived from a naturally attenuated human neonatal strain containing 1 bovine segment (G9P[11]) that was originally isolated from an asymptomatic infant at the All India Institute of Medical Sciences in 1988. The strain was further studied by Indian and U.S. investigators, with safety trials conducted in adults and children in Cincinnati, United States of America. In 2000, the strain was then licensed to Bharat Biotech International (Hyderabad, India), which developed the vaccine with clinical testing in Phase 1, 2 and 3 studies in India. The current vaccine formulation requires -20 °C storage, although the product may be stored at +2 to +8 °C for the final 6 months prior to expiry. Several different presentations have been licensed, but the manufacturer expects the main presentation to be in a 5-dose vial, which could be used for 8 hours after opening. An oral antacid buffer is currently administered prior to administration of the vaccine.

The randomized, double-blind, placebo-controlled Phase 3 study was carried out with active monitoring for safety in 4532 infants who received the rotavirus vaccine and 2267 placebo recipients. The study was conducted during their routine childhood immunization series, and the subjects were followed up to the age of 2 years. There was no imbalance noted between the Rotavac and placebo groups with respect to adverse events, death or intussusception.

There were 11 confirmed cases of intussusception; importantly, no case occurred in proximity to the time of vaccination. The earliest case following receipt of placebo was 36 days post dose 3. The earliest case following receipt of Rotavac was 112 days post dose 3. The lack of a temporal association argues strongly against a causative relationship between Rotavac and intussusception since most rotavirus vaccine-attributable cases are expected to occur within the first week following vaccination. The observed incidence of confirmed intussusception was 94 per 100 000 child-years (95% confidence interval [CI]: 41–185) among vaccinated infants and 71 per 100 000 child-years (95% CI:15–206) among those who received placebo. This incidence is similar to that measured, in the absence of vaccine, from countries with active surveillance systems for intussusception.

As the available safety data support further use of the vaccine, a post-licensure study of at least 45 000 vaccinated infants is planned. However, based on the experience with similar vaccines, it will be important that additional data be continuously collected in order to assess the risk of intussusception as well as to identify any other rare adverse events that may occur. Based on

## Profil d'innocuité d'un nouveau vaccin antirotavirus vivant atténué

La gastro-entérite à rotavirus demeure une cause majeure de morbidité et de mortalité chez le jeune enfant. Deux vaccins sont actuellement d'utilisation courante dans les programmes nationaux de vaccination. Un nouveau vaccin, le Rotavac, a été homologué en Inde en janvier 2014. Il dérive d'une souche néonatale naturellement atténuée chez l'homme et renfermant 1 segment d'origine bovine (G9P[11]), isolée à l'origine chez un nourrisson asymptomatique au All India Institute of Medical Sciences en 1988. Cette souche a ensuite été étudiée par des chercheurs indiens et américains, avec des essais d'innocuité menés chez des adultes et des enfants à Cincinnati, États-Unis d'Amérique. En 2000, une licence d'exploitation de la souche a été délivrée au Bharat Biotech International (Hyderabad, Inde), qui a mis au point le vaccin avec des essais cliniques en phases 1, 2 et 3 en Inde. La présentation actuelle du vaccin nécessite une conservation à -20 °C, bien que le produit puisse être stocké entre +2 °C et +8 °C dans les 6 derniers mois précédant la date de péremption. Plusieurs présentations ont été homologuées, mais le fabricant s'attend à ce que la principale d'entre elles soit un flacon de 5 doses, pouvant être utilisé pendant 8 heures après ouverture. Un tampon antiacide oral est actuellement administré avant de donner le vaccin.

L'essai randomisé, en double aveugle, contre placebo en phase 3 a été mené avec une surveillance active de l'innocuité chez 4532 nourrissons ayant reçu le vaccin antirotavirus et 2267 le placebo. L'étude a eu lieu pendant les séries de la vaccination systématiques des enfants et les sujets ont été suivis jusqu'à l'âge de 2 ans. Aucune disparité n'a été notée entre le groupe ayant eu le Rotavac et le groupe du placebo pour ce qui est des effets indésirables, des décès ou de l'invagination intestinale (intussusception).

Il y a eu 11 cas confirmés d'invagination intestinale; point important, aucun ne s'est produit à un moment proche de la vaccination. Le cas le plus précoce après administration du placebo est survenu 36 jours après la 3<sup>e</sup> dose. Après administration du Rotavac, le cas le plus précoce s'est produit 112 jours après la 3<sup>e</sup> dose. L'absence de lien temporel plaide fortement contre toute relation de cause à effet entre le Rotavac et l'invagination intestinale, la plupart des cas attribuables aux vaccins antirotavirus survenant normalement au cours de la première semaine après la vaccination. L'incidence observée de l'invagination intestinale confirmée a été de 94 pour 100 000 années-enfants (intervalle de confiance [IC] à 95%: 41-185) chez les nourrissons vaccinés et 71 pour 100 000 années-enfants (IC à 95%: 15-206) chez les sujets sous placebo. Cette incidence est similaire à celle mesurée en l'absence de vaccins dans les pays dotés de systèmes de surveillance active de l'invagination intestinale.

Les données disponibles sur l'innocuité étant favorables à la poursuite de l'utilisation du vaccin, une étude après homologation sur au moins 45 000 nourrissons vaccinés est prévue. Toutefois, sur la base de l'expérience acquise avec des vaccins similaires, il sera important de collecter continuellement des données supplémentaires pour évaluer le risque d'invagination intestinale, ainsi que pour identifier tout autre événement indé-



the experience with other rotavirus vaccines, the infrastructure of sentinel sites that exists in India should be utilized for continued intussusception surveillance in order to fully characterize the safety profile of this new rotavirus vaccine.

### **Safety profile of a recombinant hepatitis E vaccine**

The recombinant hepatitis E vaccine (Hecolin), also designated HEV 239, encompasses amino acids 368-606 of the HEV open reading frame 2 (ORF2) capsid protein from HEV genotype 1 and is expressed as a non-fusion protein in *Escherichia coli*. The purified HEV 239 assembles as homodimers resulting in virus-like particles. The vaccine contains 30 µg of the purified antigen and 0.8 mg aluminium hydroxide suspended in 0.5 ml buffered saline. It is manufactured by Xiamen Innovax Biotech, Xiamen China. It was approved by the Chinese Food and Drug Administration in 2011 and has been available since October 2012.

Pre-licensure safety and immunogenicity data were presented. The vaccine was evaluated in Phase 1 and 2 pre-licensure trials designed to evaluate the optimal dose and regimen of Hecolin. The efficacy and safety of the vaccine was evaluated in a randomized, double-blind, controlled Phase 3 clinical trial in >112 000 healthy subjects 16–65 years of age irrespective of anti-HEV antibody status. That study was conducted between August 2007 and June 2009 in the Jiangsu Province of China, a region where HEV genotype 4 is the predominant genotype, with genotype 1 also circulating. Study participants were randomized 1:1 to receive either Hecolin ( $n = 56\,302$ ) or a licensed hepatitis B vaccine ( $n = 56\,302$ ) administered through intramuscular injection in 3 doses (0, 1 and 6 months). Participants were followed for 19 months.

Data showed that the vaccine was immunogenic and efficacious. To assess local and systemic solicited and unsolicited adverse events a subset consisting of 1316 participants in the Hecolin group and 1329 participants in the control group (participants from one township) were observed for 30 minutes and then assessed by home visits at 6, 24, 48 and 72 hours, as well as 7, 14 and 28 days after each dose. Other study participants were asked to report any adverse events to nearby clinics within 1 month after each dose without active follow-up visits. In addition, the investigators used data obtained from the local medical insurance system covering the whole study area (11 townships) to identify hospitalizations and deaths among the trial participants during the 19-month follow-up period. After reviewing the hospital records related to these serious adverse events, the investigators categorized them according to the Medical Dictionary for Regulatory Activities (MedDRA). Overall, safety data derived from Phase 1, 2 and 3 clinical trials suggested that the vaccine was well tolerated. Short-term (72 hours) local and systemic solicited adverse event data obtained from

sirable rare susceptible de se produire. En se fondant sur l'expérience accumulée avec d'autres vaccins antirotavirus, l'infrastructure des sites sentinelles existant en Inde devrait être utilisée pour la surveillance continue des invaginations intestinales afin de caractériser complètement le profil d'innocuité de ce nouveau vaccin antirotavirus.

### **Profil d'innocuité d'un vaccin recombinant contre l'hépatite E**

Le vaccin recombinant contre l'hépatite E (Hecolin), aussi appelé HEV 239, comprend les acides aminés 368-606 de la protéine de capsid du génotype 1 du VHE en cadre de lecture ouvert 2 (ORF2) et il est exprimé sous forme de protéine non fusionnée chez *Escherichia coli*. Le HEV 239 purifié s'assemble sous forme d'homodimères aboutissant à des pseudo-particules virales. Le vaccin contient 30 µg de l'antigène purifié et 0,8 mg d'hydroxyde d'aluminium en suspension dans 0,5 mL de tampon salin. Il est fabriqué par Xiamen Innovax Biotech, Xiamen (Chine). Il a été approuvé par l'Administration chinoise des aliments et des médicaments en 2011 et il est disponible depuis octobre 2012.

Des données avant l'homologation sur l'innocuité et l'immunogénicité ont été présentées. Le vaccin a été évalué dans le cadre d'essais en phases 1 et 2 avant homologation conçus pour examiner la dose et la posologie optimales du vaccin Hecolin. L'efficacité et l'innocuité du vaccin ont été évaluées dans un essai contrôlé randomisé en double aveugle en phase 3 sur >112 000 sujets sains âgés de 16 à 65 ans, sans tenir compte du statut des anticorps anti-VHE. Cette étude a été menée entre août 2007 et juin 2009 dans la province du Jiangsu en Chine, une région où le génotype 4 du VHE prédomine, avec aussi le génotype 1 en circulation. Les participants ont été répartis aléatoirement à égalité 1:1 pour recevoir soit l'Hecolin ( $n = 56\,302$ ), soit un vaccin homologué contre l'hépatite B ( $n = 56\,302$ ) administré en 3 doses par injection intramusculaire (à 0, 1 et 6 mois). Les participants ont été suivis pendant 19 mois.

Les résultats ont montré que le vaccin était immunogène et efficace. Pour évaluer les événements indésirables locaux ou généraux signalés spontanément ou sur demande, un sous-groupe de 1316 participants dans le groupe de l'Hecolin et de 1329 participants dans le groupe témoin (participants d'une municipalité) ont été gardés en observation pendant 30 minutes puis évalués dans le cadre de visites à domicile à 6, 24, 48 et 72 heures, puis à 7, 14 et 28 jours après chaque dose. On a demandé à d'autres participants à l'étude de signaler tout effet indésirable dans des dispensaires proches dans le mois suivant l'administration de chaque dose, sans qu'il y ait de visites actives de suivi. De plus, les chercheurs ont fait appel aux informations obtenues auprès du système local d'assurance maladie couvrant l'ensemble de la zone de l'étude (11 municipalités) pour repérer les hospitalisations et les décès chez les participants à l'essai au cours des 19 mois de suivi. Après examen des dossiers hospitaliers liés à des effets indésirables graves, les chercheurs les ont classés en suivant le *Medical Dictionary for Regulatory Activities* (MedDRA). Globalement, les données sur l'innocuité tirées des essais cliniques en phases 1, 2 et 3 donnent à penser que le vaccin a été bien toléré. Les données sur les effets indésirables locaux ou généraux signalés sur demande à

the “reactogenicity subset” that participated in the Phase 3 clinical trial showed more frequent local adverse events in the Hecolin group compared to the active control group. The solicited systemic adverse events and unsolicited adverse events occurred at similar rates between study groups. There appeared to be no difference in serious adverse events or death identified in the Hecolin group compared to the active control group. Because there was no active follow-up the number of severe adverse events and deaths among trial participants could not be ascertained.

In the Phase 3 clinical trial there were 37 women in the Hecolin group and 31 women in the placebo group who were inadvertently administered vaccine during pregnancy. The vaccine appeared to be well tolerated in pregnant women with rates of adverse events similar to those observed in matched non-pregnant women. Nineteen of the pregnant women in the Hecolin group and 14 in the active placebo group underwent elective abortion. There were 18 and 17 live births in the Hecolin and active control groups, respectively. Weight, body lengths and gestational age of the babies were comparable in the 2 groups. However, the overall sample size was too small to allow a conclusive statement on the safety of Hecolin in pregnant women and their babies. The safety of Hecolin was also evaluated in HBsAg-positive persons and the data are reassuring; however the analysis subset did not include persons with ongoing liver disease as this was an exclusion criterion for the trial.

The Chinese CDC has established an online reporting system to collect post-marketing safety information and to date has not identified any safety concerns. A small Phase 4 trial in the elderly (>65 years of age) is ongoing, as well as an extended follow-up trial of the Phase 3 study cohort. In addition, Hecolin is being used as an active control arm in an ongoing Phase 3 study of a human papilloma virus (HPV) vaccine in approximately 7300 healthy women.

In summary, available safety data on Hecolin derived from Phase 1, 2 and 3 clinical trials in healthy subjects are reassuring. However, GACVS noted that there are no safety data in paediatric subjects (<16 years of age), the elderly (>65 years of age), persons with underlying diseases or conditions such as those who are immunosuppressed persons or have liver disease and thus recommended that studies be conducted to assess the safety of Hecolin in these subpopulations. Any follow-up of those inadvertently vaccinated in pregnancy during the HPV trial should be useful to assess safety in this group. The committee also noted that there are as yet no studies to evaluate the safety and immunogenicity of Hecolin when given concomitantly with other vaccines. In addition, GACVS recommended that a Phase 4 post-marketing study be conducted once the vaccine is in more widespread use to further assess the safety profile of

court terme (72 heures), obtenues à partir du « sous-groupe de la réactogénicité » participant à l'essai clinique en phase 3, ont mis en évidence une plus grande fréquence des effets indésirables locaux dans le groupe de l'Hecolin par rapport au groupe témoin actif. Les effets indésirables généraux signalés spontanément ou sur demande se sont produits à des taux similaires dans les 2 groupes de l'étude. Il semble qu'il n'y ait pas eu de différence au niveau des effets indésirables graves ou des décès repérés dans le groupe de l'Hecolin par rapport au groupe témoin actif. Comme il n'y a pas eu de suivi actif, il a été impossible de déterminer avec certitude le nombre des effets indésirables graves et des décès chez les participants de l'essai.

Lors de l'essai clinique en phase 3, le vaccin a été administré par inadvertance pendant la grossesse à 37 femmes dans le groupe de l'Hecolin et à 31 dans le groupe du placebo. Il semble avoir été bien toléré chez les femmes enceintes, avec des taux d'événements indésirables similaires à ceux observés chez les femmes appariées qui n'étaient pas enceintes. Sur l'ensemble des femmes enceintes, 19 du groupe de l'Hecolin et 14 du groupe du placebo actif ont eu une interruption volontaire de grossesse. Il y a eu respectivement 18 et 17 naissances vivantes dans le groupe de l'Hecolin et dans le groupe témoin actif. Le poids, la taille et l'âge gestationnel des nouveau-nés ont été comparables dans les 2 groupes. Toutefois, la taille totale de l'échantillon était trop faible pour tirer une conclusion définitive sur l'innocuité de l'Hecolin pour les femmes enceintes et leurs enfants. L'innocuité du vaccin a également été évaluée chez les sujets porteurs de l'antigène de surface de l'hépatite B (HBsAg) et les données sont rassurantes; en revanche, ce sous-groupe de l'analyse ne comportait pas de personnes ayant une maladie du foie en cours, car c'était un critère d'exclusion pour l'essai.

Le CDC chinois a mis en place un système de notification en ligne pour collecter les informations sur l'innocuité après commercialisation et, jusqu'à présent, n'ont pas repéré de problèmes à ce niveau. Un petit essai en phase 4 chez les personnes âgées (de >65 ans) est en cours, ainsi qu'un essai de suivi étendu de la cohorte de l'étude en phase 3. De plus, le vaccin Hecolin est utilisé pour un groupe témoin actif dans une étude en phase 3 d'un vaccin contre le papillomavirus humain (PVH) chez environ 7300 femmes en bonne santé.

En résumé, les données disponibles sur l'innocuité du vaccin Hecolin provenant des essais cliniques en phases 1, 2 et 3 sur des sujets en bonne santé sont rassurantes. Le GACVS a relevé cependant qu'il n'y a pas de données sur l'innocuité chez les enfants (<16 ans), les personnes âgées (>65 ans), les personnes avec des maladies ou des affections sous-jacentes, comme une immunosuppression ou une maladie du foie, et a donc recommandé de mener des études pour évaluer l'innocuité du vaccin dans ces sous-groupes de la population. Le suivi des femmes vaccinées par inadvertance au cours de la grossesse dans le cadre de l'essai du vaccin contre le PVH serait utile pour évaluer l'innocuité dans ce groupe. Le Comité a noté par ailleurs qu'il n'y avait pas encore d'études pour évaluer l'innocuité et l'immunogénicité de l'Hecolin lorsqu'il est administré en même temps que d'autres vaccins. Le GACVS a recommandé de plus qu'une étude postcommercialisation en phase 4 soit menée une fois que l'usage du vaccin sera plus étendu pour évaluer davan-

Hecolin, in particular with regard to serious and rare adverse events.

### **Meningococcal A conjugate vaccine during pregnancy**

The Committee was presented with results from an open label observational evaluation of the safety of a meningococcal A conjugate vaccine in pregnancy (MenAfriVac, manufactured by the Serum Institute of India), conducted in Ghana. The vaccine is a lyophilized group A conjugate vaccine developed under the Meningitis Vaccine Project.<sup>3</sup> It contains PsA10 µg, TT conjugate 10–33 µg, aluminium phosphate adjuvant 0.3mg Al3+ and thiomersal 0.01%, in each 0.5 ml dose.

The GACVS had been following the vaccine from its initial Phase 1 and 2/3 clinical trials with just over 1100 subjects, through to licensure and the first mass immunization campaigns conducted in early adopter countries.<sup>4</sup> By the time of the last update, in June 2011, over 50 million doses had been administered. At each update, the GACVS continued to be reassured of its ongoing safety while recommending specific actions be taken to help ensure continued safety vigilance and attention to key aspects of safety. As is common, clinical trials during vaccine development and licensure did not target pregnant women, however inadvertent vaccination in pregnancy throughout the early phases had not revealed any concerns.

GACVS supported WHO's technical guidance<sup>5</sup> that MenAfriVac should be offered to pregnant and lactating women from the African meningitis belt during any stage of pregnancy or lactation, while recommending that a plan be developed to follow up women in antenatal or obstetric clinics, and to monitor pregnancy outcomes by making appropriate comparisons with unvaccinated pregnant women.<sup>6</sup>

This study was developed in response to those recommendations. The Navrongo Health Research Centre, Ghana, is part of the INDEPTH network that collects continuous longitudinal demographic and health data and outcomes within its populations. In the surveillance area (covering 2 districts – Kassena-Nankana East and Kassena-Nankana West), >156 000 individuals are part of this demographic surveillance, and receive visits by study teams about 3–4 times per year to update their demographic and health status. A mass vaccination campaign was held in Ghana between 9 and 19 October 2012, targeting individuals between 1 and 29 years of age including pregnant women. While pregnancy was not considered a contraindication during this campaign given the benefit of vaccination, some pregnant women elected not to receive the vaccine. Given the participa-

tage le profil d'innocuité de l'Hecolin, en particulier pour ce qui est des effets indésirables graves et rares.

### **Vaccin antiméningococcique A conjugué pendant la grossesse**

Le Comité a pris connaissance des résultats d'une étude ouverte d'observation sur l'innocuité du vaccin antiméningococcique A conjugué pendant la grossesse (MenAfriVac, fabriqué par le Serum Institute of India), menée au Ghana. C'est un vaccin conjugué lyophilisé contre le méningocoque du groupe A, mis au point dans le cadre du Projet de vaccins contre la méningite.<sup>3</sup> Chaque dose de 0,5 mL contient 10 µg de polysaccharide du méningocoque A (PsA), 10–33 µg d'anatoxine tétanique conjuguée, 0,3 mg de phosphate d'aluminium Al3+ comme adjuvant et 0,01% de thiomersal.

Le GACVS a suivi ce vaccin depuis les essais cliniques initiaux en phases 1 et 2/3 sur un peu plus de 1100 sujets, jusqu'à l'homologation et aux premières campagnes de vaccination de masse organisées dans les premiers pays ayant adopté le vaccin.<sup>4</sup> Au moment de la dernière mise à jour, en juin 2011, plus de 50 millions de doses avaient été administrées. À chaque mise à jour, le GACVS a été rassuré sur son innocuité tout en recommandant de prendre des mesures spécifiques pour maintenir la vigilance et l'attention portées à des aspects essentiels de la sécurité. Comme c'est souvent le cas, les essais cliniques au cours de la mise au point du vaccin et de son homologation n'ont pas porté sur les femmes enceintes, mais la vaccination par inadvertance de celles-ci au cours des premières phases n'a pas révélé de problèmes particuliers.

Le GACVS a appuyé les orientations techniques données par l'OMS<sup>5</sup> selon lesquelles le MenAfriVac doit être proposé aux femmes enceintes et allaitantes dans la ceinture africaine de la méningite quel que soit le stade de la grossesse ou de l'allaitement, tout en recommandant d'élaborer un plan pour le suivi des femmes dans les services de soins prénatals et obstétricaux afin de contrôler l'issue des grossesses en faisant les comparaisons appropriées avec les femmes enceintes non vaccinées.<sup>6</sup>

Cette étude a été mise sur pied pour répondre à ces recommandations. Le Navrongo Health Research Centre au Ghana fait partie du réseau INDEPTH, qui recueille en continu des données démographiques et sanitaires longitudinales ainsi que les issues dans les populations qu'il couvre. Dans la zone surveillée (couvrant 2 districts: Kassena-Nankana East et Kassena-Nankana West), >156 000 personnes font partie de cette surveillance démographique et reçoivent 3 à 4 fois par an la visite d'équipes de l'étude pour mettre à jour leur situation démographique et sanitaire. Une campagne de vaccination de masse a été organisée au Ghana du 9 au 19 octobre 2012, en ciblant les personnes âgées de 1 à 29 ans, y compris les femmes enceintes. Bien que la grossesse n'ait pas été considérée comme une contre-indication pendant cette campagne compte tenu des avantages de la vaccination, certaines femmes enceintes ont choisi de ne pas se faire vacciner. Du fait de la participation

<sup>3</sup> See <http://www.meningvax.org/>

<sup>4</sup> See No. 30, 2011, pp. 321–324.

<sup>5</sup> See [http://www.who.int/immunization/sage/4\\_WHO\\_Note\\_Vaccination\\_Pregnant\\_Women\\_during\\_MenA\\_conj\\_Campaigns\\_22Nov10\\_april\\_2011.pdf](http://www.who.int/immunization/sage/4_WHO_Note_Vaccination_Pregnant_Women_during_MenA_conj_Campaigns_22Nov10_april_2011.pdf)

<sup>6</sup> See No. 30, 2010, pp. 285–291.

<sup>3</sup> Voir <http://www.meningvax.org/>

<sup>4</sup> Voir N° 30, 2011, pp. 321–324.

<sup>5</sup> Voir [http://www.who.int/immunization/sage/4\\_WHO\\_Note\\_Vaccination\\_Pregnant\\_Women\\_during\\_MenA\\_conj\\_Campaigns\\_22Nov10\\_april\\_2011.pdf](http://www.who.int/immunization/sage/4_WHO_Note_Vaccination_Pregnant_Women_during_MenA_conj_Campaigns_22Nov10_april_2011.pdf)

<sup>6</sup> Voir N° 30, 2010, pp. 285–291.

tion of the districts in the INDEPTH network, this provided an opportunity to evaluate the safety of the meningococcal A vaccine by comparing the rates of pregnancy-related outcomes in vaccine recipients, with rates among unvaccinated pregnant women. In addition, a second age and season matched historical control group was assembled to document pregnancy outcomes in a time period before the immunization campaign. Outcomes included overall maternal, fetal and neonatal mortality, overall rates of spontaneous abortions, still births, perinatal deaths, prematurity, low birth weight, small for gestational age, and rates of caesarean section.

A total of 1730 pregnant women were vaccinated during the campaign, while 919 pregnant women elected not to be vaccinated. A total of 3551 pregnant women were in the historical unvaccinated control group. Comparing the outcomes, there was no significant difference in any of the pre-specified outcomes between women who had received the meningococcal A conjugate vaccine and those who had not, either in the concurrent or historical comparison groups. Mean birth weights were over or near 2900g in each group, and gestational age over 37 weeks. Rates of miscarriage and stillbirth were 1.8% in the vaccinated and 2.2% in both control groups, with prematurity 3.1% among the concurrent controls, 3.6% in the vaccinated and 5.6% among the comparison controls.

The Committee noted the quality of this study and its reassuring results. It highlighted the potential for this study methodology to examine the safety of vaccines in mass immunization contexts, especially in outcomes as complex as pregnancy. Previous attempts to study pregnancy outcomes have been less robust. Some details were more difficult to ascertain in this study, including reasons for spontaneous abortion, impact of vaccination during lactation and other factors that the demographic survey questions had not collected. However, future studies could be planned that would include additional variables added to the survey visits to address these questions.

Given that mass immunization campaigns have been staggered and another 100 million individuals are in line for vaccination over the next 2 years, opportunities for additional evaluation of meningococcal A conjugate vaccine in pregnancy will be available. This may include an opportunity to evaluate the vaccine's safety during lactation. This present study was conducted using existing infrastructure in the Navrongo Health Research Centre and thus may provide a powerful tool in these evaluations.

Overall, in the almost 4 years since MenAfriVac was rolled out in the first mass campaigns, and beginning even earlier with the clinical trials, no concerns have been identified regarding its use in pregnancy. As with other inactivated vaccines, neither pregnancy nor lactation are contraindications for vaccination in situations

des districts au réseau INDEPTH, cela a donné la possibilité d'évaluer l'innocuité du vaccin antiméningococcique A en comparant les taux pour les issues de la grossesse entre les femmes vaccinées et celles qui ne l'ont pas été. De plus, un second groupe témoin historique, apparié selon l'âge et la saison, a été réuni pour documenter les issues des grossesses à une époque antérieure à la campagne de vaccination. On a inclus dans les issues les taux généraux de mortalité maternelle, fœtale et néonatale, les taux généraux d'avortements spontanés, de naissances d'enfants mort-nés, de décès périnataux, de prématurité, de faible poids de naissance, de petite taille par rapport à l'âge gestationnel et de césariennes.

Au total, 1730 femmes enceintes ont été vaccinées pendant la campagne et 919 ont choisi de ne pas se faire vacciner. Il y avait dans le groupe témoin historique non vacciné 3551 femmes enceintes. En comparant les issues des grossesses, il n'y a pas eu de différence significative pour aucune de ces issues déterminées au préalable entre les femmes ayant été vaccinées avec le vaccin antiméningococcique A conjugué et les 2 groupes de comparaison, concomitant ou historique. Le poids moyen de naissance s'est établi au-dessus ou près de 2900 g dans chaque groupe, avec un âge gestationnel de plus de 37 semaines. Les taux de fausses couches et d'enfants mort-nés ont été de 1,8% chez les femmes vaccinées et de 2,2% dans les 2 groupes témoins, avec un taux de prématurité de 3,1% chez les témoins concomitants, 3,6% chez les femmes vaccinées et 5,6% chez le groupe témoin de comparaison.

Le Comité a pris note de la qualité de l'étude et de ses résultats rassurants. Il a attiré l'attention sur le potentiel de la méthodologie de cette étude pour examiner l'innocuité des vaccins dans le cadre des vaccinations de masse, notamment pour des résultats aussi complexes que les issues de la grossesse. Les tentatives antérieures pour étudier les issues de la grossesse ont été moins fiables. Certains détails ont été plus difficiles à déterminer pour cette étude, dont les raisons des avortements spontanés, l'impact de la vaccination pendant l'allaitement et d'autres facteurs pour lesquels les questions de l'enquête démographique ne donnaient pas de réponses. Toutefois, on pourrait planifier à l'avenir des études qui incluront ces variables supplémentaires, ajoutées aux visites dans le cadre de l'enquête pour répondre à ces questions.

Du fait que les campagnes de vaccination de masse ont été étalées dans le temps et que 100 millions de personnes supplémentaires sont prévues pour la vaccination au cours des 2 prochaines années, il y aura de nouvelles occasions de faire des évaluations supplémentaires du vaccin antiméningococcique A conjugué administré pendant la grossesse. Cela pourrait inclure la possibilité d'évaluer l'innocuité de ce vaccin pendant l'allaitement. L'étude dont nous parlons a été menée en utilisant les infrastructures existantes du Navrongo Health Research Centre et pourrait donc fournir un outil puissant pour ces évaluations.

Globalement, depuis près de 4 ans que le MenAfriVac est déployé dans les premières campagnes de vaccination de masse, et même plus si l'on inclut les essais cliniques, aucun problème n'a été repéré quant à son utilisation pendant la grossesse. Comme pour les autres vaccins inactivés, ni la grossesse, ni l'allaitement ne sont des contre-indications à la vaccination



of increased disease risk. Given the emerging evidence of the effectiveness of this meningococcal A conjugate vaccine in controlling disease in the countries of the meningitis belt in Africa, more permissive language in the package insert may be warranted.

### **Preparing for malaria vaccine introduction**

The most recent WHO malaria mortality estimate is 627 000 deaths for the year 2012. While this represents an estimated 42% reduction in global malaria mortality rates since 2000 in association with a large scaling up of WHO recommended preventive, diagnostic and treatment measures, there remains a need for additional preventive measures including vaccines. As one candidate malaria vaccine has reached the regulatory evaluation stage, GACVS considered the need for post-licensure safety assessment for when malaria vaccines become available for public use.

GACVS considers that the development of recommendations for post-licensure safety assessment of malaria vaccines is an important preparatory step, in order to provide early implementing sites with sufficient time for planning, training and improving or developing surveillance systems. Early identification of sites would also have the benefit of allowing the establishment of active surveillance for events of special interest, thereby providing background rates for those events prior to vaccine introduction. GACVS noted that the safety guidance would be developed alongside effectiveness and impact guidance and that it was important to ensure harmonisation with this guidance, as it is likely that studies could be designed to examine the impact of both safety and effectiveness. GACVS also noted the guidance was intended for use by the public sector of implementing countries to assist them to conduct independent studies and be prepared to assess data obtained by the manufacturer.

GACVS discussed the principal elements of such recommendations and suggested that the main components should cover on-going strengthening of routine systems for reporting adverse events following immunization (AEFIs), stimulated passive reporting in selected settings, such as health demographic surveillance system sites and active follow-up for specific events of interest using suitable epidemiological designs – such as case-control, self-controlled case series and cohort event monitoring – to enable testing of hypotheses and quantification of risks. These components would allow detection and evaluation of signals for rare unexpected events as well as assessment of events of interest from clinical trials – in particular febrile convulsions and meningitis. It was noted that it is important that lessons are learnt from the experience in Africa of safety studies for meningococcal serogroup A vaccine introduction, but that a key difference was that the vaccine would probably be introduced with a routine schedule rather than through large mass campaigns. It was also

dans des situations de risque accru de la maladie. Les données émergentes sur l'efficacité de ce vaccin antiméningococcique A conjugué pour lutter contre la maladie dans les pays de la ceinture africaine de la méningite justifieraient de délivrer des messages moins restrictifs dans les notices d'emballage.

### **Préparation à l'introduction du vaccin antipaludique**

L'estimation la plus récente de l'OMS concernant la mortalité par paludisme est de 627 000 décès pour l'année 2012. Alors que cela représente une baisse estimée à 42% des taux mondiaux de mortalité due à cette maladie depuis 2000, liée à une forte intensification des mesures recommandées par l'OMS pour la prévention, le diagnostic et le traitement, des mesures supplémentaires de prévention, dont les vaccins, demeurent nécessaires. Avec l'arrivée d'un vaccin candidat au stade de l'évaluation réglementaire, le GACVS a étudié le besoin d'évaluation posthomologation de l'innocuité pour les vaccins antipaludiques devenant disponibles pour un usage public.

Le Comité considère que l'élaboration de recommandations pour l'évaluation posthomologation de l'innocuité des vaccins antipaludiques est une étape préparatoire importante pour donner aux premiers sites mettant en œuvre la vaccination suffisamment de temps pour la planification, la formation, ainsi que pour l'amélioration ou la création de systèmes de surveillance. La désignation précoce des sites aurait également l'avantage de permettre la mise en place d'une surveillance active des événements présentant un intérêt particulier, donnant ainsi des taux de référence pour ces événements avant l'introduction du vaccin. Le GACVS a relevé que des orientations sur l'innocuité seront élaborées en même temps que celles sur l'efficacité et l'impact et que ce point était important pour assurer leur harmonisation, car il est probable que l'on puisse concevoir des études pour examiner à la fois l'impact de l'innocuité et de l'efficacité. Il a également noté que les orientations étaient destinées au secteur public dans les pays mettant en œuvre la vaccination pour les aider à faire des études indépendantes et à se préparer à évaluer les données fournies par le fabricant.

Le GACVS a discuté des principaux éléments de ces recommandations et proposé qu'ils couvrent le renforcement en cours des systèmes ordinaires de notification des manifestations postvaccinales indésirables (MAPI), la stimulation de la notification passive dans certaines conditions, comme les sites de surveillance démographique et sanitaire et le suivi actif de certains événements spécifiques intéressants à l'aide de modèle épidémiologiques adaptés – comme la méthode cas-témoins, les séries de cas autocontrôlées et le suivi des événements par cohorte – pour permettre de tester les hypothèses et de quantifier les risques. Ces éléments permettraient de détecter et d'évaluer les signaux concernant des événements rares et inattendus, ainsi que d'évaluer les événements intéressants survenant dans le cadre des essais cliniques, notamment les convulsions fébriles et la méningite. Il a été noté qu'il était important de tirer les enseignements de l'expérience en Afrique des études d'innocuité pour l'introduction du vaccin antiméningococcique contre le séro groupe A, à la différence essentielle toutefois que le vaccin allait probablement être introduit dans le cadre d'un calendrier de vaccination systématique plutôt que dans celui de

noted that it is important that the guidance balances the need for high quality studies with what is feasible in the settings where these studies are likely to be done. This includes, for example, use of case definitions adapted to local clinical practice. Further discussion focused on the importance of considering rare but serious events and possible mechanisms for following up vaccine recipients such as diary cards, issuing of mobile telephones or identifying patients through hospital admissions. It is expected that a guidance document will be available in mid-2015.

### **Fifteen years of GACVS: challenges and opportunities**

On the occasion of its 15th anniversary, the Committee reviewed its accomplishments and reflected on new challenges in view of the evolving public health environment. The first GACVS meeting took place on 14–15 September 1999, and the Committee's first report addressed macrophagic myofasciitis.<sup>7</sup> Since then, the Committee has met regularly twice yearly and has also been convened by telephone conference more frequently when needed. The Committee's regular reports are published soon after each meeting in the WHO *Weekly Epidemiological Record*, while urgent reports are posted separately on-line, and a compendium is available on the GACVS website maintained by WHO.<sup>8</sup> Since its establishment the Committee has produced >100 reports related to vaccine safety issues. The role of the GACVS is primarily to assess risks related to vaccine use in order to assist policy-makers in identifying benefit and risks as part of evidence-based vaccination policies. GACVS risk assessments are regularly used by WHO advisory bodies, including the Strategic Advisory Group of Experts (SAGE), the Expert Committee on Biological Standards (ECBS) as well as regional technical advisory groups related to immunization.

In addition to its regular committee reports, GACVS also issues statements in response to urgent vaccine safety issues. If required, the committee can be convened urgently by conference call in order to respond to alerts of international significance. More recently, GACVS has also looked into capacity building aspects of global vaccine pharmacovigilance. The committee has, in particular, provided advice on the development of the Global Vaccine Safety Blueprint<sup>9</sup> – WHO's strategy to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods in all countries – and is now advising on the development of specific tools for vaccine safety monitoring, including the classification of AEFI, core data elements, and indicators for surveillance systems.

grandes vaccinations de masse. Les participants ont également relevé qu'il était important que les orientations maintiennent l'équilibre entre le besoin de faire des études de grande qualité et ce qui est faisable dans l'environnement où ces études auront probablement lieu. Cela comporte, par exemple, l'utilisation de définitions de cas adaptées à la pratique clinique locale. D'autres discussions ont porté sur l'importance de tenir compte des événements rares mais graves et des dispositifs possibles pour le suivi des sujets vaccinés, comme des fiches journalières, la distribution de téléphones portables ou l'identification des patients au moyen des admissions hospitalières. Un document d'orientation devrait être disponible d'ici la mi-2015.

### **Les quinze ans du GACVS: défis et opportunités**

À l'occasion de son quinzième anniversaire, le Comité a passé en revue ses réalisations et réfléchi aux nouveaux défis devant l'évolution de l'environnement de la santé publique. La première réunion du Comité s'est tenue les 14-15 septembre 1999 et le premier rapport a traité de la myofasciite à macrophages.<sup>7</sup> Depuis lors, le Comité s'est réuni régulièrement 2 fois par an et a également été convoqué en téléconférence plus fréquemment si nécessaire. Ses rapports réguliers sont publiés peu après chaque réunion dans le *Relevé épidémiologique hebdomadaire* de l'OMS, tandis que les rapports urgents paraissent séparément en ligne; un compendium est disponible sur le site du GACVS géré par l'OMS.<sup>8</sup> Depuis sa création, le Comité a publié >100 rapports sur des questions liées à la sécurité des vaccins. Son rôle consiste principalement à évaluer les risques liés à l'utilisation des vaccins afin d'aider les responsables politiques à déterminer les avantages et les risques dans le cadre de politiques vaccinales fondées sur des données probantes. Les évaluations du risque par le GACVS sont régulièrement utilisées par des organes consultatifs de l'OMS, comme le Groupe stratégique consultatif d'experts sur la vaccination (SAGE), le Comité d'experts de la standardisation biologique (ECBS) ainsi que des groupes techniques consultatifs régionaux concernés par la vaccination.

En plus de ses rapports réguliers, le GACVS publie aussi des déclarations en réponse à des problèmes urgents de sécurité vaccinale. Si nécessaire, le Comité peut être convoqué en urgence par téléconférence afin de réagir aux alertes d'importance internationale. Plus récemment, il s'est aussi penché sur les aspects liés au renforcement des capacités en matière de pharmacovigilance mondiale pour les vaccins. Le Comité a, en particulier, donné des conseils pour l'élaboration du plan «Global Vaccine Safety Blueprint»<sup>9</sup> – une stratégie de l'OMS visant à optimiser l'innocuité des vaccins par une application efficace des principes et méthodes de la pharmacovigilance dans tous les pays –, et il émet des avis sur la mise au point d'outils spécifiques pour la surveillance de la sécurité vaccinale, dont la classification des MAEI, des données de base et des indicateurs pour les systèmes de surveillance.

<sup>7</sup> See No. 41, 1999, pp. 338–340.

<sup>8</sup> See [http://www.who.int/vaccine\\_safety/committee/topics/en/](http://www.who.int/vaccine_safety/committee/topics/en/)

<sup>9</sup> WHO 2012. Global Vaccine Safety Blueprint. WHO/IVB/12.07

<sup>7</sup> Voir N° 41, 1999, pp. 338–340.

<sup>8</sup> Voir [http://www.who.int/vaccine\\_safety/committee/topics/en/](http://www.who.int/vaccine_safety/committee/topics/en/)

<sup>9</sup> OMS, 2012. Global Vaccine Safety Blueprint. WHO/IVB/12.07.

A total of 39 experts have served on GACVS to date, the current committee being composed of 15 members. Current and past members represent all WHO regions, although a majority (26) originate from industrialized countries in Europe, North America or Australia. They provide expertise in multiple fields related to vaccine safety including epidemiology, statistics, clinical medicine, pharmacology and toxicology, infectious diseases, public health, immunology, vaccinology, pathology, ethics and health product regulation. GACVS members, in addition to participating in bi-annual in-person meetings also contribute to the work of the committee through various subgroups which develop statements on selected topics between regular meetings.

Perspectives were presented on the relevance of the work of the GACVS, including views from an immunization programme, a regulatory authority, a vaccine clinician, a vaccine communication expert, a pharmacovigilance collaborating centre, and a WHO advisory committee. The discussion highlighted several specific examples where GACVS provided timely and useful guidance. Those have addressed some time-limited issues such as the risk of Bell's palsy following intranasal vaccination in 2002,<sup>10</sup> transmissible spongiform encephalopathy raised in 2004<sup>11</sup> and conjugate meningococcal vaccines and Guillain-Barre syndrome in 2005.<sup>12</sup> Other vaccines were reviewed and re-visited over time as new evidence accumulated or in response to new concerns. An example concerned the vaccine preservative thiomersal which was first discussed in 2002; additional reassuring evidence became available over time and a more comprehensive review was provided in preparation for the United Nations Environmental Program development of a global legally binding instrument on mercury, now known as the Minamata Convention on Mercury (2013).<sup>13</sup> Similarly, evolving evidence related to the risk of intussusception associated with rotavirus vaccines has been continuously reviewed since 2005.<sup>14</sup>

The discussion highlighted the needs for an evolving approach in several domains. Particular considerations were given to: i) the evolving technical aspects of vaccine pharmacovigilance; ii) process issues related to GACVS operations; and iii) communication of GACVS findings. With respect to technical aspects, the main needs relate to the increasing number of new vaccine products that are becoming available for immunization programmes and their rapid availability for populations that are not served with robust safety monitoring systems. In some instances, some vaccines are specifically

Au total, 39 experts ont servi le GACVS jusqu'à présent, le Comité actuel se composant de 15 membres. Les membres actuels et du passé représentent toutes les Régions de l'OMS, bien qu'une majorité (26) viennent des pays industrialisés d'Europe, d'Amérique du Nord et de l'Australie. Ils apportent leur expertise dans de nombreux domaines liés à la sécurité vaccinale, comme l'épidémiologie, les statistiques, la médecine clinique, la pharmacologie, la toxicologie, les maladies infectieuses, la santé publique, l'immunologie, la vaccinologie, la pathologie, l'éthique et la réglementation des produits sanitaires. En plus de participer en personne aux réunions semestrielles, les membres du GACVS contribuent aux travaux du Comité en faisant partie de divers sous-groupes qui élaborent des déclarations sur certains sujets entre les réunions régulières.

Des points de vue ont été présentés sur la pertinence des travaux du GACVS, notamment de la part d'un programme de vaccination, d'une autorité de réglementation, d'un clinicien spécialiste des vaccins, d'un expert de la communication sur les vaccins, d'un centre collaborateur pour la pharmacovigilance et d'un comité consultatif de l'OMS. La discussion a souligné plusieurs exemples spécifiques d'orientations utiles données rapidement par le GACVS. Elles ont porté sur des problèmes limités dans le temps, comme le risque de paralysie de Bell à la suite de la vaccination intranasale en 2002,<sup>10</sup> la question des encéphalopathies spongiformes transmissibles soulevée en 2004<sup>11</sup> et celle concernant le vaccin antiméningococcique conjugué et le syndrome de Guillain-Barré en 2005.<sup>12</sup> D'autres vaccins ont été réexaminés avec un œil neuf à mesure que de nouvelles données se sont accumulées ou en réponse à de nouvelles inquiétudes. Un exemple en a été le thiomersal, agent de conservation des vaccins dont on a discuté pour la première fois en 2002; de nouvelles données probantes rassurantes sont parvenues avec le temps et un examen plus complet a été fourni en préparation de l'élaboration par le Programme des Nations Unies pour le Développement d'un instrument juridique mondial contraignant sur le mercure, désormais appelé Convention de Minamata sur le mercure (2013).<sup>13</sup> De même, l'évolution des faits connus relatifs au risque d'invagination intestinale lié aux vaccins antirotavirus a fait l'objet d'un examen continu depuis 2005.<sup>14</sup>

La discussion a souligné le besoin de faire évoluer l'approche dans plusieurs domaines. Une attention particulière a été consacrée: i) à l'évolution des aspects techniques de la pharmacovigilance pour les vaccins; ii) au fonctionnement du GACVS; et iii) à la communication des conclusions du GACVS. Concernant les aspects techniques, les principaux besoins sont liés au nombre croissant de nouveaux produits vaccinaux mis à la disposition des programmes de vaccination et à leur disponibilité rapide dans des populations qui ne sont pas couvertes par des systèmes robustes de surveillance de la sécurité. Il arrive que certains vaccins soient spécifiquement

<sup>10</sup> See No. 47, 2002, p. 393.

<sup>11</sup> See No. 1, 2005, pp. 4-5.

<sup>12</sup> See No. 2, 2006, p. 18.

<sup>13</sup> See [http://www.who.int/vaccine\\_safety/committee/topics/thiomersal/en/](http://www.who.int/vaccine_safety/committee/topics/thiomersal/en/)

<sup>14</sup> See [http://www.who.int/vaccine\\_safety/committee/topics/rotavirus/en/](http://www.who.int/vaccine_safety/committee/topics/rotavirus/en/)

<sup>10</sup> Voir No 47, 2002, p. 393.

<sup>11</sup> Voir N° 1, 2005, pp. 4-5.

<sup>12</sup> Voir N° 2, 2006, p. 18.

<sup>13</sup> Voir [http://www.who.int/vaccine\\_safety/committee/topics/thiomersal/fr/](http://www.who.int/vaccine_safety/committee/topics/thiomersal/fr/).

<sup>14</sup> Voir [http://www.who.int/vaccine\\_safety/committee/topics/rotavirus/fr/](http://www.who.int/vaccine_safety/committee/topics/rotavirus/fr/).

designed for rapid roll-out in parts of the world that report very few AEFIs and have not developed strong expertise for investigating specific concerns or actively monitoring them. This requires additional guidance from GACVS, not only in assessing available evidence but in identifying gaps in knowledge and proposing approaches that could be reasonably expected to answer the most pressing questions in those particular settings (e.g. the safety of meningococcal A conjugate vaccine used during pregnancy, as reviewed during this meeting). In addition, the methods by which vaccines are developed and produced is evolving, relying on newer technologies and processes. Likewise, individual susceptibility to vaccine reactions varies and new methodologies, including genomics, could potentially provide useful insights with respect to predisposing factors and ways to minimize such risks.

With respect to the GACVS process, the committee's independence – including from the WHO secretariat – and high level of individual expertise are the main features that can maintain the credibility and impact of its advice. Participants also highlighted the need to maintain the highest possible standards with respect to the review of scientific evidence and adjusting with evolving methodologies. This implies a greater use of systematic and graded reviews when an association between a vaccine and a particular health event has been studied in many parts of the world. However this requirement will not affect most of GACVS' work, since it has increasingly focused on accompanying the early post-licencing use of new vaccine products for which the scientific evidence is usually available from a limited number of sources. Throughout its existence, GACVS has operated through closed sessions. This confidential process was deemed necessary in order to ensure that all available data, including proprietary information, could be considered. Ensuring that committee deliberations could be protected from undue influence was another consideration. In view of evolving standards relating to committees of public importance, it was recommended that a transparency policy be developed with a view to providing more specific information on how conclusions were reached.

GACVS communication is currently directed to WHO technical audiences through the WHO *Weekly Epidemiological Record* and website. These audiences are immunization managers and policy makers in health ministries, regulatory authorities, professional organizations and immunization advisory groups in Ministries of Health. One GACVS initiative to reach out to broader audiences, and help counteract anti-immunization groups, was launched in 2003 through the creation of the Vaccine Safety Net. In order to assess information on vaccines publicly available on the internet, GACVS developed 4 categories of criteria for good information practices – regarding credibility, content, accessibility

conçus pour être lancés dans des régions du monde qui notifient très peu de MAPI et n'ont pas développé une expertise puissante leur permettant d'enquêter sur des inquiétudes particulières ou de les surveiller. Ce point nécessite des orientations supplémentaires de la part du GACVS, pas seulement pour évaluer les données factuelles disponibles, mais aussi pour déterminer les lacunes dans les connaissances et proposer des approches qui devraient raisonnablement permettre de répondre aux questions les plus pressantes dans ces circonstances particulières (par exemple l'innocuité du vaccin antiméningococcique A conjugué utilisé pendant la grossesse, un point examiné pendant la réunion). De plus, on assiste à une évolution des méthodes de mise au point et de production des vaccins, s'appuyant sur de nouvelles technologies et procédés. De même, la sensibilité individuelle aux réactions vaccinales varie et de nouvelles méthodes, dont la génomique, pourraient apporter potentiellement des perspectives utiles pour ce qui est des facteurs de prédisposition et des moyens de réduire au maximum les risques.

Pour ce qui est du fonctionnement du GACVS, l'indépendance du Comité, y compris par rapport au Secrétariat de l'OMS, et le haut niveau d'expertise individuelle sont les principales caractéristiques pouvant maintenir la crédibilité et l'impact de ses avis. Les participants ont également souligné la nécessité de maintenir les normes les plus élevées possible lorsqu'il s'agit d'examiner les preuves scientifiques et de s'ajuster à l'évolution des méthodologies. Cela implique d'avoir davantage recours aux examens systématiques et avec gradation lorsqu'un lien entre un vaccin et un événement sanitaire particulier a été étudié dans de nombreuses régions du monde. Toutefois, cette exigence n'aura pas d'incidence sur la majorité des travaux du GACVS, puisqu'il s'est de plus en plus axé sur l'accompagnement de l'utilisation de nouveaux produits vaccinaux peu après leur homologation et, dans ce cadre, les données scientifiques ne sont en général disponibles qu'auprès d'un nombre limité de sources. Tout au long de son existence, le GACVS a fonctionné à huis clos. Cette méthode de travail confidentielle a été jugée nécessaire pour s'assurer que toutes les données disponibles, y compris les informations protégées, puissent être étudiées. La garantie que les délibérations du Comité puissent être protégées d'influences indues a été une autre considération prise en compte. Au vu de l'évolution des normes liées aux comités d'importance publique, il a été recommandé d'élaborer une politique de la transparence, l'objectif étant de donner des informations plus spécifiques sur le cheminement suivi pour parvenir aux conclusions.

Les communications du GACVS sont actuellement adressées au public technique de l'OMS par l'intermédiaire du *Relevé épidémiologique hebdomadaire* et du site Web. Font partie de ce public les administrateurs de la vaccination et les responsables politiques dans les ministères de la santé, les autorités de réglementation, les organisations professionnelles et les groupes consultatifs des ministères de la santé sur la vaccination. En 2003, le GACVS a pris une initiative pour toucher un public plus large et contrecarrer les groupes anti-vaccination en créant le «Vaccine Safety Net». Afin d'évaluer les informations sur les vaccins disponibles pour le grand public sur Internet, le GACVS a mis au point 4 catégories de critères pour de bonnes pratiques en matière d'information, concernant la



and design – to which sites providing information on vaccine safety should adhere. WHO evaluates websites for their adherence to these criteria and provides a list of resources in multiple languages. Vaccine safety communication, however, should be developed further and it was proposed that WHO examine approaches taken in other sciences where public risk is an important consideration, in order to develop and promote more effective practices.

The Committee concluded that although its work is well established and recognized, it was critical to remain mindful of current vulnerabilities. The evolving global vaccination landscape requires a continuous adjustment of methods and processes. A detailed report in preparation will provide a more comprehensive account of this analysis and propose a way forward to ensure that independent advice on vaccine safety issues for WHO remains relevant and timely. ■

crédibilité, le contenu, l'accessibilité et la conception, que les sites donnant des informations sur la sécurité vaccinale doivent respecter. L'OMS évalue les sites en fonction de leur respect de ces critères et fournit une liste de ressources dans de multiples langues. Il faut cependant développer davantage la communication sur la sécurité des vaccins et il a été proposé que l'OMS examine les approches suivies dans d'autres domaines scientifiques où le risque pour le public est un élément important, afin de mettre au point et de promouvoir des pratiques plus efficaces.

Le Comité a conclu que, bien que ses travaux soient bien établis et reconnus, il était essentiel de garder à l'esprit ses vulnérabilités actuelles. L'évolution du paysage mondial de la vaccination impose un ajustement permanent des méthodes et des processus. Un rapport détaillé en préparation rendra compte de manière plus complète de cette analyse et proposera une voie à suivre pour s'assurer que les conseils indépendants sur les questions de sécurité vaccinale pour l'OMS restent pertinents et soient donnés en temps utile. ■

### 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](mailto: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](mailto:listserv@who.int)** en laissant vide le champ du sujet. Le texte lui-même ne devra contenir que la phrase suivante: subscribe wer-reh.

WWW access • **<http://www.who.int/wer/>**  
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## WORLD HEALTH ORGANIZATION IMMUNIZATIONS, VACCINES AND BIOLOGICALS

### IMMUNIZATION PRACTICES ADVISORY COMMITTEE (IPAC)

11-12 June 2014

### Final meeting report and recommendations

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#### **Opening and Introduction**

Mr Michel Zaffran, Coordinator of WHO's Expanded Programme on Immunization, officially opened the meeting. Dr Chris Morgan, the Chair, welcomed participants and acknowledged the regrets of Dr K.O. Antwi-Agyei, Dr Xavier Bosch-Capblanch, Dr Shelley Deeks, and Dr Folake Kio-Olayinka. He welcomed Mr Adama Sawadogo, representative of UNICEF replacing Dr Osman Mansoor, and expressed the regrets of Dr Majo Leroux-Lepage as the representative of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

#### **IPAC Members present:**

Christopher Morgan (Chair)  
Robin Biellik  
Jonathan Colton  
Francois Gasse  
Najwa Khuri-Bulos  
Jean Marc Olivé  
Robert Steinglass  
Carla Vizzotti

#### **Session I. Home-based vaccination records**

Ms Marta Gacic Dobo summarized the available information on format and utilization of home-based records, a useful but neglected tool. She underscored the upcoming opportunity to revitalize home-based vaccination records around the introduction of inactivated poliovirus vaccine (IPV) in many countries. Ms Skye Gilbert provided an overview of the Bill and Melinda Gates Foundation supported design contest, "Record for Life", including the process of selecting the finalists and a variety of innovative ideas from finalists.

#### **Discussion:**

The presentations were well received and followed with rich discussion. IPAC was requested to comment on presented activities and identify any additional ways to revitalize the role of home-based records within the service delivery bundle.

Integrated versus vertical approaches to home-based vaccination records were brought up by several IPAC members and participants. It was recognised that completeness of sections not related to immunization within home-based records is not well understood and poorly documented and that there is a need for additional operational research in this area. It was

also well recognized that an integrated approach can present challenges to immunization programmes in terms of coordinating with other programmes when confronted with the need to update in case of new vaccine introduction compared to a simple vaccination-only record. Furthermore, it was emphasised that home-based records should be synchronised with other monitoring tools such as facility-based records.

The current proxy measure of home-based record prevalence derived from survey results can be misleading, as it does not capture if the card was provided to a caregiver. In addition, in some areas this measure can overestimate the prevalence, as cards are based at health facilities and not with caregivers in many European countries. These instances should not detract from nor overshadow the global problem of low home-based record prevalence, particularly in low-income settings.

Improvements in home-based record prevalence may benefit more from improving community demand as much as from approaches focused on a technology push.

The issue and challenges around recording within a life course approach to immunization was also raised, including the need to document good practices. In many settings, it will take creative efforts to shift from current retention behaviours to expected retention beyond the first year of life.

Forecasting and proper stock management of home-based vaccination records is considered critical. Unnecessary extra stock of cards should be avoided, especially in case of frequent updates of immunization cards. There is a need for integration into stock management and inclusion in existing tools such as the district vaccine data management tool (DVD-MT).

The issue of whether or not to record doses received during SIAs on the home-based record was acknowledged by the presenters.

The main suggestions raised by IPAC included:

1. The need to identify the “value proposition” of the records, which may or may not be in the form of requiring caregivers to have a financial vested interest in the document. Ensuring that the records are valued by caregivers will, in many instances, address some of the household level retention issues. Encouraging school entry screening of immunization history may also assist with increasing home-based record retention and may also lead to vaccination in the case of missed doses.
2. The increasing need for greater commitment from government, and less reliance on external partners and donors for printing and financing immunization cards.
3. The essential role of adequate training of health workers on making the home-based record available and being able to communicate its contents to caregivers.
4. The importance of testing innovation and utilization of new technological solutions to home-based records within the local setting. While the ideal recording and monitoring situation is a comprehensive community-based electronic immunization registry with automatic caregiver reminders, the reality is that many countries remain far from implementing such an approach. Home-based vaccination records therefore have an important role in many settings. Solutions that introduce incremental transitions to tomorrow’s needs must be sought.

5. The value of conducting additional cost effectiveness analyses to document the marginal impact of small interventions vis-à-vis improvements in coverage, reductions in drop-out, overall improved satisfaction with the record which may lead to improved community demand/availability/utilization/retention.

IPAC members offered to review a draft guide document being developed to assist with the design and use of home-based records and provide further input.

## **Session II. Immunization Management Group (IMG) for IPV Introduction**

Three presentations were given during this session in order to provide an overview of Objective 2 of the End Game Strategic Plan and the work of the IMG in strengthening routine immunization, IPV introduction and the switch from trivalent OPV (tOPV) to bivalent OPV (bOPV).

### **A. Update on IMG and IPV introduction plans** (*Michel Zaffran, WHO/IVB/EPI*)

Mr Michel Zaffran presented the work of IMG to coordinate efforts toward the implementation of objective 2 of the polio endgame strategic plan and provided the latest country update on implementation of the IPV introduction. As of June 2014, 72 countries globally are using IPV. Out of the 126 countries targeted to introduce IPV before the end of 2015, four have introduced already, seven are planning to do so in 2014, while 73 countries have expressed their commitment to introduce the vaccine during 2015. This will represent a programmatic challenge of unprecedented magnitude. There are currently 42 countries for which there is no plan or no information on intent.

To maintain this momentum, financing options for low and middle-income countries not GAVI-eligible are being explored as these countries might be at risk of non-implementation. There are clear risks if these countries do not meet the deadlines, particularly when some of these countries fall in the Tier 2 and Tier 3 group of countries, which are at high-risk of outbreak or importation in case of the reintroduction of type 2 vaccine derived polio virus. A decision (by the Polio Oversight Board) on this financial support is expected by the end of June 2014.

Other streams of work in cold chain improvement, communications and licensing of IPV were also briefly presented.

### **B. Routine Immunization activities in priority countries** (*Rudi Eggers, WHO/IVB/EPI*)

Dr Rudi Eggers presented on the work of the routine immunization (RI) subgroup of the IMG, which promotes synergies between the Global Polio Eradication and RI strengthening. Under this plan, Global Polio Eradication initiative assets in 10 focus countries are to be utilized for RI strengthening. One of the main objectives of the IMG RI subgroup is to ensure that annual comprehensive EPI action plans clearly identify how the polio assets will be used to strengthen routine immunization. This objective is also an indicator of the polio endgame strategic plan. Currently eight out of the ten focus countries have such an annual plan which has been formally endorsed at national level (target all 10 countries by 2014).

The Bill and Melinda Gates Foundation (BMGF) grant to Chad, DR Congo and Nigeria to strengthen RI through polio was outlined. This project has shown good results in the three countries with an increase of coverage of the 3<sup>rd</sup> dose of pentavalent vaccine in the majority of

districts supported. As an example, in Nigeria, where the project was implemented in 39 polio high-risk LGAs of 10 northern states, there has been a substantial increase in the number of fixed and outreach sessions conducted during the first quarter of 2014 compared with the same period in 2013.

Other RI funding proposals from priority countries (Pakistan, Somalia, South Sudan, DR Congo, Ethiopia, India and Nigeria) were also presented in detail.

**C. Draft framework for in-country operational protocol for switch from tri-valent to bi-valent OPV** (*Alejandro Ramirez Gonzalez, WHO/IVB/EPI*)

Mr Alejandro Ramirez Gonzalez presented the draft protocol that is being developed for guiding regions and countries through the planning and implementation of the switch from tOPV to bOPV that should take place in April 2016. The protocol has 3 main areas: management and supervision, logistics and disposal, and communication. The protocol presents the major switch timelines from a global perspective but also translates the timelines into a country specific timeline, providing the main task and activities at each step.

It is envisaged that the existing national certification committees will play an important role in the switch process, both in the planning and supervision parts. At the service delivery level, there will be a need to have a cadre of switch monitors that will supervise and certify the successful switch within the given deadlines.

The importance of having a solid and well-prepared communication strategy was highlighted in several occasions throughout the discussion. Another area of critical importance that needs to be very carefully planned is the logistics involved in the removal of the tOPV from the supply chain and its safe and proper disposal.

**Discussion:**

Regarding the IMG work, IPV introduction plans and Routine Immunization activities, the following issues were discussed.

<p><b>Number of doses, preferred schedules and rationale for IPV</b></p>	<p>IPV has to be introduced in the remaining 122 countries that still do not use IPV. The IPV dose will not replace OPV, it will be provided in addition to OPV. SAGE has recommended that this dose be administered at 14 weeks or at the 1st immunization subsequent contact, together with the other scheduled vaccinations. The IPV dose is not recommended to be given in an SIA mode. (Indeed, the introduction of IPV is a risk mitigation strategy for when Type 2 OPV is withdrawn; it should therefore be given as part of the routine immunization programme. In exceptional circumstances, i.e. areas of difficult access in Nigeria and Pakistan and in the context of eradication efforts, IPV may be exceptionally given in campaigns). Alternative schedules can be considered in countries with specific epidemiologic characteristics or particular calendars in place. For instance, in countries where vaccine associated paralytic polio (VAPP) is the main concern, rather than circulating vaccine-derived polio</p>
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	virus (cVDPVs), the schedule can be adjusted and the IPV dose administered earlier (South American countries as an example).
<b>Routine Immunization coverage thresholds required for the switch</b>	No minimum coverage is required as a pre-requisite for the switch to bOPV to take place. There is a well-defined set of criteria to assess country readiness for type 2 OPV withdrawal, however this does not include coverage thresholds. As a matter of principle however, it is important that countries reach high coverage levels with all their vaccines, including IPV, and therefore the work on strengthening routine immunization is a strong component of Objective 2 of the Polio Eradication and Endgame Strategic Plan.
<b>Routine Immunization systems in the post-eradication era</b>	In the remaining polio endemic countries and areas, polio program health workers have been predominantly exposed to SIAs and eradication work, with less emphasis on routine immunization systems in the broader sense. This entire cadre of health and immunization workers should be trained in sustaining routine efforts after polio is eradicated.
<b>Bio-containment</b>	Bio-containment and stockpiles are critical for any unforeseen events in the future. This is part of objective 3 of the endgame plan. Objective 2 is focused on the safe and successful removal of Type 2 OPV.

Regarding the draft framework for the in-country operational protocol for switching from tri-valent to bi-valent OPV, the following issues were raised and discussed:

<b>OPV supply</b>	If the switch has to be delayed, enough production capacity and stock of tOPV will need to be secured to continue vaccination at least for another year. The industry has been consulted and the protocol is being discussed with UNICEF Supply Division on a regular basis. Different possible scenarios around the switch have been studied and forecasts of vaccine needs were developed accordingly. bOPV will be supplied through the same mechanisms as OPV, meaning countries procuring through UNICEF will continue to do so.
<b>Existing national committees in the management and supervision</b>	The proliferation of new committees should be avoided and, when possible, the expertise and experience of expert groups already established in-country should be tapped (e.g., the National Polio Certification Committees [NCCs]).

<b>Type 2 cVDPVs and the withdrawal of Type 2 OPV</b>	Most of the cVDPVs are caused by the Type 2 virus and withdrawing the Type 2 from the vaccine will have a direct impact on the number of cVDPVs. With the introduction of IPV and the administration of bOPV there will also be better protection against the risk of cVDPV types 1 and 3.
<b>Environmental sampling for polio viruses</b>	Environmental surveillance will continue to expand and to strengthen its capacity to detect polio viruses, not only for wild viruses but also for circulating vaccine viruses.
<b>Timing of the switch</b>	The switch has a global timeline set for the low transmission season. However this might not be the most appropriate timeframe in all parts of the globe. IPAC questioned whether there is any flexibility on this timeline. Currently, the switch is conceived as global and synchronized. The timing of the switch is based on the transmission patterns of the polio virus, coinciding with the lowest transmission time in the currently endemic areas.
<b>Communization</b>	A communication strategy is a crucial part of the switch. A comprehensive strategy will be developed to take into account the many aspects of the switch and to clearly communicate the complexities of the process.
<b>Monitoring</b>	If not all health facilities are monitored, the sense of importance and urgency may be lost. In the case that this is not feasible, a "0 case reporting" mechanism could be put into place so that all the facilities have the responsibility to at least report on their stocks.
<b>Waste Disposal</b>	Waste disposal is a very crucial part of the protocol. The end goal of the protocol is to safely dispose the remaining tOPV after the switch.

### Recommendations and Decisions by IPAC

1. The target audience/s of the switch protocol and communication documents should be clearly defined.
2. The drafting committee is encouraged to consider allowing flexibility on the timeline and dates for the global switch.
3. IPAC suggests to structure the document into two parts: firstly, the rationale and the scientific background, and secondly the operational issues: the what, how, when and who (the actual guidelines).
4. The drafting committee is encouraged to strengthen the section on waste disposal
  - a. Provide concrete guidance on the hierarchy of disposal methods (rather than simply list them).

- b. Provide references to the key global guidelines.
- c. Gather data on current methods of disposal in countries.

### **Session III. Global Updates**

#### **A. Update on Vaccine Delivery Technologies Meeting** (*Carsten Mantel, WHO/IVB/EPI*)

Dr Carsten Mantel summarized the diverse discussions and conclusions of this meeting held in Geneva, Switzerland in February 2014, attended by a broad representation of public health global stakeholders, including academia and industry. The main focus was lessons learned from prior technology development experiences as well as the landscape of new vaccine delivery, formulation, and packaging technologies.

It was agreed that among the key benefits of moving the new vaccine delivery technology agenda forward are increasing immunization coverage and safety, reduction of health care worker time spent on delivering vaccines, reduction of contamination risks and of programmatic errors. However, significant challenges were noted, including establishing consensus on public health needs, quantifying potential impact, influencing purchasers' decision-making processes, and meeting shifting and uncertain regulatory requirements. Recommendations were made on short-term and long-term goals for vaccine delivery technologies, as well as proposed steps towards coordinating and guiding the development and introduction of new technologies.

#### **B. Vaccine Presentation and Packaging Advisory Group/VPPAG** (*Debbie Kristensen, IPAC observer*)

Ms Debra Kristensen confirmed that the VPPAG serves as a valuable mechanism for dialogue across immunization stakeholders, including public and private sectors, addressing the programmatic suitability of the presentation and packaging of vaccine products. It was clarified that the group seeks consensus and provides guidance to vaccine manufacturers around presentation and packaging issues for future vaccine products, but its recommendations are not binding. Among the constraints faced by the VPPAG are the difficulty in engaging developing country manufacturers and the lack of dedicated funding. It was emphasized that anyone is welcome to listen in on the monthly teleconferences that take place on the second Tuesday of each month. The VPPAG's major areas of work for 2014 consist of guidance on barcodes, vaccine container dimensions, and insulated shipping containers. In addition, the group is in the process of updating the generic preferred product profile for vaccines.

### **Session IV. Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ)**

#### **A. Update from the Standing Committee on PSPQ**, (*Robin Biellik, IPAC Member*)

Dr Robin Biellik provided an update on the Standing Committee's operations which consist of reviewing the operational characteristics of vaccines submitted to WHO for pre-qualification (PQ) that do not comply with the "Programmatic Suitability for Pre-Qualification" (PSPQ) mandatory and/or critical characteristics in order to make a recommendation to the WHO PQ Secretariat on whether pre-qualification should proceed or not.

Two assessments have taken place since the IPAC meeting in October 2013. The first was in response to a new request for an advance opinion on a candidate malaria vaccine (not yet



formally submitted for PQ). The vaccine failed a critical requirement because it is a non-live unpreserved lyophilized product presented in a multi-dose vial. In view of the public health benefits of this vaccine, the Committee recommended that the product be accepted for PQ review, provided that specific field precautions are implemented. The issue of public health necessity triggered much discussion and it was agreed that the WHO Secretariat should provide guidance on a standardized approach to balancing the risks of potential programmatic errors against public health benefits of new vaccines. The IPAC was also reminded that advance opinions from the PSPQ Standing Committee are not binding on the PQ process, and reflect only the current situation.

The second review concerned a recommendation requested for a candidate rotavirus vaccine (formally submitted for PQ). The vaccine failed two critical characteristics: (a) thermostability data are non-compliant with the use of VVM2 and (b) the product is not ready-to-use (it requires the prior administration of an antacid buffer dose). The Committee recommended that this product be rejected for PQ review on the basis that the vaccine posed a high risk of programmatic errors, no shortage in rotavirus vaccine supply is foreseen over the next two years, and in 2016 the manufacturer plans to submit a ready-to-use, thermostable version of the same product that will be in compliance with PSPQ critical criteria.

The IPAC expressed concurrence with both of these Standing Committee decisions.

## **B. Progress of the review of the PSPQ process** (*Rudi Eggers, WHO*)

Dr Rudi Eggers presented the process and findings emerging from the thorough review of the PSPQ process held over the last few months with stakeholder input from industry and the public sector. The new PSPQ requirements will come into effect on 1 January 2015.

The main issues which emerged during the review concentrated on: (1) Antimicrobial preservatives and the definition of “inadequately preserved” vaccines; (2) antigenic stability for 28 days; (3) the management of vaccines that were pre-qualified prior to the PSPQ implementation (grandfathering); and (4) new mandatory and preferred characteristics and the transition to critical characteristics.

An opportunity to make editing inputs will remain available through 10 July 2014. It was also suggested that the language associated with preferred characteristics should be strengthened.

## **Recommendations and Decisions by IPAC**

1. IPAC members unanimously endorsed the PSPQ revisions as presented.

## **Session V. Field studies with Uniject**

Mr Philippe Jaillard, Agence de Médecine Préventive, presented on two field studies conducted in Senegal and Vietnam with the use of a compact pre-filled auto-disable device (cPAD) for pentavalent vaccine. He highlighted how population and health workers concerns on immunization safety and immunization delivery could be addressed, and the potential to enhance immunization performance and trust by building on cPAD advantages.

The main advantages of cPADs perceived by parents and health workers in Senegal and Vietnam, related to immunization safety and efficacy, were the device’s ease of use, its capacity to limit vaccine and needle exposure to dust and germs, and the assurance of delivering the

accurate vaccine dose. The main perceived constraints were related to the risk of confusion with other pharmaceutical products presented in the same device (ie: contraceptive) and that "low cost" technology may imply an inferior quality of device and product.

In the programmatic and logistics area, cPADs for pentavalent vaccines reduce both the weight and volume of waste generated and reduce dry storage capacity needs due to its integrated design, as compared to existing monodose and multidose vial presentations. Furthermore, cPADs reduce overall cold chain store requirements, depending on the presentation and formulation of the DTP-HepB-Hib vaccine in use in the country.

In addition, some vaccinators and program managers noted that cPADs may reduce missed opportunities for immunization by integrating vaccine, syringe, and needle and thereby reducing stock-outs; ease outreach or catch-up campaign efforts by reducing logistics requirements; reduce wastage in comparison with multi dose vial presentation; and reduce the time per injection and the workload to vaccinators.

Most of the challenges reported by the vaccinators regarding device handling and delivery technique may be addressed by proper training and communication.

The potential of cPADs may be further increased by using them in a controlled temperature chain; permitting trained lay health workers to immunize; and including it as an alternative presentation to existing vaccine presentations so that countries can adapt vaccine delivery methods.

## **Discussion**

IPAC discussion noted the value of considering packaging innovation and investment as a topic of programmatic research. IPAC members also noted a number of advantages presented by cPADs for vaccine injection and the benefits of this single dose presentation. Meeting participants emphasized the importance of clearly differentiating the appearance of cPAD for pentavalent or other vaccines from cPAD for contraceptive injection, and encouraged the development of appropriate training and communication materials. They also recommended the generation of more data on economic evaluation, including the cost-savings by increasing immunization coverage and limiting vaccine wastage.

It was noted that cPADs have the potential to increase immunization coverage when used in hard-to-reach areas, during outreach sessions, or when targeting specific populations. A combination of vaccine presentations (for example monodose cPADs alongside multi-dose vials) could be used. WHO and UNICEF would be critical to advising and supporting countries.

Meeting participants noted that the potential for cPAD to reduce needle stick injuries in comparison with a single dose vial presentation is limited since most injuries occur when recapping the needle.

In summary IPAC,

- Recognized the benefits of cPADs for pentavalent vaccine delivery and its potential to overcome some reasons for non-vaccination and increase vaccine coverage;
- Strongly encouraged the increased use of cPADs for vaccine delivery with an increased diversity of vaccine presentations to enable countries to adapt their immunization delivery strategy according to their local characteristics.

- Recommended that further health economic and post-implementation programmatic research be implemented to document the added value of incremental cost versus efficiency and safety, and help identify the best conditions for cPAD use by countries.
- Noted that since cPADs are a preferred characteristic in WHO PSPQ, it is hoped this sends a strong signal to vaccine manufacturers to consider expansion of cPAD use for vaccination; and
- Advocated that GAVI look favorably upon the use of cPADs, particularly for Hepatitis B birth dose.

## **Session VI. Immunization Supply Chain and Logistics**

### **A. Report-back from SAGE meeting April 2014, (*Chris Morgan, IPAC Chair*)**

Dr Chris Morgan summarized the conclusions of the April SAGE meeting, where a second session on immunization supply chains was held in April 2014, as a follow-up to the November 2013 session. Attention was drawn to the key messages from the April meeting that: (i) SAGE re-affirmed its concern about the alarming state of immunization supply chain systems in developing countries, including vaccine availability, cold chain quality, and supply chain efficiency; (ii) SAGE endorsed the IPAC "*Call-to-Action*" and affirmed the importance of the WHO-UNICEF Joint Statement on the comprehensive EVM approach; and (iii) SAGE stressed the importance of thoroughly considering immunization supply chain impact in future recommendations on the introduction of new vaccines.

### **B. GAVI Alliance Immunization Supply Strategy, (*Daniel Thornton, GAVI*)**

Mr Daniel Thornton presented an overview of the GAVI Alliance Immunization Supply Chain strategy that will be reviewed during the June GAVI Board. The strategy made the case for additional focus on and resources for immunization supply chains and outlined initiatives around: (1) supply chain network design and optimization; (2) cold chain equipment; (3) distribution systems for immunization; (4) data for management ; and (5) strengthening human resources for supply chains. Within the five pillars, four initiatives are prioritized in the short term:

- **Supply Chain Managers:** To ensure that EPI is staffed with qualified supply chain managers with appropriate capabilities and authority to oversee the entire national immunization supply chain.
- **Supply Chain Improvement Plans:** To support the development and implementation of comprehensive EVM improvement plans.
- **Supply Chain Dashboard:** To establish country data dashboards that strengthen the visibility of supply chain performance and use the information for improvement management.
- **Supply Chain Design:** To support countries in implementing supply chain network re-design and optimization approaches known to raise the performance of immunization supply chains.

During this part of the session, the IPAC was requested to provide high-level feedback on the proposed ideas that will support the implementation of the strategy. Overall, the IPAC welcomed the GAVI Strategy and felt that it was an early tangible response to the need for increased attention to this issue, as articulated in the IPAC "*Call to Action*". There were discussions on the following issues:

1. How the process to develop the strategy ensured that root-cause analyses had been thoroughly conducted. What game-changing interventions were prioritized and how.
2. How non-GAVI countries could benefit from the knowledge, tools, approach used to support GAVI countries through the strategy.
3. The perceived gaps remaining in the strategy, namely on Vaccine Arrival Reporting (VAR), and the importance of addressing such a big area.
4. Private sector engagement and cautioning about putting too much emphasis on the private sector to provide all the answers.
5. Cautioning about putting too much expectation on having a national level supply chain manager without strong support from country level partners like WHO and UNICEF and a mechanism in-country for change management.

In closing this session, the IPAC made a plea that WHO and partners continue the effort to landscape and gather all available evidence on immunization supply chain challenges and promising solutions and to continue to update the work done as part of the IPAC "*Call to Action*".


### **Closing**

Dr Morgan thanked all in attendance and summarised the proceedings. He noted that the following individuals have reached the end of their service term as members and acknowledged their service: Robin Biellik, Jonathan Colton, Francois Gasse, and Folake Kio-Olayinka. All members were thanked for their important contributions and dedication of service.

In closing, Mr Zaffran presented Dr Najwa Khuri-Bulos and Dr Xavier Bosch-Capblanch (*in absentia*), with a certificate of appreciation to acknowledge the end of their second term of service since April 2010. WHO, and specifically the Department of Immunization, Vaccines and Biologicals, greatly benefitted from the insights and contributions of Drs Khuri-Bulos and Bosch-Capblanch.

The timing of the next IPAC meeting will be determined at a later date.

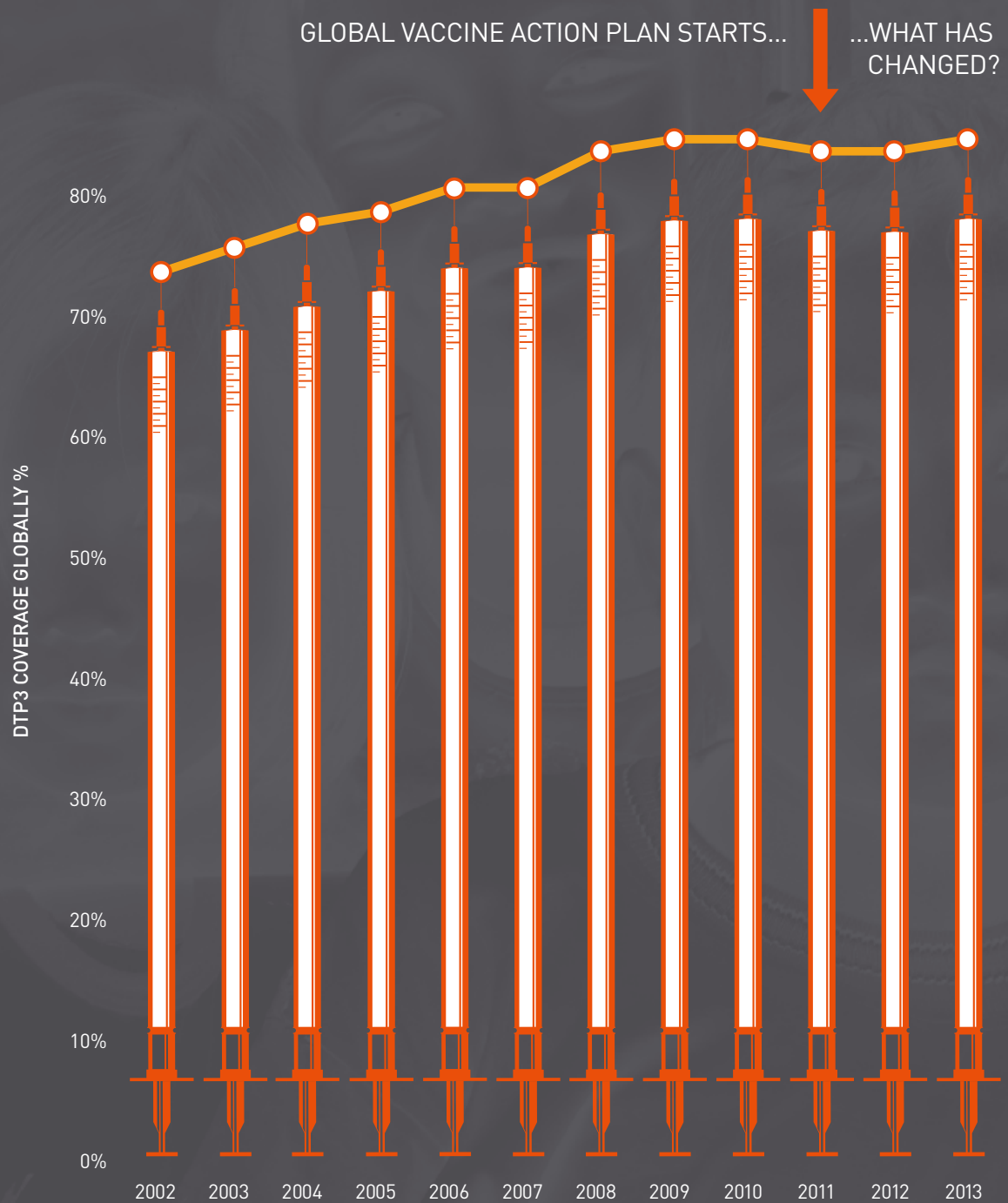
# 2014 ASSESSMENT REPORT OF THE GLOBAL VACCINE ACTION PLAN



STRATEGIC  
ADVISORY  
GROUP OF  
EXPERTS ON  
IMMUNIZATION

DRAFT – For SAGE discussion October 2014

## A TOUGH QUESTION



## EXECUTIVE SUMMARY

The Global Vaccine Action Plan has two great ambitions. First, to deliver vaccination to all - because 1.5 million children still die every year of diseases that can be prevented by the vaccines that humankind has developed. Second, to unleash vaccines' vast future potential - because their impressive history is just the foundation stone of greater achievements to come.

With these two great ambitions, the Global Vaccine Action Plan aims to make 2011-2020 the 'Decade of Vaccines'. This report provides an objective assessment of its progress to date.

### IN SAGE'S ASSESSMENT, PROGRESS IS FAR OFF-TRACK.

The Global Vaccine Action Plan set six key immunisation targets with deadlines at the end of 2014 or 2015. Just one of these six is on track to be achieved. Some have been missed multiple times before. The targets each relate to different vaccines and diseases, but common threads run throughout: failure to extend vaccination services to people who cannot currently access them at all, and failure to strengthen the healthcare system so that all doses of vaccine are reliably provided.

There is some reason for hope. There has been success in introducing new vaccines, and positive achievements in some countries. Major change is possible. The Global Vaccine Action Plan was created to end the inequity in vaccination worldwide, and hence to save millions of lives. This need remains as important and urgent as ever. It is not acceptable that the plan is failing to deliver at the scale that is required.

This report establishes five areas for priority action:

- Three years after its start date, implementation of the Global Vaccine Action Plan is patchy and slow. All countries and organizations that have committed to this endeavour should re-examine the level and nature of their contributions, and urgently make the improvements necessary to achieve results.
- Poor quality and use of data is substantially impeding program management and improvement.
- The affordability and supply of vaccines need to be urgently examined. Each may be causing a significant problem for a large number of countries, and the current lack of proper information hinders understanding and corrective action.
- Basic failures of integration mean that healthcare workers are repeatedly missing easy opportunities to offer vaccinations when people attend clinic with other problems.
- Vaccine delivery is impeded by disruptive situations, including war and major disease outbreaks (such as Ebola, currently). Such situations will always exist. Vaccines must be delivered despite them.

The SAGE recommends that countries, their technical partner agencies and donors address this report and its recommendations with the greatest possible urgency.



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## THE GLOBAL VACCINE ACTION PLAN IS VITAL

Vaccines are remarkable. They protect people from diseases that otherwise scar, kill and maim. They prevent an estimated 2 to 3 million deaths a year<sup>1</sup>. They are what we seek when a new disease appears. Relative to their great benefit, their cost is small.

### **Vaccines have an impressive history and an exciting future....**

Widespread vaccination was one of the great 20th Century public health revolutions, and their future holds greater promise still. Amidst increasing focus on the growing burden of non-communicable disease, the importance of communicable disease and of vaccines must not be forgotten. In 2014, the World Health Organization has declared two Public Health Emergencies of International Concern – the Ebola crisis in West Africa, and the international spread of poliovirus. Both are communicable diseases. Polio is vaccine-preventable and Ebola may soon become so. Vaccination will make an important contribution to the health-related Sustainable Development Goal. By keeping deadly and mutilating communicable diseases in check, vaccines are – and will remain – essential to maintaining and expanding health gains. They can be ‘game changing’ in tackling future outbreaks and epidemics. Vaccines can already prevent some cancers that are caused by viruses. They will increasingly be able to prevent non-communicable diseases, and to benefit individuals of all ages. For all of these reasons, it is important that the future potential of vaccines be unleashed. This is one of the great ambitions expressed by the Global Vaccine Action Plan.

### **...but the most pressing need is to get them to everybody**

Vaccines’ future is exciting, but the biggest need is in the present. According to the most recent WHO estimate, 1.5 million children die every year of diseases that could be readily prevented by vaccines that already exist<sup>2</sup>. This represents gross inequity. A small proportion of the world’s children simply do not receive the basic, cheap, life-protecting vaccines that parents elsewhere take for granted. Other children receive some doses, but dysfunctions in the healthcare system mean that they do not reliably receive all of the doses that they should. There is a pressing need to improve the reach and reliability of vaccine delivery, so that they properly protect all people.

To address these needs, the Global Vaccine Action Plan has two vital ambitions. First, to bolster the reach and reliability of vaccine delivery, so that all people reap the great benefits of vaccination. Second, to realize vaccines’ future potential. In setting these two great ambitions, the Global Vaccine Action Plan aims to make 2011-2020 the ‘Decade of Vaccines’.

### **This report provides an objective assessment of progress.**

It is produced by the Decade of Vaccines Working Group of the Strategic Advisory Group of Experts on Immunization (SAGE), based on analysis and deliberations throughout the year. This report makes recommendations to countries, which have primary responsibility for delivering the Global Vaccine Action Plan. It also makes recommendations to the countries’ technical partner agencies. A detailed Global Vaccine Action Plan Secretariat Report informed the Working Group’s deliberations. This covers every indicator in the Global Vaccine Action Plan monitoring and evaluation/accountability framework. This Secretariat Report is available online, along with detailed country-specific data for each of the major indicators described in this report<sup>3</sup>.

<sup>1</sup><http://www.who.int/topics/immunization/en/>

<sup>2</sup>[www.who.int/immunization/monitoring\\_surveillance/burden/estimates/en/](http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/) (estimates from 2008)

### IN BRIEF

Global Vaccine Action Plan’s two great ambitions:

(1) Vaccination for all – because 1.5 million children still die of vaccine-preventable diseases

(2) Unleash vaccines’ vast future potential

## VACCINATION FOR ALL

### PROGRESS FAR OFF-TRACK

The Global Vaccine Action Plan envisaged a world in which everybody enjoys life free from vaccine-preventable diseases. It wants to extend the full benefits of vaccination to all people, regardless of where they are born, who they are, or where they live.

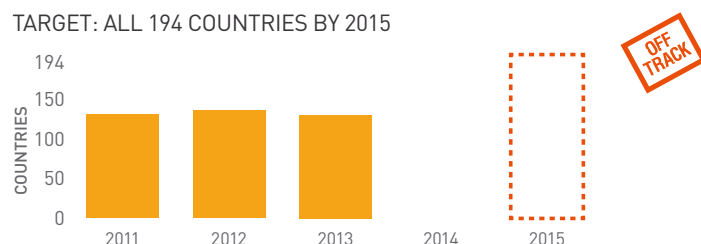
This progress is best measured using the six immunisation-specific targets of the Global Vaccine Action Plan with deadlines that are fast approaching:

- **DTP3:** National vaccination coverage of 90% in all countries by 2015, with no district's coverage less than 80%
- **Introduction of under-utilized vaccines:** At least 90 low or middle income countries to have introduced one or more such vaccines by 2015
- **Polio:** No new cases after 2014 ('interruption of transmission')
- **Maternal and neonatal tetanus:** Global elimination by end-2015
- **Measles:** Elimination from three WHO regions by end-2015
- **Rubella:** Elimination from one WHO region by end-2015

**In SAGE's assessment, only one of these six targets is on track to be achieved.** Most have seen very poor progress indeed, and some have already been missed multiple times before. These have a strong common thread. They are about improving the reach and reliability of vaccination services, so that children who are not yet properly immunized can be accessed.

### DTP3: NATIONAL VACCINATION COVERAGE OF 90%

TARGET: ALL 194 COUNTRIES BY 2015



National DTP3 coverage is the most important indicator in the Global Vaccine Action Plan. It is a direct measure of children receiving three doses of this crucial vaccine. Also, if a country has high DTP3 coverage, it has systems in place that can also deliver other vaccines. Broader still, DTP3 is a useful descriptor of how well a healthcare system is functioning. With all of these in mind, it is very disappointing to see this important target so far off track.

In 2013, 129 countries vaccinated at least 90% of their children with three doses of diphtheria-tetanus-pertussis containing vaccine ('DTP3'). The Global Vaccine Action Plan's target is for this number to reach 194 – that is, all countries – by the end of 2015. As the graph shows, the number of countries achieving 90% has not improved between 2011 and 2013. A full one-third of countries are yet to reach this target. The unavoidable conclusion is that progress towards the end-2015 target is far off-track.

### IN BRIEF

GVAP end-2014/end-2015 targets: five out of six are off-track

No improvement in national DTP3 coverage (a vital measure)

This simple graph shows only one measure, but further examination of the data only confirms stagnation. Globally, the total number of unvaccinated children remains at 22 million, with just a hint of improvement this year.

The Global Vaccine Action Plan also set an important district-level target. This aims to boost equity – to avoid, for example, a country achieving 90% national coverage but having coverage of 99% in its capital and just 60% in a poor rural area, for example. Unfortunately, it is not possible to comment on progress towards this target. District data are not available, or are invalid, from almost half of countries. This reflects a wider problem with the quality and use of vaccination data, described later.

The flat-lining of DTP3 coverage is not good news. But there are some positives:

- Over recent years, several new vaccines have been introduced. Particularly thanks to the support of Gavi, their coverage has grown rapidly. Some feared that introducing new vaccines would strain systems and cause global DTP3 coverage to drop. This has not been the case.
- Progress on DTP3 coverage has been made in some countries. Important examples are Nigeria, Ethiopia and Indonesia. Each has achieved some reduction in its number of unvaccinated children.

The major contextual challenges should also be remembered. Several of the countries with very low vaccination coverage are affected by war or other conflict – including Central African Republic, Syria and Somalia.

Unfortunately, this does not alter the overall conclusion. This vitally important target of the Global Vaccine Action Plan is way off track.

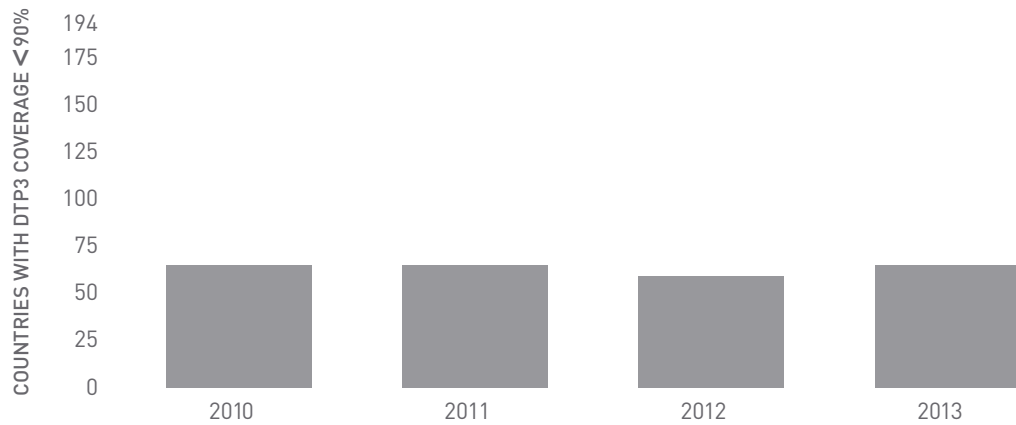
#### IN BRIEF

Insufficient district-level DTP3 data

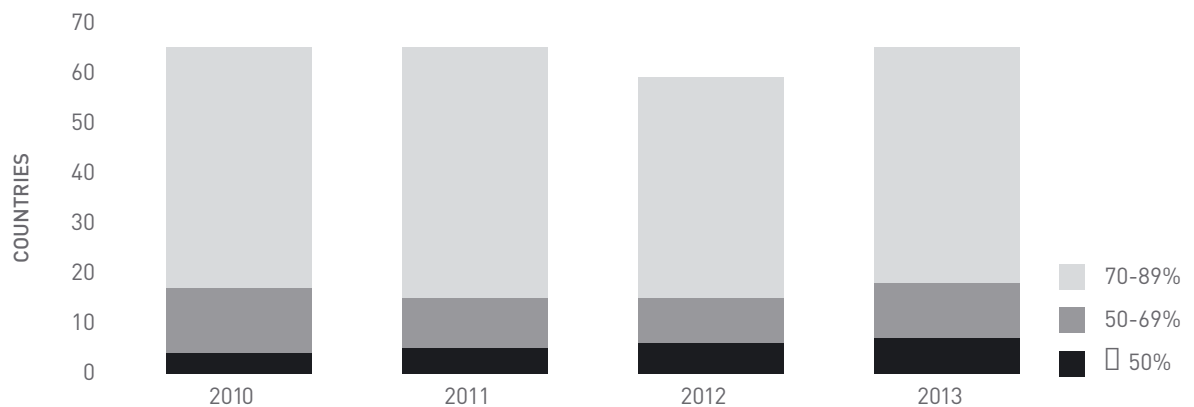
Despite some positive news, DTP3 flat-lining is deeply disappointing

### DTP3 COVERAGE: FLAT-LINING, WHICHEVER WAY YOU LOOK AT IT

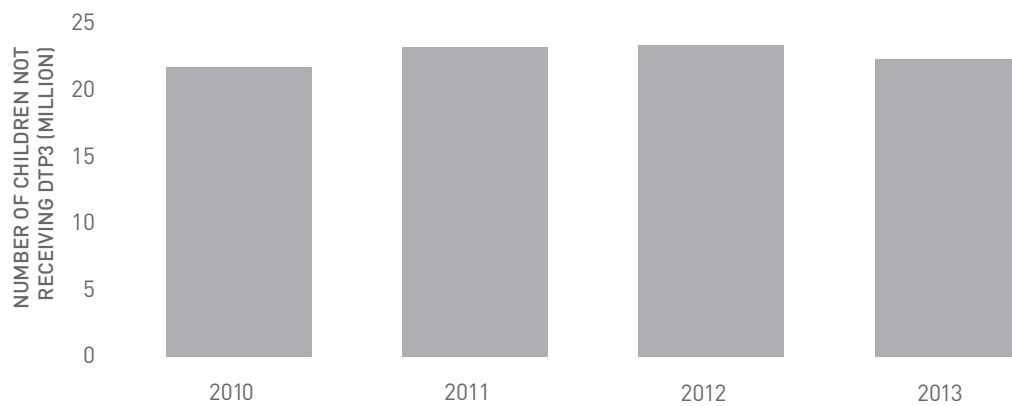
ONE-THIRD OF THE WORLD'S 194 COUNTRIES ARE NOT ACHIEVING 90% NATIONAL COVERAGE, AND THIS HAS NOT CHANGED FOR FOUR YEARS...



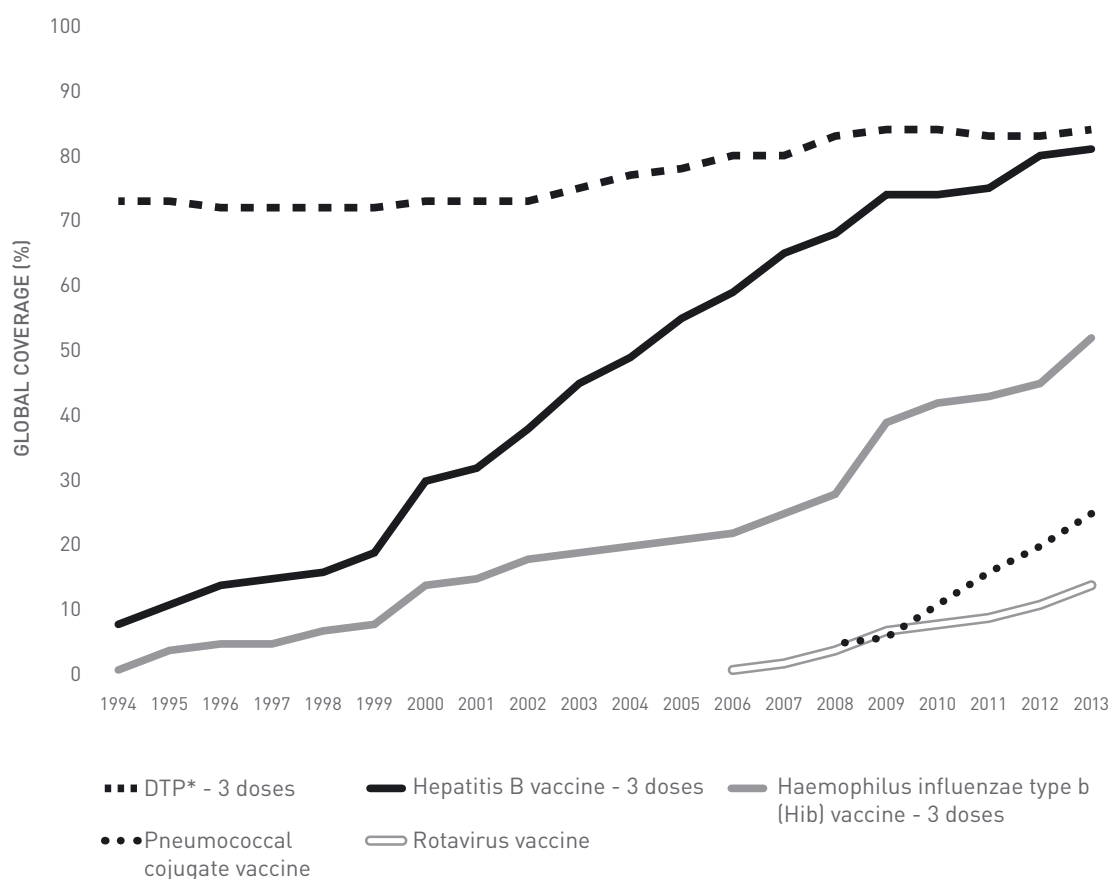
LOOKING CLOSER, THE NUMBER IN THE LOWEST BANDS IS GETTING WORSE NOT BETTER...



...AND THE TOTAL NUMBER OF UNVACCINATED CHILDREN HAS BASICALLY NOT CHANGED.



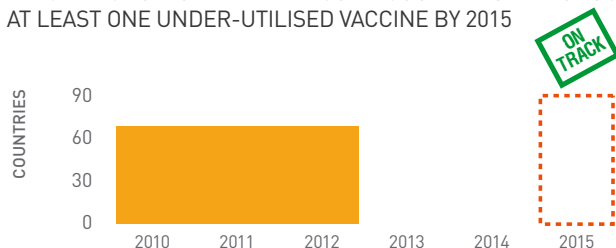
## MAJOR CHANGE IS POSSIBLE: ALTHOUGH DTP3 COVERAGE HAS HIT A PLATEAU, NEWER VACCINES HAVE BEEN INTRODUCED AT AN IMPRESSIVE PACE



\*DTP = diphtheria, tetanus and pertussis-containing vaccine

## INTRODUCTION OF UNDER-UTILISED VACCINES

TARGET: 90 LOW OR MIDDLE INCOME COUNTRIES INTRODUCE AT LEAST ONE UNDER-UTILISED VACCINE BY 2015



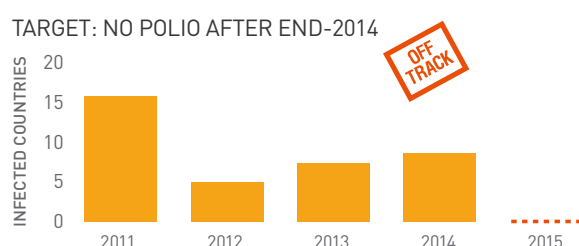
Good progress is being made towards this target. Between 2010 and 2012, 68 low and middle income countries introduced an under-utilized vaccine<sup>4</sup>. They actually introduced a total of 85 vaccines, because some countries introduced more than one. All of these introductions were sustained for at least a year. The most common new introduction was

<sup>4</sup>Hib-containing, pneumococcal, rotavirus, Human Papillomavirus (HPV) vaccine, Rubella or Inactivated Polio Vaccine (IPV)

pneumococcal vaccine. There were some supply constraints for both this and rotavirus vaccine. These constraints have now eased, so additional introductions are now likely.

The SAGE welcomes the progress towards this important target. It represents a continuation of promising work, particularly over the last decade, in accelerating new vaccine introduction.

## POLIO



The Global Vaccine Action Plan's target was for wild poliovirus transmission to be stopped globally before the end of 2014. This important target will now certainly be missed.

Promising progress was made in 2011 and 2012 – India stopped polio transmission, several longstanding outbreaks were brought to a halt, and type 3 poliovirus was probably stopped. But from late 2012 into 2013, the situation deteriorated. In Pakistan, polio vaccinators were killed. The virus spread internationally. This caused substantial outbreaks in Syria and the Horn of Africa and led, in 2014, WHO to declare a Public Health Emergency of International Concern. In 2014, valuable progress has been made in containing these outbreaks. Strong progress has also been made in Nigeria, which for years has fed polio transmission across a whole band of Africa. Most of the cases of polio in the world are now in Pakistan.

The Global Polio Eradication Initiative was established in 1988. It set a target of stopping global polio transmission by the year 2000. When this was missed, the target date was moved to 2005, then 2012, then 2014. This will therefore be the fourth time that a target for stopping global polio transmission has been set and missed.

The fact that progress is being made is welcome. Repeated failure to stop polio transmission comes at real cost. People (mainly young children) are being paralysed by, and in some cases dying from, a disease that should have been consigned to history years ago. Until every country in the world has stopped polio transmission, an intensive and expensive effort is needed to protect the rest of the world from the virus being imported. The Global Polio Eradication Initiative costs \$1 billion a year. It needs to continue, and to complete its work as quickly as possible.

## IN BRIEF

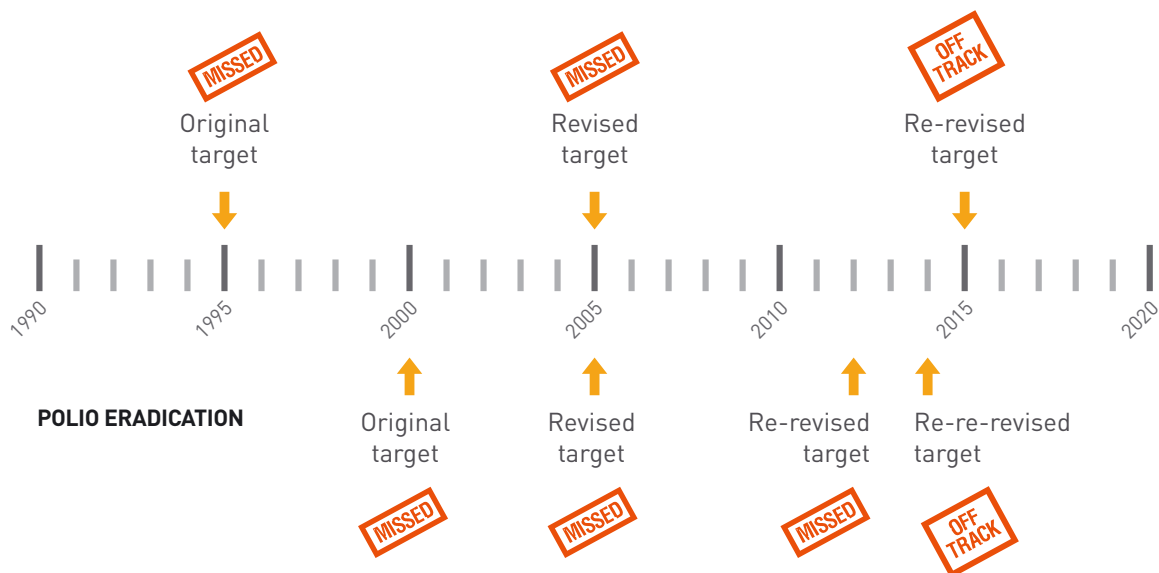
Good progress against polio, in the face of incredible challenge

Pakistan of major concern, and coming months vital for Nigeria

Global 'stop transmission' target will be missed - again

## THE HABIT OF MISSING MAJOR VACCINATION TARGETS UNDERMINES GLOBAL TRUST IN THESE EFFORTS...

### NEONATAL (AND MATERNAL) TETANUS ELIINATION



## ...AND HAS A REAL AND SUBSTANTIAL COST

### 50,000

In 2010, 15 years after the original tetanus elimination target, at least 50,000 babies died the horrible death of neonatal tetanus\*

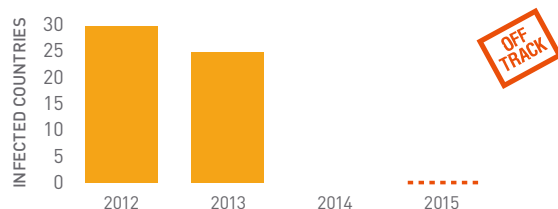
### \$1 billion

In 2014, 14 years after the original polio eradication target, the Global Polio Eradication Initiative cost \$1 billion, which could otherwise have been spent elsewhere

\*No data are available since 2010, but it is likely that tens of thousands are still dying every year

## MATERNAL AND NEONATAL TETANUS

TARGET: GLOBAL ELIMINATION BY END-2015



When a newborn baby contracts tetanus, its face and jaw lock until the baby cannot feed. The baby suffers from severe muscle spasms and convulsions. After a week of this agony, almost all infected babies die. The babies who die of neonatal tetanus are born in some of the poorest parts of the world. Its persistence is a sharp reminder of gross inequity.

Newborns and mothers are put at risk of tetanus by unclean deliveries and poor umbilical cord care. The infection can be prevented by improving this hygiene, and by vaccinating women who are pregnant or of child-bearing age. Application of these simple measures can eliminate maternal and neonatal tetanus as a public health problem (even though the tetanus bacterium itself cannot be totally eradicated).

In 1989, the World Health Assembly resolved to eliminate neonatal tetanus by 1995. This was not achieved. In 1999, the Maternal and Neonatal Tetanus Eradication Initiative launched, setting a target date of 2005, subsequently shifted to the 2015 target date that is endorsed by the Global Vaccine Action Plan. Meanwhile, tens of thousands of newborn babies continue to die from tetanus (some 58,000 according to the latest data, which are from 2010).

It should be considered deeply unacceptable that this disease, wiped out from most of the world, still affects its poorest people. Its first global elimination target was missed 20 years ago. And now this target – set at end-2015 as one of the first tangible targets of the GVAP – is set to be missed yet again.

Some progress is being made. The SAGE particularly commends India and China for their sustained focus. China has eliminated the disease as a result, and India is making good progress towards doing so in 2015. Both India and China have focused substantially on hygienic delivery, using skilled birth attendants and encouraging women to give birth in health centres. This approach has the great advantage of also improving maternal and neonatal care more generally.

The goal of eliminating tetanus is embarrassingly underfunded. For 2015, the funding gap (\$90m) dwarfs the funds available (\$10m) by a factor of nine. If this persists, it is simply inconceivable that the global elimination goal will be achieved by 2015, or any time soon after.

### IN BRIEF

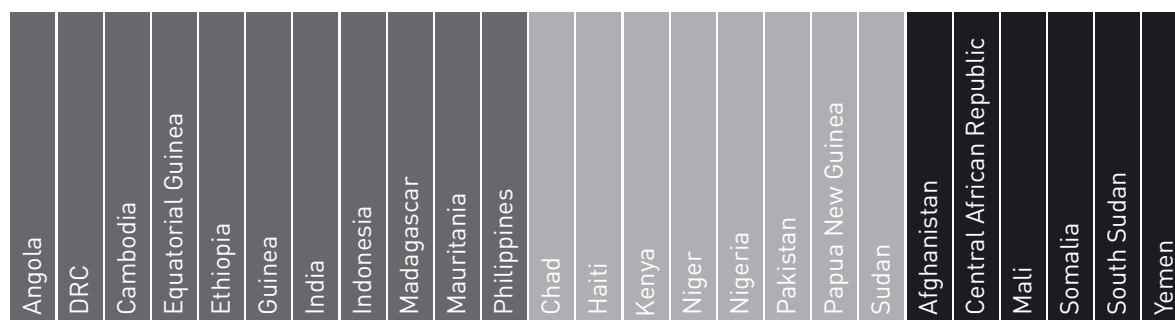
Tetanus: a horrible disease

End-2015 elimination goal off-track, and missed twice before

Gross underfunding: urgent action needed



## NEONATAL AND MATERNAL TETANUS: 25 COUNTRIES STILL NEED TO ELIMINATE

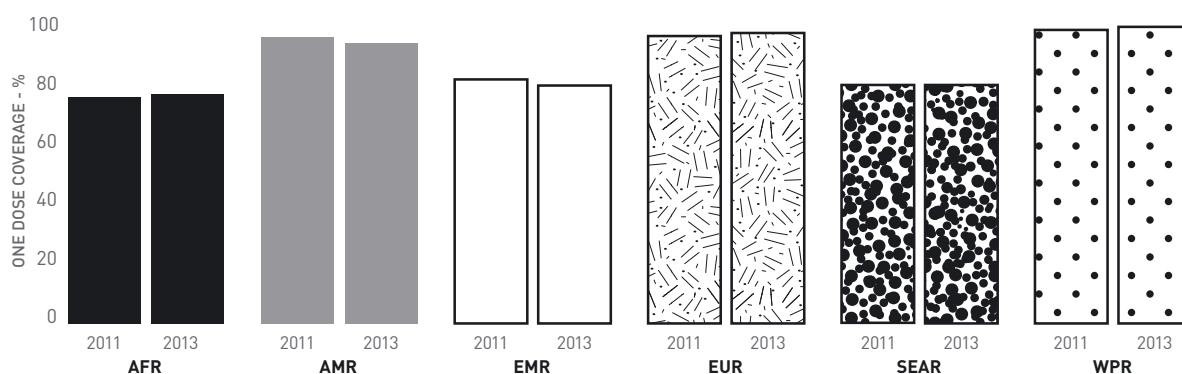


11 COUNTRIES ARE CLOSE TO ELIMINATION

8 COUNTRIES ARE DRASTICALLY  
BEHIND DESPITE RELATIVELY  
STABLE POLITICAL SITUATIONS

6 COUNTRIES ARE BEING  
SET BACK BY POLITICAL  
INSTABILITY

## MEASLES: ONE-DOSE COVERAGE LITTLE CHANGED IN TWO YEARS



## MEASLES

TARGET: ELIMINATION FROM THREE MORE REGIONS\* BY END-2015



The measles vaccine has saved millions of lives. Measles mortality and morbidity has fallen by 90% since its introduction. At the turn of the millennium, 500 thousand people (mainly children) died from measles. By 2012, this figure had fallen by three-quarters – to 122 thousand.

Three WHO regions have vowed to wipe out measles altogether by the end of 2015. All regions have vowed to do so by the end of 2020. Unfortunately, as with polio and tetanus, these grand words are not being matched by the funding and action to make them a reality.

\*Four regions in total, including AMR. Data for other regions are in the GVAP Secretariat Report

The three regions aiming for elimination by the end of 2015 are EMR, EUR and WPR. Of these, EMR and EUR are markedly off track. WPR was making the strongest progress, but this was set back in 2013 by major outbreaks in China, Philippines and Vietnam. Each region can point to some areas of good progress. But nobody could reasonably conclude that any of the regions is on track to eliminate measles by 2015.

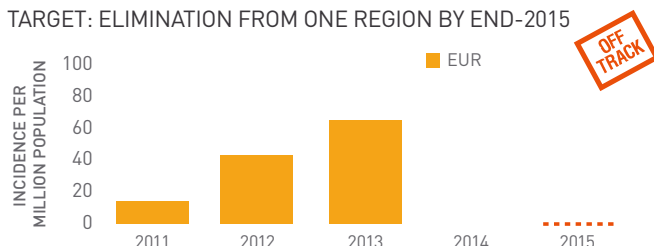
Eliminating measles is not easy. It requires 95% coverage in every district. Even if national coverage is above 95% (as it is in many countries in EMR, EUR and WPR), just one weak district is enough for this highly contagious virus to continue circulating.

Globally, coverage has not changed over the last five years. It remains stubbornly at 84%. This is high enough coverage to prevent hundreds of thousands of deaths, but not enough to eliminate measles transmission. Measles incidence has halved over the last three years, but the number of countries with ongoing transmission has only fallen slightly. And getting from 84% nationally to 95% in every district is a very long way to go before the year 2020. Six large countries have a particularly important role. India, Nigeria, Ethiopia, Indonesia, Pakistan and DR Congo are responsible for more than four-fifths of all measles cases worldwide.

One WHO region – AMR – eliminated measles in 2002. But Brazil has become re-infected, and transmission has continued there for more than a year. Three regions (SEAR, AFR and EMR) still have coverage of 80% or less. This is a very long way from the 95% in every district that will be required to eliminate measles. A huge amount of work and political commitment lies ahead if their elimination goals are to be achieved, as is pledged for the end of the decade.

## RUBELLA

TARGET: ELIMINATION FROM ONE REGION BY END-2015



Work to eliminate rubella lags behind that for measles. Again AMR leads the way – rubella was eliminated there in 2009. Globally, rubella vaccine coverage is just 40%. One third of countries have not yet introduced the vaccine. Surveillance is weak, so the burden of rubella is not well understood. The Global Vaccine Action Plan aims for five regions to have eliminated rubella by 2020, but so far only two have established such a goal – AMR for 2010 (which was achieved) and EUR for 2015, which is not on track. SEAR has established a 2020 goal of accelerating rubella control, but this is not an elimination goal.

Combination vaccines allow children to be protected against measles and rubella simultaneously, at a small additional cost for the combination vaccine. Failure to use this vaccine in the measles elimination effort is a major missed opportunity to simultaneously eliminate rubella (which is actually more easily eliminated than measles is). There is no good reason why rubella should be lagging behind measles in the way that it is.

\*Two regions in total, including AMR. Data for other regions are in the GVAP Secretariat Report

## IN BRIEF

Measles vaccine is a major lifesaver

Elimination targets not on track

95% coverage required in every district: A long way to go

Rubella lags far behind measles: A missed opportunity

## THE COMMON THREADS: SYSTEMS, INTEGRATION, WILL

Each of these targets is about a different vaccine or disease, but the common threads are strong. The route to achieving all of these targets is through **strengthening immunisation systems**. There is no mystery to it – once vaccination coverage is raised to a high enough level, these viruses and bacteria will have nobody to infect. There are two parts to this strengthening:

1. Reaching those who are completely unvaccinated, by extending services to them – those who live in remote or inaccessible areas; those who are nomadic; those who are part of a marginalized social group. In short, putting a stop to the persistent inequity in the distribution of vaccines.
2. Better serving those who are under-vaccinated – who receive some vaccine doses, but are not reliably covered in the way that they should be. Improving this reliably involves strengthening the healthcare system in a number of ways. It means having enough healthcare workers, with the right skills. It means having the records, the facilities, and the cold chain. It means strengthening links between the different parts of the system. It means having skilled managers who can oversee and improve the system. Importantly, these are the building blocks of any healthcare system – vital for vaccination, and far more besides.

So the targets are disease-specific, but the improvements needed to achieve them are largely shared. Such efforts should therefore be integrated as tightly as possible, both with one another, and with other work to improve and deliver healthcare.

A further common thread is political will. These targets can all be achieved in countries truly want to achieve them. They will not be achieved otherwise.

These common threads illustrate why the Global Vaccine Action Plan is so valuable. It aims to end inequity in vaccination. It aims to pull the vaccination goals together – with one another, and with broader healthcare system strengthening. It is countries' joint expression of their will to use the great tool of vaccination to protect global public health, and achieve momentous goals.

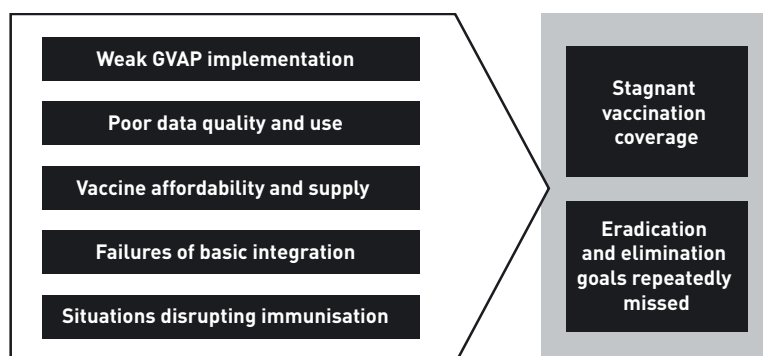
But the final common thread, at the moment, is that all of the end-2014 and end-2015 targets are off-track. The next section of this report looks at what needs to change.

## IN BRIEF

Common threads to all targets:  
strengthening systems,  
political will

## FIVE PRIORITY PROBLEMS

The Global Vaccine Action Plan is far off track. In response, the SAGE recommends that actions focus particularly on addressing five priority problems. Each problem is major, but each can be tackled, with a reasonable expectation that doing so will improve progress considerably.



### 1. WEAK GVAP IMPLEMENTATION

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

Declaring that 2011-2020 should be the 'Decade of Vaccines' was a helpful start, but by itself achieves little. The creation of a Global Vaccine Action Plan is useful, but the document's mere existence has little effect – as is being seen. As ever, the key lies in implementation.

It would be tragic if the opportunity to use the Global Vaccine Action Plan is not taken. The Global Vaccine Action Plan has major strengths:

- It pulls the strands of global vaccination work together. These strands inter-link. Working on them in combination is far better than treating them as standalone goals and programs.
- It shines a spotlight on the need to deliver vaccines equitably and to realise vaccines' future potential. It should help countries and partners hold one another to account for doing so.
- Through the World Health Assembly, it was adopted by all members states of the World Health Organization
- A wide array of forums and organisations were involved in its development and launch. They can contribute to achieving its goals.

As it stands, implementation is patchy and slow. It is little surprise that progress towards its targets is so consistently off-track. It is worrying to hear that a number of countries and some key stakeholders are barely aware of the plan.

Notably, measles elimination is a major stated priority for which the required structures – particularly national verification committees and regional verification commissions – have not yet been fully established.

## IN BRIEF

Getting back on track: Five priority problems to tackle

GVAP: a great opportunity, full implementation now urgent

These have a vital technical role, and also help demonstrate countries' true commitment to the goal.

The World Health Assembly endorsed the Global Vaccine Action Plan in 2012. More than two years on, most of the WHO regions are only now on the cusp of having Regional Vaccine Action Plans agreed by their regional committees of health ministers. It is disappointing that they did not do so in 2012 or in 2013. Now, at least, these regional plans need to be quickly developed and implemented. The SAGE will ask for a formal report from each region every year. It is important that there are solid mechanisms for monitoring and for exchange of best practices. The World Health Assembly resolution on the Global Vaccine Action Plan asked that from 2013, regional committees hold a special annual session in which countries report on progress, lessons learnt, challenges and plans. Every country endorsed the Global Vaccine Action Plan. Every country needs to urgently develop its own plan to contribute, before any more of the decade slips away. Accountability is a crucial part of implementation. Countries' plans need to specify not just what they intend to do, but what monitoring and accountability mechanisms they will use to be sure that it gets done.

Civil society organizations were involved in producing the Global Vaccine Action Plan. They now need to be involved in producing results. They can (and in some places already do) deliver vaccines, mobilize volunteers, help improve data quality, and help people to understand the value of vaccines. They need to be involved in a proper way. Governments should consider devolving specific tasks to civil society organizations, then holding them accountable for the results. Conversely, civil society organizations can play a useful role in holding governments to account.

Two influential global forums played a pivotal role in establishing the Global Vaccine Action Plan. At the World Economic Forum in Davos in 2010, Bill Gates challenged the world to make this the 'Decade of Vaccines'. At the World Health Assembly in 2012, health ministers accepted the challenge on behalf of their countries, endorsing the Global Vaccine Action Plan. The participants in both of these forums wanted this plan. They now have an important role to play in helping to implement it.

The implementation of the Global Vaccine Action Plan needs a hefty injection of urgency. The plan strikes at the heart of global health inequity. It involves building up vaccination services as a fundamental building block of healthcare. This major opportunity needs to be taken.

## IN BRIEF

Civil society role crucial

Major delays in agreeing regional action plans

Hefty dose of urgency required

## THE SAGE RECOMMENDS THAT:

- Regions and countries rapidly finalize their own vaccine action plans based on the Global Vaccine Action Plan, using this assessment report as a further guide, and establishing bodies to guide and monitor implementation
- The heads of the technical agencies that co-signed the Global Vaccine Action Plan report to the 2015 World Economic Forum in Davos on the plan's establishment, its lack of progress so far, and what forum participants – who supported its concept in 2010 – can do to help its implementation
- The Global Vaccine Action Plan and SAGE's assessment reports remain as standing items at the World Health Assembly until 2020
- The Director-General of WHO convene a special session at the 2015 World Health Assembly for countries with vaccination coverage of less than 80%, to which each Minister of Health is asked to bring details of the country's vaccination coverage and corrective action plan
- Countries give civil society organizations substantially more formal involvement in the delivery and improvement of vaccination services, establishing clear responsibilities for which they are accountable
- Every region establish a regional verification commission, and every country a national verification committee, to scrutinize progress towards the measles elimination targets

## 2. POOR DATA QUALITY AND USE

### **Poor quality and use of data is substantially impeding program management and improvement**

Our 2013 GVAP Assessment Report said that improving data quality should be the number one priority for vaccination programs, and for the vaccination infrastructure globally. This remains the case. At the 2014 World Health Assembly, a number of countries supported this priority. Having accurate data is the foundation for performance improvement, from the local level up. Used well, data are the cornerstone of accountability – demonstrating whose performance is strong and whose is weak. If data are accurate, even simple analysis can provide important insights on which to improve coverage. By contrast, managing a program with poor quality data is like navigating through the fog with an out-of-date map.

There are few data to describe countries' human resource capacity, and this is of particular concern in relation to the quality of data. If frontline staff are over-worked, accurate recording of data can be one of the first things that is missed particularly if they have little reason to think of data as important. Program managers need to have sufficient time and skill to improve and use data.

Key technical agencies are acting to improve data quality, in several areas. Appropriately, they are particularly focusing on data being accessible at the right time and in the right format, so that they are usable as well as accurate. They are working to improve the availability, design and use of home-based records, which are the most basic building block of data capture in some countries. It is vital to improve healthcare facilities' records too, because these provide community level administrative

data. They are working to improve target population estimates, and are standardizing survey methods. They are also looking at how technology can improve the recording, reporting analysis and use of data. This is a long-term process. Electronic systems have an important role to play, but are no panacea. Some countries and regions are making strong use of health information systems, and it is important that this learning is spread. Having data is only the first step towards using them to make improvements.

As data quality is improved, it should be anticipated that the reported level of vaccination coverage may change (it might increase, it might decrease). Programme managers should be reassured that having accurate data is what matters the most.

Data quality and use should be a top-of-the-agenda item. The SAGE will return to this issue in its future Global Vaccine Action Plan Assessment Reports.

#### THE SAGE RECOMMENDS THAT:

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

### 3. VACCINE AFFORDABILITY AND SUPPLY

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

No vaccination program can function without vaccine supply. In 2013, more than 40% of low and middle-income countries suffered a national-level stock-out of at least one vaccine that lasted at least one month. This information comes from data reported by countries to WHO and UNICEF using the Joint Reporting Form. The problem is affecting countries of all sizes. If anything, 40% may be an under-estimate.

This is a shocking finding. Yet these data came as no surprise to technical agency staff who are in touch with many countries day to day. They describe some countries having vaccine stockouts every month, for different reasons.

This is deeply worrying. It might be having a major impact on the availability of vaccines in healthcare facilities, which in turn would impede coverage. More information is needed. First, what is the scale of the problem? "At least one stockout for at least one month" does not illustrate the full number and duration of stockouts. Second, how badly is this affecting vaccine availability in healthcare facilities? It is possible that local supply is not being affected, if the national stock-outs are quickly dealt with. On the other hand, it may be affected substantially. It is also possible that local stockouts are occurring even when vaccines are available in a national store. Third, why is this happening? What is the root cause? Are countries not organizing vaccine

#### IN BRIEF

Data quality remains top priority

Poor data stifles progress

Good work ongoing to improve data quality and use

supply well? Is there a cash flow problem? Or are there real problems with the global availability and supply of some vaccines?

This needs full and urgent investigation. There is a pressing need to better understand the root cause in each context. Understanding and fixing these will make vaccination systems more robust and may measurably contribute to increases in global vaccination coverage.

**Vaccine affordability** is crucial. Vaccines can only be provided to all who should benefit if they can be sustainably purchased, but at a price that also provides sufficient reward and incentive for industry. There has been particular concern about the affordability of newer vaccines for middle-income countries that do not receive Gavi funding (because they are ineligible for it, or because they were previously eligible but have now graduated from Gavi support). . There is concern that for some countries and certain vaccines, price may be the main barrier to introduction, and that for other countries, vaccine procurement costs may take too great a bite out of the overall healthcare budget and therefore not be sustainable.

Information on vaccine prices (complemented by other data) is key to assessing affordability and market dynamics. Both UNICEF and the PAHO Revolving Fund now make price information available for the vaccines that they buy through pooled procurement. Many countries finance and procure vaccines on their own, though, and price information for these countries is sparse.

To address this, recent global efforts have tried to collect vaccine price information from countries. There have been two main initiatives: the Vaccine Product, Price and Procurement (V3P) database, and a pilot in two regions of WHO/UNICEF Joint Reporting Form. (In future, the V3P database will be the main mechanism for reporting and recording price data from countries and the Joint Reporting Form will provide a link to this.) . To date, only 17 countries have provided information to the V3P - and in just one case is this data validated and cleared for public sharing. Another 27 countries provided information through the pilot Joint Reporting Form mechanism, but it was far from comprehensive. In short, there is a real shortage of information about how much countries are paying for vaccines.

Because vaccine pricing is not transparent, the affordability of vaccines for countries cannot be properly evaluated. Why the lack of transparency? The price collection mechanisms are relatively recent, so countries may not yet be fully aware of them or their importance. It is also known that some countries accept confidentiality clauses with manufacturers, in exchange for perceived preferential pricing, but it is unclear to what extent this may impact reporting

It is vital that greater transparency be brought to this important area. This is crucial to evidence-based assessment of the scale and scope of market imbalances, and will allow solutions to be developed once the problems are understood. It will enable open and fair discussions about appropriate levels of financing for procurement, and how vaccine pricing differs among countries.

Self-procuring countries may believe they hold little power in vaccine markets that are often dominated by very few firms, and in which they may lack market knowledge and deep expertise in procurement and

## IN BRIEF

National vaccine stock-outs in 40% of low and middle-income countries in 2013

Need urgent investigation into scale, impact and why



negotiation. But countries can exercise more control over these issues than they may realize, particularly if they commit to sharing information and working together. Solutions that meet their needs can be facilitated by others, but should be driven by their input. This begins with, but is not limited to, price information.

The pharmaceutical industry has played a vital role in developing vaccines and making these accessible, particularly through Gavi. They have a crucial role to play in achieving the great ambitions of the Global Vaccine Action Plan. Achieving a proper balance between affordability and industry incentives can be complicated, but SAGE recognizes it as essential to achieving sustainable increases in coverage and realizing the benefits of new vaccines. Market transparency is critical in achieving this.

Two important issues of vaccine availability have been described – the first to do with supply, the second to do with affordability.

#### THE SAGE RECOMMENDS THAT:

- Technical agencies conduct urgent assessments of (i) the extent to which the reported national-level stock-outs are affecting local vaccine supply and delivery, and (ii) the root causes of these stock-outs
- Countries lead an effort to change the rules of the game on vaccine affordability, to create the transparency that is in their interest. They can do this by making pricing information publicly available, and by collaborating to develop solutions.
- Technical partners support countries to improve the transparency of vaccine pricing. Agencies themselves should do everything possible to share pricing data.

#### 4. FAILURES OF BASIC INTEGRATION

**Basic failures to integrate mean that healthcare workers are repeatedly missing easy opportunities to offer vaccinations when people attend clinic with other problems.**

How often does it happen that a child is overdue for a vaccination, attends a healthcare facility for another reason, and is not offered the vaccination while he or she is there? A recent meta-analysis<sup>5</sup> suggests that a full one-third of children who come to healthcare facilities are due a vaccine but are not offered it. Every time this happens, an easy opportunity is missed. People often talk about how difficult it is to 'reach the last child', but many of these children are passing right in front of our eyes and not being vaccinated.

Not only children are affected. The same study shows that almost half of women of child-bearing age were not offered tetanus vaccination when they attended a healthcare facility for another reason. These problems have existed for many years. Data suggest that there has been little improvement in them over the last 20 years.

The first reason for this is basic failure of integration and joined-up thinking. Women come to an antenatal clinic, at which the healthcare worker is not thinking about vaccination and so offers vaccine neither to the women nor to their accompanying children. Yet the next morning, the same healthcare worker is running a vaccination clinic. Children are brought to see a nurse because they have a mild illness, and nobody asks to see their vaccination card. Yet the day before, the same room was full of children with vaccination cards. In short, it is as if the left hand does not know what the right hand

#### IN BRIEF

Vaccine affordability – price transparency crucial

Middle-income countries may be at particular risk

Countries, technical partners and pharma-industry need to address this together

is doing. This is how programmatic silos at global and national level can unfortunately affect what happens in healthcare facilities. Even when the same staff delivers the different services, they are too often not well linked together.

Once the problems are identified, simple solutions can work well. The design and use of healthcare records can be changed, to prompt staff. If there are not enough staff, community volunteers can help. Fixing this problem also needs to be part of improving integration within healthcare more generally.

There is another important reason why opportunities are missed, which has a different solution. If a healthcare worker sees a child with a mild febrile illness, he or she may believe that this is a contraindication to giving a vaccine. Field experience suggests that this is likely a widespread problem. This issue needs to be dealt with through clear evidence-based guidance, clearly communicated to healthcare workers.

#### THE SAGE RECOMMENDS THAT:

- Countries conduct studies to understand how opportunities to vaccinate people are being missed by healthcare workers, and act to reduce their incidence
- WHO develop guidelines on how to fully integrate vaccination into the operation of all aspects of the healthcare system
- Countries ensure that healthcare workers understand and follow WHO or national guidelines on what does, and does not, contraindicate vaccination, particularly in relation to childhood febrile illness, so that vaccines are not avoided unnecessarily

### 5. SITUATIONS DISRUPTING IMMUNISATION

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

When armed conflict starts, vaccination coverage tends to plummet. Less than half of children in Central African Republic, Syria and Somalia received three doses of DTP vaccine in 2013. Unfortunately, the world is never free of war. It forms part of the environment in which vaccines must be delivered. With an ambition to extend vaccination to all people, conflict cannot be an exception.

The link between war and poor coverage is not absolute. In Afghanistan, DTP3 coverage is at least 70%. When polio spread into Syria, a number of partners mounted a quick and effective vaccination response. There is a lot to learn from these, and other, situations in which good progress is made in the face of adversity. In response to war, vaccination programs must have a plan for refugees, for receiving communities, and for those left behind.

War is not the only disruptive environment in today's world. Earthquakes and major climatic events can severely disrupt vaccination. Other health emergencies can do so also. The current Ebola outbreak is a prominent example of this. Vaccination rates are already dropping. The

#### IN BRIEF

Missed opportunities: Children, pregnant women and adults are attending healthcare facilities but not being vaccinated

<sup>5</sup>Shiruti A, Agence de Medecine Preventive, 2014

attention of frontline healthcare workers is being diverted, and providers are frightened to deliver services. Vaccination program managers are being seconded away, to help in the Ebola response. Supply chains are disrupted. Even populations' trust of healthcare services, and therefore of vaccination, risks being impaired. Measles outbreaks are already occurring in Ebola-affected countries, and outbreaks of others vaccine-preventable diseases are likely to follow.

There needs to be specific focus on minimizing the disruption that situations like war and outbreaks (including the Ebola outbreak) cause to vaccination. Complex and difficult situations are a fact of life, and global vaccination programs need to become more resilient in the face of them. There is currently WHO guidance, developed with input from SAGE, on how immunisation can help mitigate the risks associated with humanitarian emergencies – but not on how routine immunisation (or equivalent) services can be continued in spite of these and other challenges.

#### THE SAGE RECOMMENDS THAT:

- WHO, through SAGE, expand its existing guidance on immunisation in humanitarian emergencies to detail how routine and other immunisation services are best maintained despite disruptive situations such as war and disease outbreaks

#### IN BRIEF

Vaccination despite conflict – can and must be done

Ebola – major threat to vaccination

Disruptive situations inevitable: must succeed regardless

# UNLEASHING VACCINES' FUTURE POTENTIAL

## BASELINE REPORT

Most of this report has been about making full use of the vaccines available today. The other ambition of the Global Vaccine Action Plan is about the future:

Vaccines have vast future potential. Their development and use has already saved millions of lives, but vaccine science has enormous further potential. In future generations, vaccines against HIV and malaria could make these diseases go the same way as diphtheria, smallpox and polio have before them.

The Global Vaccine Action Plan sets ambitious and important research and development goals. It aims, by the end of the decade, for at least two major new vaccines to have been developed, licensed and launched:

- **A universal flu vaccine.** This would stop the need for annual re-vaccination to protect against the seasonal influenza epidemics in which up to half a million people currently die. It would also eventually protect against flu viruses with pandemic potential.
- **A vaccine for another disease of major public health relevance that is not currently vaccine-preventable.** To assess progress towards this goal, the SAGE examines the current state of vaccine research for a sample of seven infectious diseases<sup>6</sup>. These seven were chosen because they represent a range of different infection types. Tracking them provides a reasonable assessment of how vaccine science is progressing overall. They are a sample, not a priority list.

The plan also aims, by the end of the decade, for **proof of concept of a vaccine that prevents HIV, malaria or TB with 75% or greater efficacy**<sup>7</sup>. These three diseases together cause three million deaths a year. Only TB currently has a vaccine in use. It is only 50% effective and, given in childhood, does not prevent disease in adulthood.

## PROGRESS: A FULL PIPELINE, BUT SLOW FLOW

In 2014, the GVAP secretariat summarized progress towards each of these important goals. For the rest of the decade, the SAGE will examine progress every two years, using this 2014 summary as a baseline<sup>8</sup>.

For each of HIV, TB and malaria, the vaccine development pipeline is well populated. For TB, 13 candidate vaccines are the subjects of clinical trials. Many of these would be given as boosters to the existing BCG vaccine. For malaria, there are now 30 candidate vaccines under trial. Most aim to prevent infection with the malaria parasite from causing disease. Others work differently, aiming to prevent infected individuals from transmitting the disease to others. For HIV, there is currently a list of 40 candidate vaccines - but most are still in pre-clinical development, and many may not progress beyond this phase.

<sup>6</sup>The sample of seven infectious diseases is: dengue, hepatitis C, cytomegalovirus, respiratory syncytial virus, group A streptococcus, leishmaniasis, and helminth infections.

<sup>7</sup>The definition of this indicator will be re-visited by the Working Group

<sup>8</sup>There is no single source global record of the number of candidate vaccines under development. The numbers presented here come from clinical trial databases and from experts, but may not be wholly complete.

## IN BRIEF

GVAP sets important, ambitious research and development goals

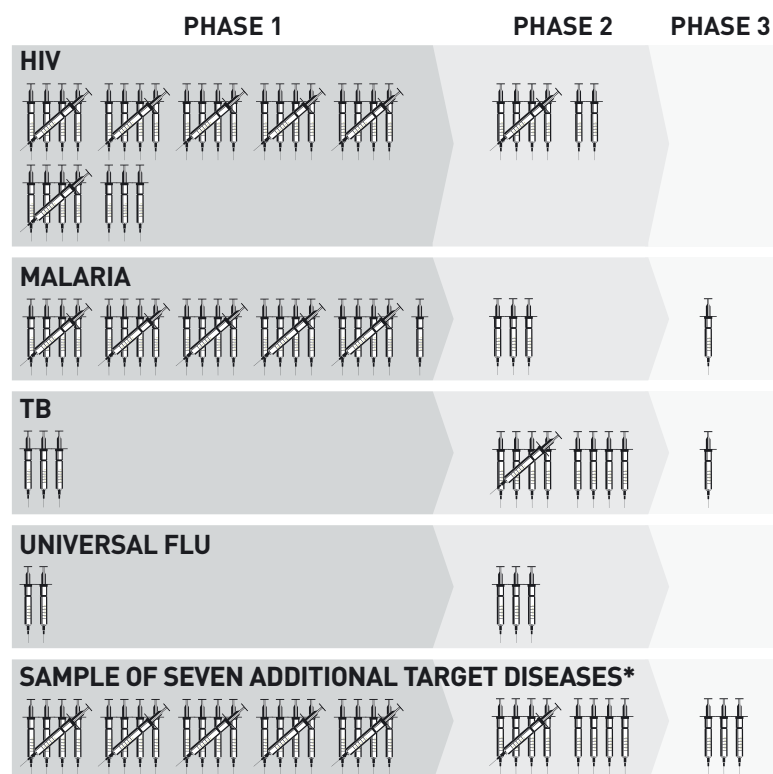
A candidate vaccine's prospects of reaching licensure increase substantially as it passes successfully through the phases (I to III) of clinical trials. One malaria and one TB vaccine are currently in phase III trials. The malaria vaccine is furthest advanced. Depending on its trial results, expected in late 2014, it might be licensed in 2015. This is a welcome development, but this vaccine is unlikely to meet the GVAP's target of 75% efficacy.

Five universal flu candidate vaccines are in clinical trials. Detailed analysis, available in the GVAP Secretariat Report, illustrates that a good range of technologies and approaches are being employed to address the major scientific challenges that flu presents. Of note, the definition of what constitutes a universal flu vaccine leaves room for interpretation.

Finally, across the sample of seven other diseases, a total of 37 candidate vaccines are currently in clinical trials. Three (one for each of dengue, cytomegalovirus and schistosomiasis) are in phase III trials. A wide range of approaches is being tried. In sum, this represents a promising volume of research. As stated above, this is only a sample of seven diseases. Notably, accelerated trials to develop an Ebola vaccine are also being undertaken.

For all of these diseases – particularly HIV, malaria and TB – there are important preventative strategies that do not involve vaccination and have been widely employed to good effect. A highly effective vaccine would be a major additional contribution.

## THE VACCINE PIPELINE: CLINICAL TRIALS IN PROGRESS



The volume of research is promising, but the scientific challenges and technical barriers are very great. As it currently stands, the SAGE does not expect a universal flu vaccine to be licensed by the end of the decade. There is greater hope that a vaccine against another disease will be licensed and launched.

## THE BOTTLENECKS

Developing vaccines is inherently complex. It involves stretching the boundaries of scientific knowledge. Few candidate vaccines make it through the rigorous phases of trial. Accepting this, the strategic question for the SAGE is: Are conditions optimal for vaccine research and development to proceed as fast as possible, or is anything other than the inherent scientific challenge standing in the way of progress?

A number of bottlenecks are slowing progress:

- Supporting the research base – many great research ideas are not receiving resources, limiting the number of candidate vaccines and so the chances of developing effective vaccines
- Lengthy clinical trials – pre-clinical research has been accelerated, but clinical trials are increasingly taking longer and costing more. Efficiency could be improved through innovative trial designs and developing new validated biological markers for safety and efficacy.
- Clinical trial reporting – There are too often delays and even biases in the publication of clinical trial results. Failing to publish clinical trial results in a timely manner introduces risk and inefficiency. Rapid development requires timely sharing of knowledge. Otherwise people make scientific, policy and funding decisions that are not as fully informed as they could be. A WHO committee (the Product Development for Vaccines Advisory Committee) is developing an approach that WHO could take to tackle this issue. The SAGE emphasizes that WHO and other parties will need to work together and take a hard line to resolve this problem.
- Development pathways – Manufacturers and regulatory agencies should continually look for ways to increase the speed of the vaccine development and licensing process. Delays in developing vaccines cost lives. In response to the current Ebola outbreak, regulators have shown substantial flexibility, employing innovative and rapid means of assessing the safety and efficacy of new therapeutic agents. Acceleration is possible when lives are on the line. Lives are continually being lost, and acceleration – whilst maintaining safety – should be a constant aim.
- Coordination – many different parties are working towards vaccine development. There is greater potential, particularly for TB and HIV, for them to be more in more open, frequent dialogue with one another.

The GVAP research and development goals are ambitious – but their achievement would save millions of lives. Only two things should be allowed to limit the speed of vaccine development: the inherent complexity of the scientific task, and the necessity of ensuring safety.

## IN BRIEF

Tackling process bottlenecks can speed up scientific development

## NEW TECHNOLOGIES FOR VACCINE DELIVERY

The process of giving a vaccine can be improved in so many ways. Needle-free devices can reduce the risk of spreading infection. Pre-filling of syringes can increase the number of children vaccinated per hour. Injecting into the skin, instead of muscle, can allow smaller doses to be given. These innovations, and many more, are described in the GVAP Secretariat Report. Given their potential benefits, it is disappointing that no new vaccine delivery technology has been launched in a low or middle income country since 2010.

The technical challenges are not small. New delivery methods often require extensive investment in testing and manufacturing equipment, and to be attractive must provide substantial improvements over the current technologies. Greater clarity amongst developers about what countries want will help focus attention on the approaches that hold the greatest promise. Countries and the global technical agencies need to clearly communicate what products would be most desirable.

Some products have been developed but not yet launched. The GVAP technical agencies can do more to encourage and support countries in introducing improved vaccine delivery methods. Cost is a particular consideration. The new technologies often cost more per dose given. Most countries take the cost of the vaccine and the consumables (syringes, needles, etc) into account when they decide which to purchase. A more complete calculation would consider the full costs of vaccination – including the training of personnel, and the time taken to give vaccine – and the full benefits of different methods, such as improved safety. WHO is developing a ‘total system cost effectiveness framework’ to help countries conduct this fuller calculation. This need not be over-complex, and must be rapidly developed and deployed. It is an important step in demonstrating the benefits of new technologies, where these exist, and therefore in incentivizing industry to develop them and bring them to market.

There is unrealized transformative potential here – both from individual innovations and from their deployment in combination. The SAGE GVAP Working Group will revisit progress in two years and hopes to see considerable change.

## VACCINE DISTRIBUTION

Vaccines are distributed far and wide, from their place of manufacture to the hands of the millions of healthcare workers who administer them. This requires many different technologies, particularly to transport, refrigerate and monitor the vaccine. Every year, new technologies are developed and are ‘prequalified’ by WHO, indicating to countries that they are judged effective and safe. There are now 252 such vaccine delivery products. This represents a 50% increase since 2010.

The distribution challenge is particularly compounded by the need to keep most vaccines cold throughout their journey. Manufacturers are therefore showing interest in the idea that some vaccines might safely be transported and stored at a somewhat higher temperature, at least for the last part of their journey. This ‘controlled temperature chain’ (rather than the normal ‘cold chain’) could be cost-saving, helpfully reducing the requirement for refrigeration, which can be a challenge in remote areas with unreliable electricity.

## IN BRIEF

New ways of giving vaccines – great promise here

Technologies may cost more to buy but create savings down the line

Controlled-temperature chain: unrealized potential

One vaccine, MenAfrivac, has been licensed and used in a controlled temperature chain. This has been very successful and provides a model for what can be achieved. Manufacturers are clearly interested in having other vaccines similarly licensed, which is a positive development.

Countries are not yet jumping at the idea of controlled-temperature chain-licensed vaccines, though. In particular, they are concerned about causing confusion amongst vaccination staff who have, for decades, been trained on the importance of maintaining the cold chain. It is important that countries are helped with this. A controlled-temperature chain could be cost saving. Manufacturers will only continue to have vaccines re-licensed for controlled-temperature chain use if countries show interest in using them.

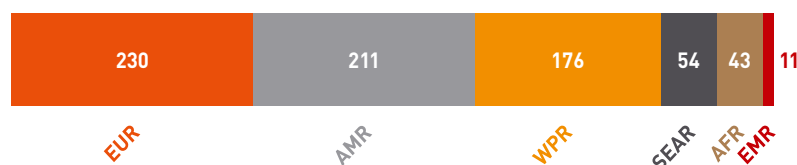
### VACCINE TRIALS: INSTITUTIONAL AND TECHNICAL CAPACITY

Every region of the world should have a solid base of countries competent in hosting and managing vaccine trials. The GVAP aims to achieve this by the end of the decade.

In the last year (May 2013-May 2014), 725 vaccine clinical trials were registered in 64 countries. There are trials in every region, but it is clear that some countries and regions have far greater capacity than others. In each region, between 28% and 45% of countries registered at least one trial – except for EMR, where just three countries (14%) did so.

#### 725 VACCINE TRIALS IN 64 COUNTRIES:

MORE THAN HALF IN EUR AND AMR



Priority should be given to enhancing the capacity of regulatory committees and agencies. These play a crucial role in the planning, approval and oversight of clinical trials. They allow trials to proceed smoothly and safely. In AFR, there has been strong work on this front. This needs to continue, and other regions may wish to learn from it.

Greater research capacity is not just required in laboratories. Operational and implementation-focused research is also vital, to understand how to most effectively and efficiently deliver vaccines in practice.

The SAGE is concerned about a persistent trend of vaccine (and other) trials being carried out in a lower income country but overseen, analyzed and published by researchers from higher income countries.

This does too little to build countries' own capacity to conduct trials.

It is untenable and even ethically questionable. Those in lower income countries too often do the 'heavy lifting', the glory goes elsewhere, and talent is not developed in the way that it needs to be.

### IN BRIEF

Vaccine trials: strong regulatory bodies key

Researchers in lower income countries should lead work, not just do the 'heavy lifting' for others



## CONCLUSION

The Global Vaccine Action Plan was established for very good reasons, to meet major and important needs. Progress towards its key targets is clearly far off-track. This should cause alarm bells to ring loudly. Vaccines are not being delivered equitably or reliably. Through vaccination, diseases such as tetanus and polio should have been consigned to history several years ago – previous targets for doing so have repeatedly been missed.

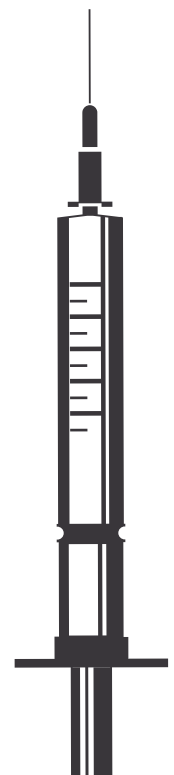
The five off-track targets are closely related. They are not separate, competing endeavors, but close cousins. The key to achieving all of them lies in strengthening immunisation systems.

There are clear areas in which focused action can produce considerable improvement. This report has identified five that are particularly important. If these are acted upon, real progress can be made.

The Global Vaccine Action Plan sets important ambitions. If countries and their partners are to achieve these, dramatic change is needed. If they can do so, millions of deaths will be prevented.

This report's recommendations need to be implemented with great urgency. The 'Decade of Vaccines' is one-third through, and the Global Vaccine Action Plan is an opportunity that should not be lost.

The SAGE, through its Global Vaccine Action Plan Working Group, will re-examine the situation annually.



## ANNEX

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United States National Institute of Allergy and Infectious Diseases  
United Nations Children's Fund  
World Health Organization

## ANNEX

### ADDITIONAL RECOMMENDATIONS TO THE DECADE OF VACCINES / GLOBAL VACCINE ACTION PLAN SECRETARIAT

The SAGE's main recommendations are made within the body of this report. In addition, the SAGE Working Group on the Decade of Vaccines makes the following recommendations to the Decade of Vaccines Secretariat:

1. The following additions should be made to the GVAP Secretariat report in 2015:
  - a. A report from each WHO region on the implementation of its Regional Vaccine Action Plan
  - b. A report from the GVAP secretariat agencies setting out their response to, and actions taken to achieve, the recommendations addressed to them in the SAGE GVAP Assessment Report 2014
  - c. A report from the GVAP secretariat agencies on progress being achieved in improving data quality, including country case studies
2. The GVAP Secretariat report in 2016 should include a wider landscape analysis of candidate vaccines in development, to supplement the analysis of vaccines against the sample of seven sentinel diseases reported in 2014. The secretariat could perhaps attempt to list all vaccine trials in phase 2 and beyond.
3. Case studies should be written and disseminated to illustrate (i) the licensing of MenAfriVac for use in a controlled-temperature-chain, (ii) the impact of the introduction of one or more new vaccine delivery technologies
4. A small number of countries (perhaps 3-4) should be invited to present to the SAGE GVAP Working Group in February 2015, to describe the actions that they are taking to improve vaccination coverage
5. The definition of indicator 4.2 should be expanded to include technologies that improve safety and efficiency of vaccine delivery, as follows: "New platform delivery technology defined as a new mechanism for delivering vaccines to individuals that facilitates coverage, improves efficacy or safety, or reduces the cost of vaccine or delivery"
6. Work should continue to develop and/or select indicators that provide more valid and useful information about vaccine demand than the current indicators are able to
7. Countries should be encouraged and helped to use the online GVAP immunisation dashboard tools to review their performance

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**Strategic Advisory Group of Experts on Immunisation (SAGE)  
2014 ASSESSMENT REPORT  
OF THE GLOBAL VACCINE ACTION PLAN**

[Full report available at: [www.who.int/immunization/global\\_vaccine\\_action\\_plan/en/](http://www.who.int/immunization/global_vaccine_action_plan/en/) ]

## **SUMMARY**

### **Vaccines are remarkable.**

They protect people from developing diseases that otherwise scar, kill and maim. They prevent more than two million deaths a year. Relative to their great benefit, their cost is small. They have an impressive history and an exciting future.

### **The Global Vaccine Action Plan is vital.**

At the moment, 1.5 million children die every year of diseases that are readily prevented by vaccines. There is gross inequity. One-fifth of the world's children do not receive these simple, cheap, life-protecting interventions that parents elsewhere take for granted – or receive a partial set, and so are not wholly protected. There is a pressing need to expand and strengthen the delivery of vaccines, so that they protect all people.

### **The Global Vaccine Action Plan has two great ambitions, to make 2011-2020 the Decade of Vaccines:**

- To deliver vaccination to all – and through this: to end inequity in vaccination, eradicate polio globally, eliminate maternal and neonatal tetanus globally, and eliminate (guided by regional targets) measles and rubella.
- To unleash vaccines' vast future potential – because their impressive history is nothing in comparison to what they could yet achieve.

In setting these two great ambitions, the Global Vaccine Action Plan aims to make 2011-2020 the 'Decade of Vaccines'. SAGE's 2014 Assessment Report of the Global Vaccine Action Plan examines the progress made to date.

### **Progress is far off-track**

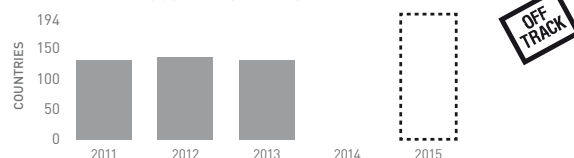
The Global Vaccine Action Plan set six immunisation targets with deadlines that are fast approaching – one at the end of 2014, four at the end of 2015. Just one of these six targets is on track to be realized (see figure overleaf). Indeed, most have seen very little progress. Some have been missed multiple times before.

The Global Vaccine Action Plan was created to end the inequity in vaccination worldwide, and hence to save millions of lives. This need remains as important and urgent as ever. **It is not acceptable that the plan is failing to deliver.**

## IMPENDING GVAP TARGETS: FIVE OF SIX ARE OFF-TRACK

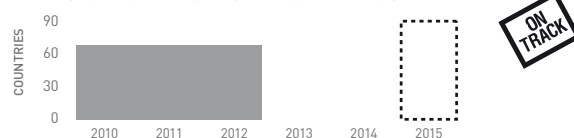
### DTP3: NATIONAL VACCINATION COVERAGE OF 90%

TARGET: ALL 194 COUNTRIES BY 2015



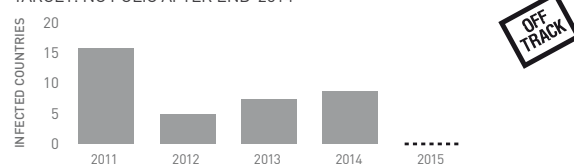
### INTRODUCTION OF UNDER-UTILISED VACCINES

TARGET: 90 LOW OR MIDDLE INCOME COUNTRIES INTRODUCE AT LEAST ONE UNDER-UTILISED VACCINE BY 2015



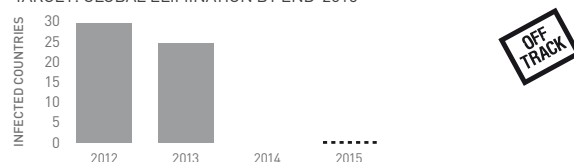
### POLIO

TARGET: NO POLIO AFTER END-2014



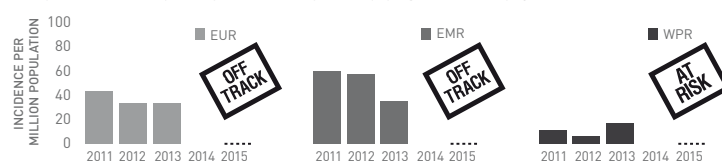
### MATERNAL AND NEONATAL TETANUS

TARGET: GLOBAL ELIMINATION BY END-2015



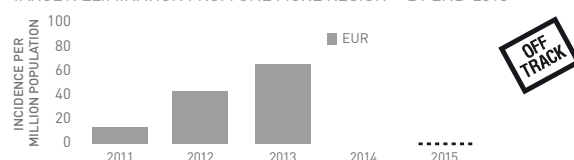
### MEASLES

TARGET: ELIMINATION FROM THREE MORE REGIONS\* BY END-2015



### RUBELLA

TARGET: ELIMINATION FROM ONE MORE REGION\*\* BY END-2015

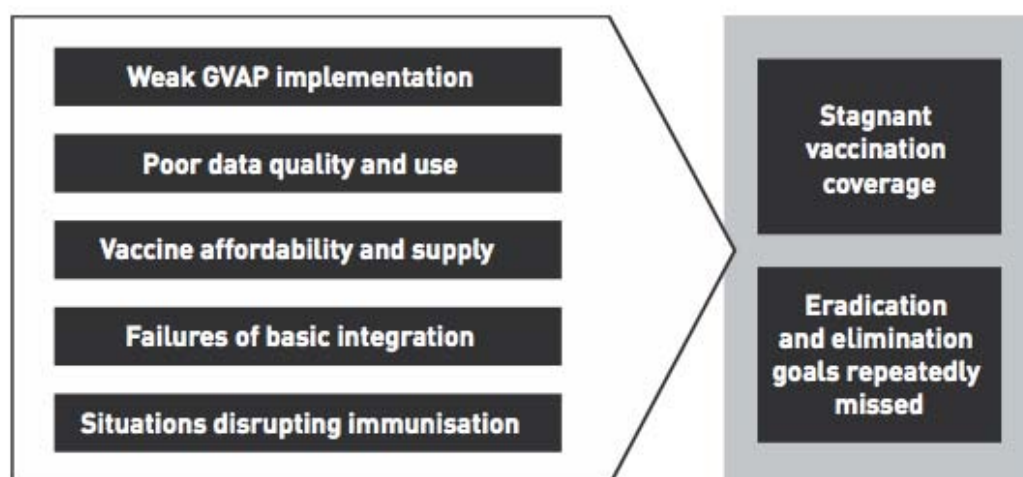


\*Four regions in total, including AMR. Data for other regions are in the GVAP Secretariat Report

\*\*Two regions in total, including AMR. Data for other regions are in the GVAP Secretariat Report

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**Addressing five priority problems will help bring the Global Vaccine Action Plan back on track**



To get the Global Vaccine Action Plan back on track, the SAGE recommends that action focus particularly on addressing five priority problems. Each problem is major, but each can be tackled, with a reasonable expectation that doing so will improve progress considerably.

Each problem is detailed in the full 2014 Assessment Report, and is summarized below.

### **1. WEAK GVAP IMPLEMENTATION**

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

The SAGE recommends that:

- Regions and countries rapidly finalize their own vaccine action plans based on the Global Vaccine Action Plan, using this assessment report as a further guide, and establishing bodies to guide and monitor implementation
- The heads of the technical agencies that co-signed the Global Vaccine Action Plan report to the 2015 World Economic Forum in Davos on the plan's establishment, its lack of progress so far, and what forum participants – who supported its concept in 2010 – can do to help its implementation
- The Global Vaccine Action Plan and SAGE's assessment reports remain as

- 
- standing items at the World Health Assembly until 2020
- The Director-General of WHO convene a special session at the 2015 World Health Assembly for countries with vaccination coverage of less than 80%, to which each Minister of Health is asked to bring details of the country's vaccination coverage and corrective action plan
  - Countries give civil society organizations substantially more formal involvement in the delivery and improvement of vaccination services, establishing clear responsibilities for which they are accountable
  - Every region establish a regional verification commission, and every country a national verification committee, to scrutinize progress towards the measles elimination targets

## **2. POOR DATA QUALITY AND USE**

**Poor quality and use of data is substantially impeding program management and improvement**

The SAGE recommends that:

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

## **3. VACCINE AFFORDABILITY AND SUPPLY**

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

The SAGE recommends that:

- Technical agencies conduct urgent assessments of (i) the extent to which the reported national-level stock-outs are affecting local vaccine supply and delivery, and (ii) the root causes of these stock-outs
- Countries lead an effort to change the rules of the game on vaccine affordability, to create the transparency that is in their interest. They can do this by making pricing information publicly available, and by collaborating to develop solutions.
- Technical partners support countries to improve the transparency of vaccine pricing. Agencies themselves should do everything possible to share pricing data.

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#### **4. FAILURES OF BASIC INTEGRATION**

**Basic failures to integrate mean that healthcare workers are repeatedly missing easy opportunities to offer vaccinations when people attend clinic with other problems.**

The SAGE recommends that:

- Countries conduct studies to understand how opportunities to vaccinate people are being missed by healthcare workers, and act to reduce their incidence
- WHO develop guidelines on how to fully integrate vaccination into the operation of all aspects of the healthcare system
- Countries ensure that healthcare workers understand and follow WHO or national guidelines on what does, and does not, contraindicate vaccination, particularly in relation to childhood febrile illness, so that vaccines are not avoided unnecessarily

#### **5. SITUATIONS DISRUPTING IMMUNISATION**

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

The SAGE recommends that:

- WHO, through SAGE, expand its existing guidance on immunisation in humanitarian emergencies to detail how routine and other immunisation services are best maintained despite disruptive situations such as war and disease outbreaks



## **Global vaccine action plan**

### **Report by the Secretariat**

1. An earlier version of document EB134/13 was considered and noted by the Executive Board at its 134th session.<sup>1</sup> Paragraphs 9, 12 and 15 below have been updated.

#### **ACTION BY THE HEALTH ASSEMBLY**

2. The Health Assembly is requested to note the report.

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<sup>1</sup> See the summary records of the Executive Board at its 134th session, second meeting, section 1.

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**EXECUTIVE BOARD**  
**134th session**  
**Provisional agenda item 6.2**

**EB134/13**  
**6 December 2013**

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# **Global vaccine action plan**

## **Report by the Secretariat**

1. In May 2012, the Sixty-fifth World Health Assembly endorsed the global vaccine action plan in resolution WHA65.17 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, using the proposed accountability framework to guide discussions and future actions.
2. In May 2013, the Sixty-sixth World Health Assembly noted the Secretariat's report with its proposed framework for monitoring, 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.<sup>1</sup>
3. An executive summary of the Global Vaccine Action Plan Assessment report<sup>2</sup> of the Strategic Advisory Group of Experts on immunization follows.

## **EXECUTIVE SUMMARY OF THE REPORT OF THE MEETING**

4. Vaccines and immunization have created a healthier world. Progress is being made towards polio eradication. Measles and neonatal tetanus deaths are on the decline and new vaccines are being introduced into the national programmes of low- and middle-income countries with associated reductions in morbidity and mortality. Still, national governments, development partners and international agencies must invest more to meet the Decade of Vaccines' goals of disease eradication or elimination and to reduce mortality and morbidity from vaccine-preventable diseases.

### **Data quality improvement**

5. Accurate immunization coverage and disease surveillance data are critical for making better programmatic decisions, meeting immunization targets and monitoring progress toward disease

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<sup>1</sup> See document WHA66/2013/REC/3, summary record of the tenth meeting of Committee A, section 2.

<sup>2</sup> [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/sage\\_dov\\_gvap\\_progress\\_report\\_2013.pdf](http://www.who.int/immunization/global_vaccine_action_plan/sage_dov_gvap_progress_report_2013.pdf).

reduction. Hence, data quality improvement is selected as the theme for the progress report of the global vaccine action plan in 2013. In many countries, the quality of currently available data are inadequate to inform the proper management of the immunization programmes and often programme managers in these situations lack confidence in the available data for decision-making. High quality data provide the cornerstone for accountability at all levels. National governments must take the responsibility to have the right data available at the right time and at the right places for the effective and efficient implementation of their national programmes by making greater investments for the improvement of data quality as well as enhance data transparency.

6. Improvement of data quality has to become the highest priority for all stakeholders. Priority should be placed on improving immunization coverage and vaccine-preventable disease surveillance data. Development partners and technical agencies must collaborate to establish a step-by-step, country-tailored approach to strengthen data quality at all administrative levels and provide guidance to countries on validating coverage and surveillance data. National Immunization Technical Advisory Groups should play an important role to independently monitor progress and data quality at the national level. Regional Immunization Technical Advisory Groups should support and catalyse activities of the National Immunization Technical Advisory Groups.

7. The availability of new information and communications technologies provide an opportunity for improving the recording, reporting and analysis of immunization data at all administrative levels. National programmes should develop plans to make use of these tools to improve their immunization information systems and improve data quality on vaccine coverage and disease surveillance.

8. In order to improve data quality, the Strategic Advisory Group of Experts on immunization recommends that:

- countries should conduct regular, timely reviews of data, including data quality, at all administrative levels, including the district level, to monitor programme performance;
- all countries should establish systems to monitor subnational data (district level) and report subnational coverage estimates to WHO by 2015;
- technical agencies should promote and provide guidance on the use of new information and communication technologies to improve the recording and reporting of data;
- technical agencies should review, revise and standardize the methodology for collection and analysis of vaccine-coverage survey data, including the use of sero-surveys.

### **Improving immunization coverage**

9. Currently, only 59 (30%) of countries were assessed to be meeting the coverage target of at least 90% nationally and 80% in every district (or similar administrative level) with three doses of diphtheria, tetanus and pertussis-containing vaccines (DTP3) in children  $\leq 12$  months of age. Many countries – mainly in the African, South-East Asia and Eastern Mediterranean regions – will not meet routine immunization coverage targets by 2015. Even more worrying is that immunization coverage has remained low, stagnant or even decreasing in several of these countries. These countries should urgently intensify efforts to improve programme performance, utilizing administrative and survey data to direct their corrective actions. Civil society needs to be meaningfully engaged in policy dialogues so that reasons for low coverage are better understood and interventions are tailored to address identified problems. Countries, agencies and all development partners must engage with the vaccine industry to closely monitor the global supply of vaccines and ensure sufficient supply into the future. They should

anticipate and take timely actions to mitigate the risks of vaccine supply shortfalls that contribute to low coverage.

10. In order to improve immunization coverage, the Strategic Advisory Group of Experts on immunization recommends that:

- countries falling short of reaching coverage targets should urgently identify barriers and bottlenecks and implement targeted approaches to increase and sustain coverage based on a systematic review of community and district levels data;
- countries with a DTP1-DTP3 drop-out rate greater than 10% should review programme policies and performance and urgently implement measures to reduce dropout;
- all countries should establish or strengthen capacity for vaccine pharmacovigilance to detect and respond to adverse events to enhance confidence in immunization programmes.

### **Accelerating efforts to achieve disease eradication or elimination**

11. As the world nears the final stages of the polio eradication effort, the challenges to achieve success have increased. It is imperative that all stakeholders now redouble their efforts to complete the job, as failure would represent a failure not only for the immunization community but for public health. Efforts toward meeting this goal should also strengthen immunization programmes and health systems, using the polio eradication initiative's assets and knowledge.

12. All countries are urged to establish national action plans to introduce at least one dose of inactivated poliovirus vaccine (all countries endemic for poliomyelitis should establish such a plan by mid-2014 and other high-risk countries by end-2014) and switch from the use of trivalent oral polio vaccine to bivalent oral polio vaccine once absence of all circulating vaccine-derived poliovirus 2 is confirmed globally for at least six months.

13. Although the Decade of Vaccines' 2012 milestone for neonatal tetanus elimination was met (10 additional countries eliminated neonatal tetanus by 2012, defined as less than one case per 1000 live births in each district), the goal of neonatal tetanus elimination is one that has been long delayed. As this is a relatively easy goal to achieve, it is crucial that all future milestones are met and the verification of elimination in all remaining countries is achieved by 2015.

14. Measles and rubella/congenital rubella syndrome elimination, while long accomplished in the Region of the Americas, is a new challenge for other regions. Currently, in addition to the Region of the Americas, only the Western Pacific Region is on track for reaching the regional measles elimination target; the African, European and Eastern Mediterranean regions are not on track and the South-East Asia Region has only just established an elimination goal and target year. Political commitment at all levels is needed to secure the investments required to achieve measles and rubella/congenital rubella syndrome elimination. Ninety-five per cent coverage with two doses of measles-containing vaccines is required in all districts and nationally (through routine immunization and/or supplementary immunization activities) to achieve measles elimination. Furthermore, it is essential that measles and rubella surveillance is increased to meet verification standards, monitor progress and take timely action.

15. To accelerate progress towards achieving elimination of measles and rubella/congenital rubella syndrome, the Strategic Advisory Group of Experts on immunization recommends that all countries should:

- establish or update their national plans to accelerate measles and rubella/ congenital rubella syndrome elimination. These should include details for strengthening overall health and immunization systems in order to ensure that the 95% vaccination coverage targets nationally and in all districts are met;
- strengthen case-based surveillance for measles and rubella and ensure timely and complete reporting, and establish or strengthen surveillance for congenital rubella syndrome.

### **Enhancing country ownership of national immunization programmes**

16. Optimal performance requires that countries take ownership of their national programmes, establish good governance and invest the required resources. This requires that countries have processes to track immunization expenditures, identify resource gaps and take measures to fill the gaps.

17. The global vaccine action plan calls upon countries to report their national immunization expenditures (on per person basis). However, the data quality on immunization expenditures is inadequate to draw conclusions about expenditure trends.

18. National Immunization Technical Advisory Groups provide a means for national governments and other stakeholders to receive unbiased, critical advice on policy recommendations and for monitoring the successes and failures of the programmes. Even though the number of such Technical Advisory Groups that meet the functionality criteria has increased significantly in recent years, it is noted that many countries are still lagging behind in the establishment of such a body, particularly in the African and Western Pacific regions. The capacities of National Immunization Technical Advisory Groups to use evidence-based approaches need to be further strengthened with the support of all technical agencies and development partners.

19. To improve country ownership, the Strategic Advisory Group of Experts on immunization recommends that countries should: improve processes to track and report immunization expenditures using the System of Health Accounts<sup>1</sup> and establish and/or strengthen National Immunization Technical Advisory Groups and use them to advise on policy recommendations.

### **ACTION BY THE EXECUTIVE BOARD**

20. The Board is invited to take note of the report.

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<sup>1</sup> The System of Health Accounts is a framework developed through collaboration between the Organisation for Economic Co-operation and Development, the European Union and WHO for the systematic description of financial flows related to health care. The aim of the System is to describe the health care system from an expenditure perspective both for international and national purposes ([http://www.who.int/nha/sha\\_revision/en/](http://www.who.int/nha/sha_revision/en/)).

**WHO 67<sup>th</sup> WORLD HEALTH ASSEMBLY**  
**GLOBAL VACCINE ACTION PLAN, ITEM 12.2**  
**Geneva, 21st May 2014**  
**SUMMARY OF THE SESSION**

Fifty-four speakers including 50 representatives from Member States<sup>[1]</sup>, one observer<sup>[2]</sup>, civil society organizations<sup>[3]</sup> and the GAVI Alliance took the floor during the discussion on the Global Vaccine Action Plan (GVAP).

Delegates commended the Strategic Advisory Group of Experts (SAGE) on immunization for an excellent assessment report<sup>[4]</sup> and took note of the recommendations, particularly on the need to improve data quality.

While Member States acknowledged WHO's fundamental role in facilitating the rollout of the GVAP, they also highlighted the need for all stakeholders, particularly national governments to play a leading role in making the needed investments in immunization and in monitoring programme performance.

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

- Sustainable access to vaccines — especially the newer vaccines — at affordable prices for all countries, especially the middle-income countries who are not eligible for funding support from the GAVI Alliance;
- Technology transfer to facilitate local manufacture of vaccines as a means of ensuring vaccine security;
- Guidance to improve data quality including the use of new technologies like electronic registries;
- Assistance on risk communication and management to address misinformation in some countries and communities on the need for immunization and its impact on vaccination coverage; and
- Support countries to review the evidence and conduct economic analysis leading to informed decisions based on local priorities and needs.

In its response, the WHO secretariat, while taking note of all the issues raised by the delegates also reminded the Assembly that the GVAP progress report indicated that the world was not on track to achieve some of the key immunization goals for the decade and urged for more concerted action by all immunization stakeholders.

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<sup>[1]</sup> Brazil; Cote d'Ivoire; Jamaica; Malaysia; Bahrain; Colombia; Thailand; Lebanon; Republic of Korea; China; Ecuador; Burundi; Indonesia; Japan; Vietnam; Russia; Iraq; Kenya; Surinam; Congo; Oman; Spain; Togo; Mexico; Namibia; Maldives; Morocco; South Africa; Germany; Mongolia; Algeria; Iran; India; Egypt; Barbados; Burkina-Faso; Jordan; Costa Rica; UAE; Uruguay; Tunisia; USA; Ethiopia; Trinidad-Tobago; Grenada; Azerbaijan; Malawi; Libya; Argentina; Tanzania.

<sup>[2]</sup> Taipei

<sup>[3]</sup> International Pharmacists Federation and MSF

<sup>[4]</sup> WHA 67, Document A67/12, [http://apps.who.int/gb/ebwha/pdf\\_files/WHA67/A67\\_12-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_12-en.pdf)

# **BACKGROUND PAPER ON JAPANESE ENCEPHALITIS VACCINES**

Prepared by the SAGE Working Group on  
Japanese encephalitis vaccines

October 1, 2014

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## 1. Introduction

### 1.1 Background

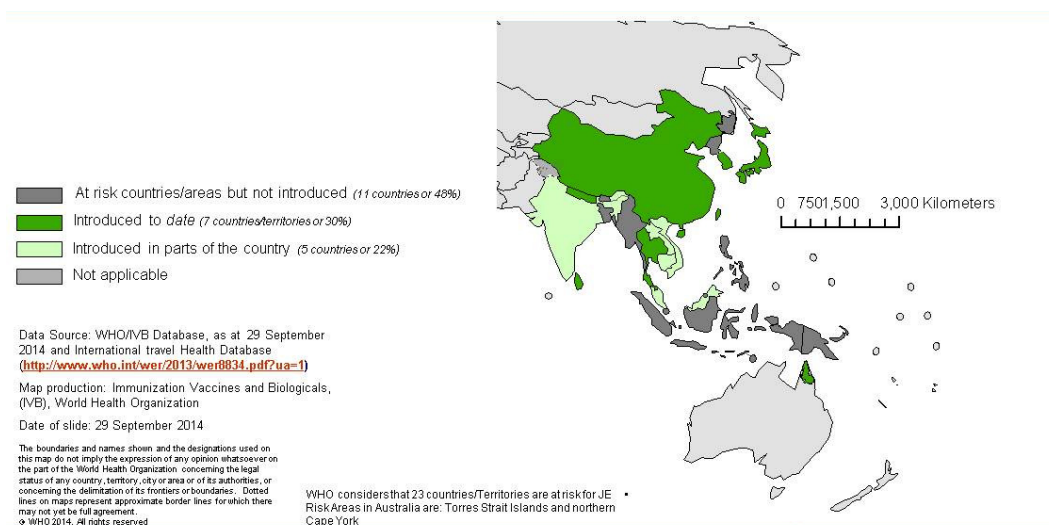
Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia. The pathogen is a mosquito-borne flavivirus, and its transmission is maintained through a enzootic cycle with *Culex* mosquitos, pigs and water birds. Symptomatic JE, most commonly manifest as encephalitis, is rare and thought to occur in approximately 1 in 250 infections. However, of JE cases, the case fatality rate can be as high as 30%, and permanent neurologic or psychiatric sequelae can occur in 20-30% of survivors, such as paralysis, recurrent seizures, or inability to speak. There is no antiviral treatment for patients with JE, and clinical care is supportive to relieve symptoms and stabilize the patient.

Among available control strategies, such as vector control and animal vaccination, human vaccination is the most effective tool against JE. Although human vaccines have been available since the early 1960s, there are still unnecessary JE morbidity and mortality due to a lack of vaccination programs in high risk areas. Of the 24 countries considered endemic to JE, half have no routine JE vaccination program (Figure 1).

The last WHO vaccine position paper (VPP) on JE vaccines was published in 2006. A number of developments have occurred that require revision of the JE VPP, including widespread availability of inactivated Vero cell vaccines, a GMP-compliant live attenuated vaccine, and a live chimeric vaccine. While previously inactivated mouse brain-derived vaccines were the primary product used globally, there are now a number of other products that were either previously limited to local production or not yet licensed. Three products are now WHO prequalified vaccines and eligible for UN procurement.

As a result of the recent availability of WHO prequalified vaccines, Gavi, the Vaccine Alliance, has opened a financing window to support vaccination campaigns among those aged 9 months to 14 years in at-risk areas. This support is contingent upon countries then introducing JE vaccine into the routine vaccination program in these areas.

This changing product landscape and improved access to JE vaccines necessitates a revised WHO VPP on JE vaccines. In addition, many countries have gained experience with JE vaccination, and these experiences were reviewed. This Background Paper describes the relevant data reviewed by the SAGE Working Group on JE Vaccines (Appendix 1) and the resulting proposed recommendations for JE vaccine use (Section 7), for SAGE deliberation and consideration.



**Figure 1.** Areas at risk of JE and use of JE vaccines, 2014

## 2. JE epidemiology and burden of disease

A recent systematic review of the literature estimates 67,900 cases of JE each year, with approximately 13,600 to 20,400 deaths, and an overall incidence rate of 1.8/100,000 (Campbell 2011). An estimated 3 billion people live in the 24 countries in the WHO South East Asia and Western Pacific regions at risk of JE. Most infections are asymptomatic or mild, such as fever and headache. Although severe clinical disease is rare (about 1 case per 250 infections), JE disease can be devastating. The case-fatality rate can be as high as 30%, with 20-30% of survivors suffering permanent intellectual, behavioral, or neurological problems.

Japanese encephalitis is a single-stranded RNA virus in the family *Flaviviridae*. Genetic sequences of JE are categorized into five genotypes. While genotype 3 used to be the predominantly circulating genotype, there has been a shift towards circulation of genotype 1, with genotype circulation associated with temperate and tropical climates (Schuh 2013).

JE is transmitted by *Culex* mosquitos (primarily *Culex tritaeniorhynchus*) and circulates in an enzootic cycle between mosquitos, pigs, and/or aquatic birds that serve as amplifying hosts. With these animal reservoirs, JE cannot be eliminated but can be controlled with universal human vaccination. Humans are considered dead-end hosts, with viraemia too low for further transmission.

The first case of JE was documented in 1871 in Japan. Because JE is predominantly, although not exclusively, a rural disease, and laboratory confirmation is challenging, the true reach of the virus and burden of disease is not well understood. The current estimate of nearly 68,000 cases, which took into account similar ecological zones and existing vaccination programs to predict incidence in areas without data, is a rough estimate. Incidence estimates are dynamic as the level of virus transmission varies from year to year, but vaccination programs are increasingly helping to control disease. Better surveillance is needed to improve the estimate of the burden of disease. Underreporting is a key problem for understanding the burden of JE disease, but attempts were made to address this to the extent possible in the Campbell 2011 estimate. Some studies used in the

Campbell estimate relied on an incomplete network of sentinel hospitals and were subject to underreporting, which could result in a biased estimate. There were other potential sources of error including (i) a lack of standardized laboratory testing methods (ii) incomplete collection of clinical samples (e.g. failure to collect and test both acute- and convalescent-phase samples); and (iii) the co-circulation of other cross-reactive flaviviruses (especially dengue viruses) in some JE-endemic areas. Surveillance data are needed to fully understand the local and global burden of JE and better identify areas at risk of disease. Epidemiology of JE in neighboring countries (States or Provinces in large countries) with similar ecological profiles may be useful to determine JE disease burden.

Some countries are identifying JE in new areas, suggesting expansion due to changing land use patterns or vector adaptation. Cases have even been detected in cities such as Kathmandu, Nepal, and New Delhi, India, in the absence of rural travel (Partridge 2007, Kumari 2013).

Annual incidences vary by age group, and have been estimated to be in the range of 5.4 per 100,000 in the 0-14 year age group, and 0.6/100,000 in the  $\geq 15$  year age group (Campbell 2011). These values mask tremendous variation across regions, with incidence in the younger age group estimated as high as 12.6/100,000 in some high incidence areas (e.g. parts of China, Democratic People's Republic of Korea). While traditionally considered a childhood disease, available data suggest that in many areas of the world it is a disease of all ages. As the numbers of cases in children decrease due to successful vaccination programs, there is frequently a shift to a greater proportion of cases in older, unvaccinated age groups. But even in some areas without vaccination programs, such as Bangladesh, over 50% of cases are in the adult age groups (Hossain 2010). In Thailand, 69% of individuals 20-24 years had protective levels of neutralizing antibody, and by 40 years of age, approximately 10% of the population did not have protective levels of antibody titers. (Yoocharoon 2009). Among a sample of 12-18 year-olds in the Philippines (unvaccinated), the seroprevalence rate was just 44% (Dubischar-Kastner 2012b). These data suggest an important proportion of adults are still susceptible. How severity differs by age group is not well understood, in part because of the lack of follow up of many cases. The age-specific incidence may be considered when designing immunization programs, and some countries, such as Nepal, have chosen to conduct campaigns in which all individuals over one year of age were vaccinated in select areas.

WHO guidelines for JE surveillance are available<sup>1</sup>. Because there are no clinical signs of JE that distinguish it from other causes of encephalitis, acute encephalitis syndrome (AES) cases should be laboratory-tested for JE. WHO recommends testing for the presence of JE virus-specific IgM antibody in a single sample of CSF or serum, using an IgM-capture ELISA specifically for JE antibody, as the preferred method for laboratory confirmation. A more detailed approach to diagnostics for surveillance is outlined in the WHO guidelines.

### ***2.1 Risk of JE in the context of immunization programs***

Because JE virus transmission is preserved in the enzootic cycle, elimination is not currently possible and susceptible individuals will continue to be at risk of disease even when few cases are observed due to good vaccination programs. As human are believed to be dead end hosts, vaccination has no impact on transmission and thus offers no indirect protection. Environmental sampling has

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<sup>1</sup> [http://whqlibdoc.who.int/hq/2003/who\\_v&b\\_03.01.pdf](http://whqlibdoc.who.int/hq/2003/who_v&b_03.01.pdf)

demonstrated continued virus circulation despite few apparent cases, e.g. in Japan, highlighting the importance of continued vaccination.

### 3. Methods for Working Group Evidence Review

#### 3.1 Key topics for consideration

Per the SAGE Guidelines for the Development of Evidence-Based Vaccine-Related Recommendations<sup>2</sup>, important questions were identified for review to inform proposed recommendations. Eleven policy questions were identified (Appendixes 2 and 3), which were further stratified into three critical questions and eight important questions. Available evidence for the three critical questions was identified through a systematic literature search (see section 3.2).

**Box 1.** Critical and important policy questions for JE vaccine recommendations

##### **Critical policy questions**

1. What is the effectiveness (including immunogenicity) of JE vaccines?
2. What is the risk of serious adverse events following JE vaccination?
3. Is there need for a booster dose following immunization with the primary series of JE vaccination?

##### **Important policy questions**

4. Can JE vaccines be safely and effectively co-administered with other vaccines?
5. Can JE vaccines be safely and effectively used in special populations?
6. What is the role of inactivated mouse brain-based JE vaccines in the context of other products?
7. What is the appropriate age of administration for JE vaccines in the routine immunization schedule?
8. What is the appropriate JE vaccine introduction strategy in an endemic country without a vaccination program?
9. What is the impact of JE vaccine introduction on JE disease at a country or regional level?
10. What is the cost-effectiveness of JE vaccination?
11. What is the global prevalence and disease burden of JE?

#### 3.2 Data retrieval and synthesis

The primary method to identify relevant data was a systematic search of the literature using PubMed, Embase, the Cochrane Clinical Trial Database, Index Medicus for South-East Asia Region (IMSEAR), and the Western Pacific Region Index Medicus (WPRIM). A convenience search of the China Academic Journals Full-text Database was also done (The systematic review protocol is available upon request). The search was completed initially on February 27, 2014 and updated on June 4, 2014. The search was general for JE vaccines and so covered all topics in the critical questions. The search was also capitalized upon for data to address the non-critical questions. Articles in non-English languages were reviewed by native speakers when possible. No articles were excluded due to the study population or type of study. Animal studies were excluded.

<sup>2</sup> [http://www.who.int/immunization/sage/Guidelines\\_development\\_recommendations.pdf](http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf)

Two independent reviewers screened all abstracts for inclusion, followed by a full text screen. References were categorized by the type of vaccine studied and the data available to answer policy questions. Working Group members and/or the Secretariat reviewed the evidence and presented the data and key conclusions at a face-to-face meeting of the Working Group 10-12 June, 2014.

Additional data not yet published were sought and provided to the WG by PATH, Chengdu Institute of Biological Products, Valneva, and Sanofi Pasteur. A catalogue of clinical trials and results available on [clinicaltrials.gov](http://clinicaltrials.gov) was also done. WHO-HQ with WPRO and SEARO also conducted a survey of JE-endemic countries to determine if countries had additional unpublished data that could be useful to the recommendation development process. These multiple data inputs were further reviewed and considered by the WG in their formulation of proposed JE vaccine recommendations.

#### **4. Overview of JE vaccines**

Approximately 15 JE vaccines are currently in use globally (Appendix 4). All vaccines are based on genotype 3 virus strains. Given the large number of vaccines in use, focus was placed on vaccines that are internationally distributed and/or WHO prequalified. Given a shift in the vaccine landscape away from mouse brain-derived vaccines, emphasis was also placed on non-mouse brain vaccines. The four major types of JE vaccines are:

1. Inactivated Vero cell vaccines
2. Live attenuated vaccines
3. Chimeric vaccines
4. Inactivated mouse brain-derived vaccines

##### **4.1 Inactivated Vero cell vaccines**

A number of inactivated Vero cell JE vaccine products have become available in the last five years (Appendix 4). The most widely marketed inactivated Vero cell vaccine is the IC51 inactivated Vero cell-derived vaccine, developed by Valneva Scotland Limited (formerly Intercell Biomedical) and known as IXIARO in the US and Europe (JESPECT in Australia and New Zealand), and first licensed in 2009. A vaccine manufactured by Biological E was developed through a technology transfer agreement with Intercell; this vaccine, JEEV, was WHO pre-qualified in July, 2013, for 18-49 year-olds, and in June, 2014, for 12-35 month olds. Clinical studies in support of an indication for 3-17 year olds are on-going. Other inactivated Vero cell products include two from Japan (JEBIK V manufactured by Biken, and ENCEVAC manufactured by Kaketsuken), one from China (JEVAC manufactured by Liaoning Chengda Biolotechnology Co), and a second from India (JENVAC manufactured by Bharat Biotech). These different vaccine products are based on different JE strains and are recommended for use based on different schedules, frequently with boosters. JEBIK V and ENCEVAC have no adjuvant, while the others contain aluminium hydroxide adjuvant.

IXIARO is based on the JE SA14-14-2 vaccine virus produced in Vero cells, and consists of inactivated, purified virus antigen. It is alum-adjuvanted and contains phosphate buffered saline as excipient and protamine sulphate in residual amounts (in contrast to inactivated mouse brain-derived vaccines, which contain gelatin and murine proteins). It is licensed for individuals from 2 months onwards in non-endemic settings.

#### **4.2 Live attenuated vaccines**

The live attenuated SA 14-14-2 vaccine is manufactured by the Chengdu Institute of Biological Products (CDIBP) and has been licensed in China since 1988. It is frequently referred to as the live attenuated SA 14-14-2 vaccine, or its trade names CD.JEVAX or RS.JEV (for the rest of this document it will be referred to as CD.JEVAX). It is licensed and used in several countries in Asia (Table 1, Appendix 4). The SA 14-14-2 vaccine virus is produced in primary hamster kidney cells. It contains gelatin, saccharose, human serum albumin, and sodium glutamate as excipients. A standard dose is not less than 5.7 log plaque forming units (PFU) per ml.

In partnership with PATH, CDIBP built a new GMP-compliant facility (approved by the Chinese Food and Drug Administration in 2011), and in October 2013, the CDIBP live attenuated vaccine was WHO prequalified for individuals starting at 8 months of age. Two other live attenuated vaccines are manufactured in China but are not exported (and were not reviewed).

#### **4.3 Chimeric vaccines**

Only one product in this class has been licensed. Sanofi Pasteur developed a live attenuated chimeric viral vaccine, marketed as IMOJEV, prequalified by WHO in September 2014. It was created using recombinant DNA technology by replacing the premembrane (prM) and envelope (E) coding sequences of the yellow fever live attenuated 17D vaccine virus with the SA 14-14-2 live attenuated JE vaccine virus. The vaccine was first licensed in Australia in 2012 and is now also in use in the public sector in Malaysia and Brunei and licensed in the Philippines, Thailand, and Myanmar. It is licensed in individuals 9 months of age and older. Each dose contains 4.0-5.8 log PFU. Mannitol, lactose, glutamic acid, potassium hydroxide, histidine, human serum albumin, and sodium chloride are excipients.

#### **4.4 Inactivated mouse brain-derived vaccines**

Inactivated mouse brain vaccines were first developed in the 1960s. Many countries have produced or continue to produce their own mouse brain-derived vaccine products (e.g. Vietnam, Thailand and the Republic of Korea). In 2006, Biken, formerly a major producer of a globally-distributed mouse brain-derived JE vaccine (JEVAX) discontinued manufacture of the product, leading to a major shift in the product use across the globe (Table 1).

In 2006, the WHO position paper stated that mouse brain-derived vaccines should be gradually replaced by new generation JE vaccines. Given this, and the continued agreement with this statement, mouse brain-derived vaccines were not reviewed systematically, in contrast to the other categories of products.



**Table 1.** Overview of JE vaccine use by country, sector, and scale. Results are based on a 2014 country survey, a WER/MMWR joint report (Baig 2013), and expert information. This table reflects commercialization of products, not just licensure.

Current JE-Endemic Country Vaccine Use			
Country	Vaccine (Public market)	National/ Subnational	Vaccine (Private market)
Australia	Chimeric	Subnational	Chimeric, Vero cell (inactivated)
Bangladesh	None	NA	None
Bhutan	None	NA	None
Brunei Darussalam	Chimeric	Subnational	Chimeric
Cambodia	Live attenuated	Subnational	Mouse brain (inactivated)
China	Live attenuated	National*	Vero Cell (inactivated) Live attenuated
Democratic People's Republic of Korea (the)	None	NA	Unknown
India	Live attenuated Inactivated Vero cell (adults)	Subnational	Mouse brain (inactivated) Vero Cell (inactivated)
Indonesia	None	NA	None
Japan	Vero Cell (inactivated)	National	Vero Cell (inactivated)
Lao People's Democratic Republic (the)	Live attenuated	Subnational	None
Malaysia	Chimeric	Subnational	None
Myanmar	None	NA	Chimeric (expected 2015)
Nepal	Live attenuated	Subnational	Live attenuated
Pakistan	None	NA	Unknown
Papua New Guinea	None	NA	None
Philippines (the)	None	NA	Chimeric
Republic of Korea	Mouse brain (inactivated) Live attenuated	National	Vero Cell (inactivated) Live attenuated
Russian Federation (the)	None	NA	Unknown
Singapore	None	NA	Vero Cell (inactivated)
Sri Lanka	Live attenuated	National	Mouse brain (inactivated)
Thailand	Mouse brain (inactivated) Live attenuated**	National	Live attenuated Chimeric
Timor Leste	None	NA	None
Vietnam	Mouse brain (inactivated)	Subnational	None

\*Excluding non-endemic provinces

\*\*Distribution limited geographically

## 5. Review of the evidence for critical issues

### 5.1 General principles

The following three topics were identified as critical to be reviewed for the policy decision: protection against disease, vaccine safety, and duration of protection. For vaccine protection, three measures are theoretically acceptable: vaccine efficacy, vaccine effectiveness, and immunogenicity. There have only been two efficacy trials of a JE vaccine in the past (Hsu 1971, Hoke 1988), both of which enrolled over 65,000 children. Clinical trials of JE vaccines currently use immunological endpoints as a surrogate of protection, because the rarity of disease is such that efficacy trials would be too large to be feasible. The generally accepted immunological surrogate of protection is a serum

neutralizing antibody titer of at least 1:10 as determined in a 50% plaque reduction neutralization assay (PRNT<sub>50</sub>). Seroconversion is defined as PRNT<sub>50</sub> titer <10 at baseline and ≥10 post vaccination at time of serum sampling, or a 4-fold rise from a baseline titer of ≥10 (Hombach 2005, WHO TRS 2014). Immunogenicity analyses are influenced by the virus strain used in the PRNT<sub>50</sub> assay (homologous vs. non-homologous) as well as the cell substrate (e.g. use of LLC-MK2 cells elicit higher GMTs than Vero cells). **Immunogenicity results should be considered in the context of the serological assay reagents, and caution should be exercised in doing any cross-study comparisons for these reasons.** There are no current concerns about a deficiency for cross-protection across the five genotypes, and there is no evidence of clustering of vaccine failures even though there is increasing replacement of genotype 3 by genotype 1 strains. International reference reagents for standardizing PRNT<sub>50</sub> titers are urgently needed, and a collaborative study has been initiated. Vaccine effectiveness studies have been undertaken for mouse brain-derived vaccines and the live attenuated vaccine but have not been possible for inactivated Vero cell vaccines or chimeric vaccine. In the following review, the PRNT<sub>50</sub> neutralization assay results reported are done using homologous virus unless otherwise specified.

Another important issue is the relevance of natural boosting (i.e. boosting the vaccine-induced immune response by exposure to wild circulating virus), and implications for booster doses. Particularly for newer vaccines with limited follow up time in endemic areas, it is unclear how long protective level of antibodies will last, and whether natural boosting contributes to maintaining protective antibody level. Due to this ambiguity, data from endemic areas were the primary source for recommendations, without presumption that natural boosting will be sufficient. However, data available from some settings in which vaccinated children who are followed longitudinally found some vaccinees were seronegative at one visit and seroprotected at a subsequent visit (e.g. Sohn 2008). This observation suggests that natural boosting occurs but whether these children were protected prior to the boost cannot be determined. **In summary, the Working Group concluded that there should be positive evidence of vaccine breakthrough cases to justify a global recommendation for booster doses given the programmatic and financial implications.** However, policy makers should base their national recommendations on a careful assessment in their own epidemiologic situation and should have mechanisms in place to monitor for vaccine failure to feedback into national recommendations for booster doses.

**Table 2.** Currently available evidence by vaccine type

	Immunogenicity data	Efficacy data	Effectiveness data
Inactivated mouse brain vaccines	✗	✗	✗
Inactivated Vero cell vaccines	✗		
Live attenuated vaccines	✗		✗
Chimeric vaccines	✗		

For safety monitoring, a better definition of cases of serious adverse events, using standard case classifications, such as the Brighton Collaboration definitions, and more active case investigation

would be valuable. Future immunization campaigns should be accompanied by strengthened AEFI monitoring and investigation activities.

Encephalitis has not been established as causally related to vaccination with live attenuated, including chimeric, JE vaccines. However, it is important to thoroughly investigate any occurrence of a neurological illness that occurs in temporal association with JE vaccination to rule out this possibility. Coincidental cases of encephalitis should be expected (and have been reported), especially during mass campaigns. An appropriate investigation will help maintain confidence in the vaccination program.

## **5.2 Inactivated Vero cell-based vaccines**

### **5.2.1 Available data**

The vast majority of publicly available data on inactivated Vero cell-based vaccines have been generated for a single product, IXIARO, developed by Valneva. Ten studies have contributed immunogenicity data, eight of which were among adults from non-endemic settings up to 3 years after the primary series. Two observational studies have also been done collecting immunogenicity data from travelers and military personnel. There are no effectiveness data at this time.

There are only limited data available for the WHO prequalified product JEEV (Biological E), which for pre-qualification purposes was considered “sufficient given the acceptance of the degree of similarity between JEEV and IC51 (IXIARO) in terms of same raw materials (cell banks and virus seed banks), same process flow and compliance of the two vaccines with the same in-process controls and release specifications.”<sup>3</sup> Therefore, the review of the evidence was entirely based on IXIARO, the only vaccine currently with broad international distribution. There are additional locally produced and distributed inactivated Vero cell vaccines such as JENVAC (Bharat Biotech), JEBIKV (Biken), ENCEVAC (Kaketsuken), and JEVAC (Liaoning Chengda Biotechnology Co). Any extension of recommendations to other products should be done with careful consideration and caution.

### **5.2.2 Immunogenicity of a primary series**

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[http://www.who.int/immunization\\_standards/vaccine\\_quality/pq\\_266\\_je\\_1dose\\_biologale\\_updated\\_vpsar.pdf](http://www.who.int/immunization_standards/vaccine_quality/pq_266_je_1dose_biologale_updated_vpsar.pdf)

**Table 3.** Clinical trials of inactivated Vero cell vaccine (IXIARO): seroprotection rates (95%CI) by time since first dose (of two dose series given 28 days apart).

Study ID	Country	Age	N	2M	6M	12M	15M	18M	2Y	3Y	Serology*	Reference/Notes
IC51-221**	India	1-3Y	24	95.7 (87.3-104)							SA 14-14-2/ Vero	Kaltenbock 2010
IC51-323**	Philippines	2-6M		100 (NR)							SA 14-14-2/ Vero	Dubischar-Kastner 2012a
IC51-323**	Philippines	6-12M		95 (NR)							SA 14-14-2/ Vero	Dubischar-Kastner 2012a
IC51-323**	Philippines	1-3Y	1869	97 (NR)							SA 14-14-2/ Vero	Dubischar-Kastner 2012a
IC51-323**	Philippines	3-12Y		94 (NR)							SA 14-14-2/ Vero	Dubischar-Kastner 2012a
IC51-323**	Philippines	12-18Y		77 (NR)							SA 14-14-2/ Vero	Dubischar-Kastner 2012a
IC51-325**	Philippines	2M-17Y	300	100 (NR)	86*** (NR)	89.9 (NR)			89 (NR)	90.1 (NR)	SA 14-14-2/ Vero	Dubischar-Kastner Quoted with permission Taubert 2007
IC51-301**	USA, Germany, & Austria	18-80Y	430	98 (NR)							SA 14-14-2/ Vero	Schuller 2008A / CDC 2011 / EMEA SPC
IC51-301 & 302W**	Austria, Germany, & Romania	18-86Y	181	99 (96.1-99.7)	95 (90.8-97.4)	83 (77.3-88.1)			82 (75.5-86.7)	85 (78.3- 89.7)	SA 14-14-2/ Vero	Lyons 2007
None**	USA	18-49Y	25	95 (NR)	100.0 (NR)	100.0 (NR)		90.0 (NR)	87.5 (NR)		SA 14-14-2/ Vero	Schuller 2009/ Dubischar-Kastner 2010A
IC51-304/ IC51-305**	Germany & Northern Ireland	18-76Y	115	97.3 (94.4-100.0)	82.8 (74.9-88.6)	58.3 (49.1-66.9)			48.3 (39.4-57.3)		SA 14-14-2/ Vero	Kaltenbock 2009
IC51-308**	Austria & Germany	18Y+	58	98.2 (NR)							SA 14-14-2/ Vero	Eder 2011
IC51-311	Austria & Germany	19-66Y	198				69.2 (62.4-75.2)				SA 14-14-2/ Vero	

\*Serology measured by PRNT<sub>50</sub> neutralization assay

\*\*Seroconversion rates reported

\*\*\*Month 7

**Table 4.** Observational studies of inactivated Vero cell vaccine (IXIARO): seroprotection rates (95%CI) by time since first vaccination (of two dose series given 28 days apart).

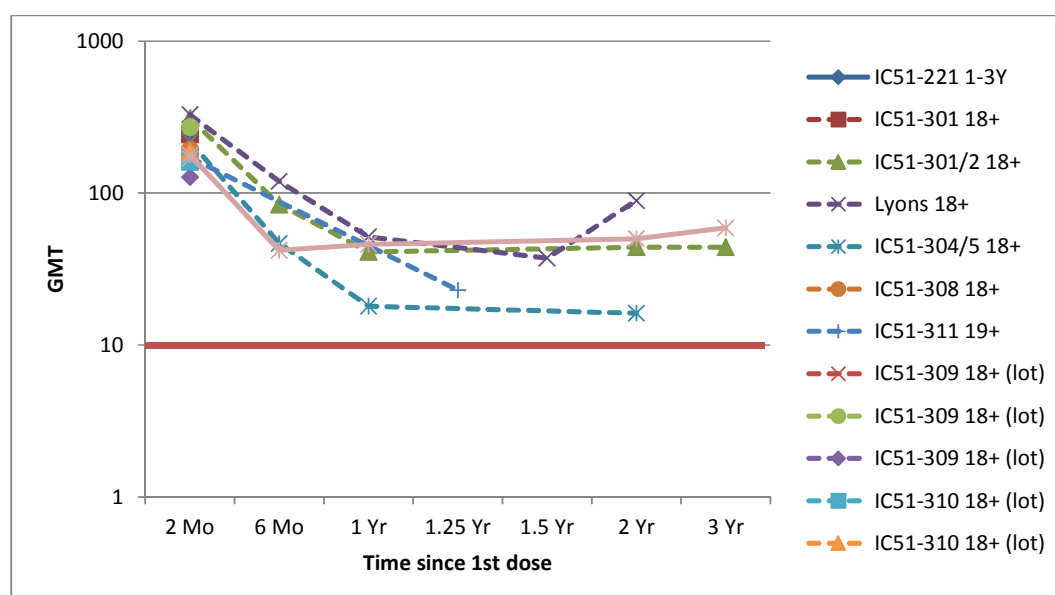
Study ID	Country	Age	N	2M	2Y	Serology*	Reference/Notes
382/E7/07	Finland & Sweden	18-69Y	31**	94 (NR)	87 (NR)	Nakayama/LC- MK2	Erra 2012/ Erra 2013
382/E7/07	Finland & Sweden	18-69Y	31**	97 (NR)	93 (NR)	SA 14-14-2/LC- MK2	Erra 2012/ Erra 2013
NA	USA	19-41Y	70	93 (NR)		SA 14-14- 2/Vero	Woolpert 2012

\*Serology measured by PRNT<sub>50</sub> neutralization assay

\*\*Decreased to 15 participants at 2 years

Across multiple studies in adults, high rates of seroprotection have been found one month following completion of the two-dose primary series (Table 3). In the largest study of 430 adult vaccine recipients, the seroprotection rate was 98% and the GMT was 244 (Tauber 2007). Among children living in an endemic setting, there are two studies, one in India (N=24 vaccinees aged 1-3 years; Kaltenböck 2010) and one in the Philippines (N=1,411 IXIARO vaccinees aged 2 months - 17 years, 396 assessed for immunogenicity; Dubischar-Kastner 2012a). In the small Indian study, 95.7% (95% CI: 87.3-100) of vaccinees who received the age appropriate dose<sup>4</sup> were seroprotected one month following the second dose with a GMT of 201 (95% CI: 106-380). In the Philippines, the age appropriate dose<sup>4</sup> elicited the following titers in the 2-<6 months, 6-<12 months, 1-<3 years, 3-<12 years, and 12-<18 years age groups, respectively: 637, 367, 258, 235, and 171.

**Conclusions:** Inactivated Vero cell vaccines (based on two doses of IXIARO given in the indicated age range, generally starting at 2 or 6 months, at a one month interval) have evidence of seroprotective neutralizing antibody titers at 1 month after primary immunization. The seroprotection rates and GMTs gradually decline over the following 12 months post immunization.



**Figure 2.** Reported GMTs from clinical trials by time since first dose (participants received 2 doses of IXIARO administered 28 days apart). No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

### 5.2.3 Long-term protection

Data in adults from non-endemic settings suggest a decline in seroprotection rates and GMTs in the 24 months following primary immunization (Tables 3 and 4). One study in Austria, Germany, and Romania found seroprotection rates dropped from 99% (95% CI: 96.1-99.7) at one month following the primary series to 82% two years later and 84.9% (95% CI: 78.3-89.7) three years later (Schuller

<sup>4</sup> 0.25ml 2 months to <3 years of age, 0.5ml 3-18 years of age.

2008a; CDC 2011); however, these results were obtained from a study population among which some had previously been exposed or vaccinated against tick-borne encephalitis (TBE). Another study compared participants who tested positive by TBE ELISA to assess the impact of previous TBE vaccination: one month following completion of the primary series 96% were seropositive (GMT 573.9) compared to 91% (GMT 186.7) among TBE ELISA negative participants (Schuller 2008b). Another study in Germany and Northern Ireland (where there is no TBE) found seroprotection rates dropped from 97.3% (95% CI: 94.4-100.0) to 48.3% (95% CI: 39.4-57.3) over a two-year period (Schuller 2009; Dubischar-Kastner 2010a). A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection.

In a follow-on from a clinical trial in European adults, 198 subjects were given a booster dose 15 months following primary vaccination (Eder 2011). While 69% were seroprotected prior to the booster dose, 100% were seroprotected one month after the booster, and 98.5% were seroprotected 12 months after the booster. The GMTs were 22.5 pre-booster, and 900, 487, and 361 at 1, 6, and 12 months after the booster.

In another small study, adult participants not seroprotected at 6 or 12 months following primary vaccination were given a booster dose at month 11 or 23, respectively; one month following the booster dose 100% were seroprotected with high GMTs (Dubischar-Kastner 2010a). Among those boosted at 11 months, the seroprotection rate was still 100% at 13 months after the booster.

There are limited data for IXIARO in children and in endemic settings. In the Philippines study, follow-up was continued for 36 months after the primary series (Dubischar-Kastner 2014 and unpublished, quoted with permission from Valneva). One hundred fifty participants received a booster at month 12, and 150 participants did not. Among those that did not receive a booster, the seroprotection rate at three years was 90%. The GMT decreased between 2 month and month 7, but then was relatively stable through the 3 years of follow up (49-52). Data by age is similar, although the sample size in some age groups was very small (e.g. 16 participants). When children were given a booster the response was rapid and strong. There are some limitations, as it was a small study with a small number of children across a broad age range.

**Conclusions:** Available data on IXIARO given to adults in non-endemic settings suggest a booster will be needed if the primary series was completed more than 1 year previously, consistent with the manufacturer's indication. Booster doses elicit a rapid and robust immune response when given 11-23 months post primary series, and high levels of seroprotection persist for at least one year following the booster. Based on preliminary data from one study of 150 children in the Philippines adequate seroprotective titers may persist for at least three years after the primary immunization. Further studies across a variety of transmission settings and a more detailed assessment of the Philippines study will provide further evidence on the booster needs of IXIARO when used in children living in endemic settings.

#### 5.2.4 Safety

Two pooled safety analyses of adult vaccination have been published. In the first pooled analysis, safety data for IXIARO from seven clinical trials were reviewed in comparison to the trial comparators (placebo (PBS+alum) or mouse brain-derived JE vaccine JE-VAX) (Dubischar-Kastner 2010b; Table 5). For solicited local adverse events up to six days after first vaccination, frequencies were comparable; however, following the second and third doses, they were higher in the JE-VAX

group, particularly for hardening, swelling, and redness. Severe local reactions occurred at a rate of 3.2% in the IXIARO group, 3.1% in the placebo group, and 13.8% in the JE-VAX group. Solicited systemic adverse events occurred within a week after the first dose in a similar proportion of participants across the three groups (33% IXIARO, 29% JE-VAX, 31% placebo). There was a higher incidence of systemic reactions after the first dose than after the second or third doses. Three and one half percent of participants experienced a hypersensitivity reaction or allergy-associated adverse events in the IXIARO group, 5.5% in the JE-VAX group, and 3.7% in the placebo group. One case of death of a 70-year old woman diagnosed with adenocarcinoma of the lung was reported in the IXIARO group after the second vaccination, which was judged unrelated to the vaccine. In summary, in adults there was comparable tolerability and reactogenicity with placebo (adjuvant alone) and mouse brain-derived JE vaccine except for local reactions. A significantly lower frequency of severe local reactions was reported for IXIARO compared to mouse brain-derived JE vaccine.

**Table 5.** Overview of adverse events (AE) in subjects with at least one AE following IXIARO, JE-VAX, or placebo across 7 clinical trials (from Dubischar-Kastner 2010b). AEs were graded by the investigator as follows: *mild*: awareness of signs or symptoms, but easily tolerated; *moderate*: discomfort enough to interfere with usual activity; *severe*: incapable of work or usual activity. Serious AEs were defined based on the standard ICH-E6 guideline from July 2002.

Subjects with at least one of:	IXIARO (N=3558)	JE-VAX (N=435)	Placebo (N=657)
Any AE	64.1%	64.1%	61.2%
Severe AE	5.8%	4.4%	6.4%
AE leading to withdrawal	0.8%	1.8%	0.8%
Serious AE	1.1%	0.7%	2.0%
Death*	0.0%	0.0%	0.0%
AE considered related to vaccine	38.3%	34.3%	38.8%
Severe AE considered related to vaccine	2.4%	1.4%	2.7%
AE leading to withdrawal considered related to vaccine	0.4%	0.9%	0.2%
Serious AE considered related to vaccine	0.0%	0.0%	0.0

\*One death occurred in IXIARO group but considered unrelated

The most recent analysis includes a summary of safety data across 10 clinical trials in 4,043 adult vaccinees as well as the first 12 months of post-licensure passive reporting data (Schuller 2011). Sixty-six percent of all clinical trial participants experienced any adverse events (39% considered vaccine related). The most common vaccine-related adverse events were headache (19%), myalgia (13%), fatigue (10%), flu-like illness (9%), and nausea (5%).

In reviewing post-marketing data for the first 12 months following vaccination in Europe, the US, and Australia, 25 reports of AEFIs were submitted, with an overall rate of reporting of 10.1/100,000 doses distributed (consistent with reporting rates for other new vaccines). The most frequently reported AEFIs were rash, fever, and headache. The reporting rate for serious AEFIs was 1.6 per 100,000 doses distributed (4 serious AEFIs: neuritis, meningism, oropharyngeal spasm, and iritis). Hypersensitivity reactions were observed at a rate of 3.6 per 100,000 doses compared to 8.4 per 100,000 doses reported for the mouse brain-derived vaccine JE-VAX in the USA.

In a clinical trial of children aged two months to one year in the Philippines, a similar percentage of participants receiving IXIARO (N=131) or Prevnar (N=64) experienced solicited (58.0% vs. 59.4%),

unsolicited (72.5% vs. 65.6%), and serious (0% vs. 1.6%) adverse events up to Day 56 after the first vaccination (European Assessment Report 2013).

**Table 6.** Rates of serious adverse events or medically attended adverse events up to day 56 (28 days post dose 2). Total numbers were back-calculated from percentages when not reported.

Age group	Ixiaro 0.25 mL	Ixiaro 0.5 mL	Prevnar	HAVRIX 720
≥ 2 months to < 1 year	50/131 (38.2%)	-	27/64 (42.2%)	-
≥ 1 year to < 3 years	171/640 (26.7%)	-	-	47/213 (22.1%)
≥ 3 years to < 12 years	7/100 (7.0%)	24/301 (8.0%)	-	6/100 (5.9%*)
≥ 12 years to < 18 years	-	4/240 (1.7%)	-	3/80 (3.8%)

\*Discrepancy between back-calculation (6/100) and reported percentage (5.9%).

For IXIARO, in children and adolescents from two months to <18 years the safety profile is comparable with licensed vaccines (pneumococcal conjugate and hepatitis A vaccines) in regards to frequency and severity of local and systemic adverse events.

GACVS has reviewed data on IXIARO (and JEEV) and determined it has an acceptable safety profile (GACVS 2013).

**Conclusions:** Inactivated Vero cell vaccine (specifically IXIARO) has an acceptable safety profile based on currently available data. According to the WHO prequalification assessment, these data can be considered to support the safety of JEEV. However, because of the potential for minor differences in the manufacturing process, which may accumulate over time for the two vaccines, the safety data reported from IXIARO might not apply to the safety of JEEV in the future. Safety of JEEV should be monitored.

### 5.3 Live attenuated vaccines

#### 5.3.1 Available data

As the live attenuated SA 14-14-2 vaccine (CD.JEVAX) has been licensed and in use in China since 1988, studies in China have contributed to the acceptance of the safety and effectiveness profile (e.g. Zhou 2001, Zhou 1999, Ma 1993, Wang 1993). However, due to the passage of time since the studies were completed, the non-randomized design, limited detail in the methods sections, possible minor variations in the vaccine, and use of a 2-dose schedule in some studies, focus was given to studies of the CDIBP live attenuated vaccine that have been published more recently, especially those employing GMP compliant vaccine lots. In addition to studies primarily focused on the live attenuated vaccine, it has also been used as a control in investigational studies of other products. In total, seven RCTs and three observational studies contributed to the immunogenicity and safety data. Four effectiveness studies, public regulatory assessments, and post-licensure safety monitoring data that contributed to the evidence review. All trial data are limited to infants and children; there are no clinical trial data on immunization of adults.

#### 5.3.2 Immunogenicity of a single dose



**Table 7.** Clinical trials of live attenuated JE vaccine: seroprotection rates (95%CI) by time since vaccination.

Study ID	Country	Age	N	28D	6M	1Y	2Y	3YR	Serology	Reference/Notes
JEV01/02	Philippines	8M	70	92.1 (84.3-96.7)		90.4 (81.9-95.8)	81.1 (71.5-88.6)	79.3 (69.3-87.2)	Beijing-1/LLC-MK2	Victor 2014, clinicaltrials.gov
JEV01/02	Philippines	10M	173	90.6 (85.3-94.4)		86.1 (80.6-90.6)	80.7 (74.6-85.9)	81.9 (75.8-87.0)	Beijing-1/LLC-MK2	Victor 2014, clinicaltrials.gov
JEV05	Bangladesh	10-12M	146	86.3 (79.8-91.0)					Beijing-1/LLC-MK2	Zaman 2014 (original facility)
JEV05	Bangladesh	10-12M	195	82.1 (76.1-86.8)					Beijing-1/LLC-MK2	Zaman 2014 (GMP lot 1)
JEV05	Bangladesh	10-12M	192	80.2 (74.0-85.2)					Beijing-1/LLC-MK2	Zaman 2014 (GMP lot 2)
JEV05	Bangladesh	10-12M	194	84.5 (78.7-89.0)					Beijing-1/LLC-MK2	Zaman 2014 (GMP lot 3)
JEC07	Thailand	9-18M	150	99.3 (96.3-100.0)	97.2 (93.1-99.2)	97.3 (93.1-99.2)			JE-CV/Vero	Feroldi 2014
JEC07	Thailand	9-18M	150	97.3 (93.1-99.2)	89.0 (82.7-93.6)	87.5 (81.0-92.4)			SA 14-14-2/LLC-MK2	Feroldi 2014
JEC12	Korea	12-24M	136	99.1 (NR)					JE-CV/Vero	Kim 2013

**Table 8.** Observational studies of live attenuated JE vaccine: seroprotection rates (95%CI) by time since vaccination.

Study ID	Country	Age	N	28D	90D	4Y	5.5Y	Serology	Reference/Notes
NA	Korea	1-3Y	68	96 (NR)				SA 14 (UTMB)	Sohn 1999
NA	Thailand	9-15M	140	89.3 (83.1-93.4)	95 (90.0-97.6)			Beijing-1&SA 14-14-2/LLC-MK2	Chotpitayasunodh 2011
NA	Thailand	9-11M	93		95.7 (NR)			Beijing-1&SA 14-14-2/LLC-MK2	Chotpitayasunodh 2011
NA	Thailand	12-15M*	47		93.6 (NR)			Beijing-1&SA 14-14-2/LLC-MK2	Chotpitayasunodh 2011
NA	Nepal	1-15Y	69			89.9 (NR)	63.8 (NR)	Beijing-1&SA 14-14-2/LLC-MK2	Sohn 2008

\* Subset of 9-15M study reported above

PATH has sponsored two RCTs in children administered a single dose of vaccine at ages 8-12 months, in the Philippines and in Bangladesh (Victor 2014, Zaman 2014). Seroprotection rates<sup>5</sup> at 28 days post-vaccination in the Philippines study were 92.1% (95% CI: 84.3-96.7) and 90.6 (95% CI: 85.3-94.4); the latter result was in the group administered measles vaccine one month prior. In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)<sup>6</sup>. Two lots were not equivalent with a seroprotection rate difference of -4.33 (-11.94-3.31). When reviewed for WHO prequalification, the results were considered sufficient to support the consistency of the lots (WHO PSAR 2013). The seroprotection rate was 97.3% (95% CI: 93.1-99.2) for the live attenuated vaccine when used as a control in a chimeric JE vaccine RCT in children aged 9 months to 18 years in Thailand (Feroldi 2014). In a similar study in children 12-24 months in Korea, the seroprotection rate was 99.1% (Kim 2013)<sup>7</sup>. These results are consistent with immunogenicity results from observational studies in children in Korea and Thailand (Sohn 1999; Chotpitayasunondh 2011)<sup>8</sup>.

GMTs measured from these studies are more variable (Figure 3), although GMTs and the lower bound of associated 95% confidence intervals are always magnitudes above the accepted protection threshold of 10. At 28 days post-vaccination GMTs were 203 (95% CI: 141-293) and 139 (95% CI: 110-178) in the Philippines (Victor 2014), while GMTs ranged from 52.8 (95% CI: 42.9-65.1) to 77.3 (95% CI: 59.6-100.4) in Bangladesh (Zaman 2014). GMTs were 370 (95% CI: 291-470) in 9-18 month-olds in Thailand (Feroldi 2014). Due to variable challenge viruses and serological assays, and the lack of standardized reagents, overall, it was considered critical that the GMT and confidence intervals were above the accepted correlate of seroprotection.

**Conclusion:** Live attenuated vaccine (CD.JEVAX) has evidence of seroprotective neutralizing antibody titers post-immunization. This is based on an age of administration of ≥8 months.

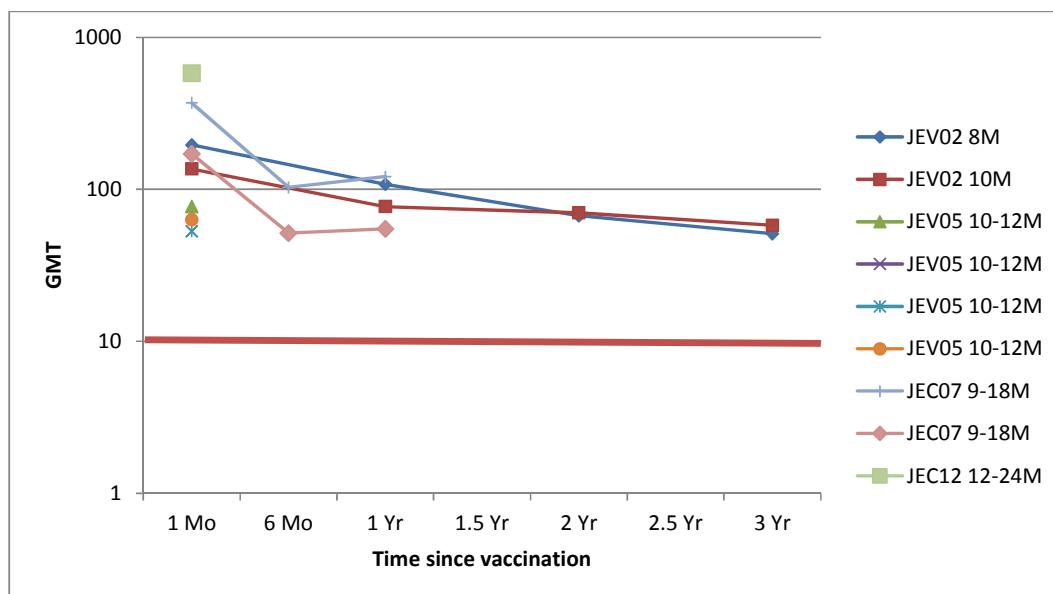
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<sup>5</sup>PRNT<sub>50</sub> using the non-homologous Beijing-1 strain in LLC-MK2 cells

<sup>6</sup>GMP lot B and original facility, respectively

<sup>7</sup>PRNT<sub>50</sub> using JE chimeric virus strain in Vero cells

<sup>8</sup>PRNT<sub>50</sub> using Beijing-1 and SA 14-14-2 in LLC-MK2 cells



**Figure 3.** Reported GMTs for live attenuated vaccines (CD.JEVAX) from clinical trials by time since vaccination. No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

### 5.3.3 Long-term immunogenicity

Long-term immunogenicity data are limited. The PATH study in the Philippines measured immunogenicity of a single dose of CD.JEVAX (and no other vaccine administered for at least 28 days) for three years (quoted with permission from PATH, publication pending)<sup>9</sup>. Among 8 month-olds administered a single dose of CD.JEVAX, seroprotection was measured at 90.4% (95% CI: 81.9-95.8), 81.1% (95% CI: 71.5-88.6), and 79.3% (69.3-87.2) at 1 year, 2 years, and 3 years post vaccination. Among 10 month-olds, the corresponding seroprotection rates were 86.1% (95% CI: 80.6-90.6), 80.7% (95% CI: 74.6-85.9), and 81.9% (95% CI: 75.8-87.0). These figures are consistent with 12-month immunogenicity results from a study of Thai children aged 9-12 months (Feroldi 2014). A convenience study in Nepal of 69 individuals vaccinated at ages 1-15 years found seroprotection rates of 89.9% and 63.8% at four and five years after vaccination, respectively (Sohn 2008).

GMTs appear to decrease gradually over the first 1-2 years post vaccination. In the Philippines study, GMTs among 8 month-old vaccines declined from 108 (95% CI: 70-167) to 67 (95% CI: 46-99) to 51 (95% CI: 37-71) at 1, 2, and 3 years after vaccination (NCT00412516 results). Among 10 month-old vaccinees, the corresponding GMTs were 77 (95% CI: 60-98), 70 (95% CI: 54-92), and 58 (95% CI: 45-73). Data beyond three years is not currently available. In Thailand (Feroldi 2014; NCT01092507 results), immunogenicity dropped from 171 (95% CI: 138-212) 28 days post-vaccination to 51.4 (95% CI: 41.6-63.6) six months post-vaccination and 54.8 (95% CI: 43.9-64.8) one year post-vaccination. These data may be suggestive of a plateauing in immune response.

<sup>9</sup> PRNT<sub>50</sub> using the non-homologous Beijing-1 strain in LLC-MK2 cells

Available data suggest a good anamnestic response in individuals given a second dose (booster) of live attenuated vaccine (Choi 2013, Sohn 2008). In the Sohn study conducted in Nepal described above, those who were seronegative 5.5 years after primary immunization were given a booster dose. The GMTs among these seronegative children were 169 and 392 at seven days and one month after the booster, respectively. The seroprotection rate was 76% and 82% at these same time points.

#### 5.3.4 Effectiveness

Following a mass vaccination campaign in Nepal in 1999 (in children aged 1-15 years), effectiveness using case-control studies was measured at different time points after the campaign. Shortly after the campaign, an outbreak of JE occurred that allowed for an immediate assessment of effectiveness. Between one week and one month post-campaign, vaccine effectiveness was estimated at 99.3% (95% CI: 94.9-100) (Bista 2001). Vaccine effectiveness was then estimated at 98.5% (95% CI: 90.1-99.2) (Ohrr 2005) and 96.2% (95% CI: 73.1-99.9) (Tandan 2007) at one year and five years post-campaign. The outbreak experienced shortly after the campaign may have boosted immunization. A case-control study in India estimated vaccine effectiveness at 94.5% (95% CI: 81.5-98.9) six months following a mass campaign (Kumar 2009). A more recent case-control study in India estimated vaccine effectiveness at 84% (95%CI: 53-95) at 0-38 months post-vaccination (Murhekar 2014). All of these studies were based on a relatively small number of cases (20-35). A study conducted more than 20 years ago in China estimated vaccine effectiveness at 80% (95%CI: 44-93), which covered cases identified up to 14 years post-vaccination (Hennessy 1996). This same study estimated vaccine effectiveness at 97.5% (95%CI: 86- 99.6) with two doses. Children had received JE vaccine as part of the routine immunization program in China, and the study authors noted the quality of the program at that time, in terms of maintenance of the cold chain and vaccine administration techniques, was unknown.

Some countries, including China and recently India, administer CD.JEVAX as a two-dose series. Informal discussions with countries suggest much of the rationale for a two-dose schedule comes from programmatic reasons, primarily enhancing coverage and vaccinating missed children rather than a concern about protection with one dose.

**Conclusion:** Available immunogenicity data indicate children vaccinated with a single dose at  $\geq 8$  months have adequate seroprotective titers at three years. Good vaccine effectiveness up to five years was demonstrated in children vaccinated at 1-15 years of age in an endemic area. Studies and continued monitoring when used in vaccination programs are needed to assess whether a booster dose is warranted. Based on available but limited data, currently no booster is recommended. Careful long-term follow up is needed to monitor for potential vaccine failure (i.e., the need for a booster dose), in particular because one study in Bangladesh utilizing vaccine from the new GMP compliant facility showed somewhat lower levels of seroprotection one month following vaccination compared to results using vaccine from the old facility. Program monitoring and/or special studies should be considered in different endemic settings where the level of natural boosting may vary. Continued monitoring of seroprotective titers beyond year three is encouraged. Individuals given a booster dose respond rapidly with a good anamnestic response.

#### 5.3.5 Safety

Data from multiple RCTs (including primary vaccination, booster vaccination, and co-administration studies) as well as post-marketing surveillance data and available case reports were reviewed. In

children aged nine months to six years, live attenuated vaccine had moderately higher frequency and severity of local and systemic adverse reactions, including fever, compared to chimeric vaccine (Feroldi 2014; Kim 2013). No vaccine-related serious adverse reactions or deaths were reported in RCTs (up to 7 months follow up) except for two cases of pyrexia in children aged 12-23 months (Table 9, Study 2).

**Table 9.** Comparison of chimeric vaccine IMOJEV and live attenuated vaccine CD.JEVAX in 2 observer-blind RCTs (Feroldi 2014, Kim 2013). Study 1 included children 9-18 months, study 2 included children 12-23 months.

	IMOJEV		CD.JEVAX	
	Study 1	Study 2	Study 1	Study 2
	N=146	N=137	N=152	N=137
<b>Children experiencing at least one:</b>	%	%	%	%
<b>Solicited injection site reaction (day 0-7)</b>	<b>37.7</b>	<b>32.8</b>	<b>44.1</b>	<b>40.9</b>
- Injection site tenderness	30.1	25.5	37.5	27.7
- Injection site erythema	17.8	16.8	23.0	24.1
- Injection site swelling	6.2	4.4	7.9	7.3
<b>Solicited systemic reaction (day 0-14)</b>	<b>45.2</b>	<b>52.6</b>	<b>57.9</b>	<b>53.3</b>
- Fever	16.4	24.6	21.7	25.0
- Vomiting	14.4	6.6	26.3	10.2
- Crying abnormal	19.2	19.7	25.7	25.5
- Drowsiness	17.1	16.8	25.0	24.1
- Appetite loss	21.9	27.7	35.5	29.2
- Irritability	28.1	22.6	38.2	26.3
<b>Unsolicited AE</b>	<b>34.7</b>	-	<b>50.0</b>	-
-related injection site reactions	1.4	-	0.7	-
-related systemic reactions	0	-	0	-
<b>SAEs</b>	<b>9.5</b>	<b>12.4</b>	<b>11.8</b>	<b>13.1</b>
- related SAEs	0	0	0	1.5 (pyrexia in 2)

In an older trial in China (Liu 1997) among 26,239 participants aged one, two, or six years, health centers were randomized to vaccinate (13,275 children) or to not vaccinate (12,964 children). Study participants were followed up for one month post vaccination. All illnesses prompting a health center visit during the 30-day study period including the diagnosis were recorded. At day 30 parents underwent a structured interview regarding hospitalizations and illnesses that occurred since the initial visit. Rates of adverse health outcomes reporting to the health center were comparable between groups.

Passive reporting of adverse events following vaccination with the live attenuated vaccine has been undertaken in China (Liu 2014). Based on 23 million doses distributed between 2005-2012, 1426 adverse events were reported (61 per million doses), although this is likely an underestimate as is typical with all passive surveillance systems. Nearly forty percent of reports were allergic reactions, usually generalized rash. The most frequently reported event was fever greater than 38.6°C (22.37 reports per million doses), followed by generalized rash (21.86 reports per million doses). There were 36 SAEs and 31 neurologic events reported including three cases of viral encephalitis, two

cases of encephalopathy, and two cases of ADEM. Reports on cases of encephalitis and 2 deaths following administration of CD.JEVAX were found non-conclusive but were judged unrelated to the vaccine (Jia 2011; Liu 2014). However, this emphasizes the need for more complete investigations of neurological illness following vaccination.

GACVS has reviewed data on the live attenuated vaccine on multiple occasions and determined it has an acceptable safety profile (GACVS 2013, GACVS 2008, GACVS 2007, GACVS 2005).

**Conclusion:** Live attenuated (CDIBP) vaccine has an acceptable safety profile based on currently available data.

## **5.4 Chimeric vaccines**

### **5.4.1 Available data**

As a new vaccine, the chimeric JE vaccine (IMOJEV®) is well characterized in clinical trials. In total, seven RCTs for safety and immunogenicity were conducted with published results in endemic countries (three additional RCTs from non-endemic settings). No observational studies are yet available. Data from the endemic setting ranges from 9 months to 10 years, however the number of vaccinees in the 9-12 month age group was limited to around 60 across two studies.

### **5.4.2 Immunogenicity of a single dose**

**Table 10.** Clinical trials of chimeric JE vaccine: seroprotection rates (95%CI) by time since vaccination.

Study ID	Country	Age	N	28-30d	42d	6 M	1 YR	2 YR	3 YR	4 YR	5 YR	Serology	Reference/Notes
JEC07	Thailand	9-18M	149	99.3 (96.2-100.0)		94.5 (89.4-97.6)	88.1 (81.6-92.9)					JE-CV/Vero	Feroldi 2014
JEC07	Thailand	9-18M	149	97.2 (93.1-99.2)		84.1 (77.2-89.7)	76.8 (68.9-83.4)					SA 14-14-2/LLC-MK2	Feroldi 2014
JEC12	Korea	12-24M	137	100.0 (NR)								JE-CV/Vero	Kim 2013
JEC01	Thailand	12-24M	200	96 (92-98)		87 (NR)	82 (NR)	80 (NR)	75 (NR)	74 (NR)	65.6 (NR)	JE-CV/Vero	Chokephaibulkit 2010a / Quoted with permission from Sanofi Pasteur
JEC02*	Thailand & Philippines	12-18M	1059	95.0 (93.3-96.3)				80.3 (NR)				JE-CV/Vero	Feroldi 2012 & 2013
JEC02 (subset)	Thailand & Philippines	12-18M	591	100 (99.4-100.0)			88.2 (85.3-90.7)					JE-CV/Vero	Feroldi 2010
JEC04*	Taiwan	12-18M	110		97.9 (NR)		96.6 (NR)					JE-CV/Vero	Huang 2014 (JE-CV followed by MMR)
JEC04*	Taiwan	12-18M	220		NR		96.8 (NR)					JE-CV/Vero	Huang 2014 (MMR followed by JE-CV)
JEC15	Philippines	36-42M	46	89.7 (75.8-97.1)								JE-CV/Vero	Feroldi 2013
H-040-004*†	India	9M-10Y	33	100 (NR)								JE-CV/Vero	clinicaltrials.gov
H-040-004*†	India	9M-10Y	33	25 (NR)								Nakayama/?	clinicaltrials.gov
H-040-004*†	India	9M-10Y	33	82 (NR)								Indian WT/?	clinicaltrials.gov
H-040-009*	USA & Australia	18-65Y	410	99.1 (97.5-99.8)								JE-CV/Vero	Torresi 2010
H-040-009*	USA & Australia	18-65Y	410	80.9 (76.4-84.9)								Nakayama/Vero	Torresi 2010
H-040-005*	Australia	18-55Y	202 -> 93	99 (96-100)		97 (93-99)	95 (87-99)	90 (81-96)			94 <sup>#</sup> (82-99)	JE-CV/LLC-MK2	Nasveld 2010a
H-040-008*†	USA	18-65Y	30	100 (NR)		92 (NR)	92 (NR)					JE-CV/Vero	clinicaltrials.gov

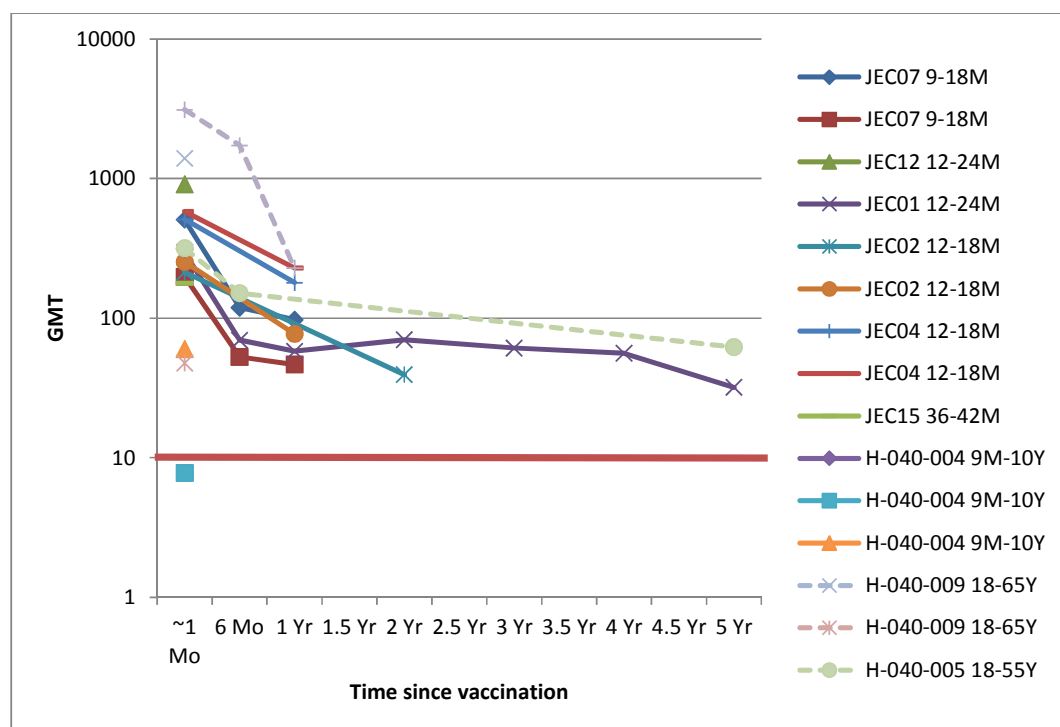
\*Seroconversion rate reported at 28-30d and 42d

# Only 45% of original study population remained in the study at this time point

† Used data from clinicaltrials.gov and calculated percentage

High seroprotection rates one month post-vaccination were reported. In the lowest age group (9-18 months), the seroprotection rate was estimated at 99.3% (95% CI: 96.2-100.0) (Feroldi 2014) . Similar results were found in Korea (Kim 2013) among 12-24 month-olds (seroprotection 100%, 95% CI: NR) and in Thailand and the Philippines among 12-18 month-olds (seroprotection 95.0%, 95% CI: 93.3-96.3) (Feroldi 2012). Among 36-42 month-olds, 89.7% (95% CI: 75.8-97.1) were seroprotected one month post vaccination. Lower seroprotection rates were found with some serological assays in a small study in India (e.g., against Nakayama strain and Indian strains, both genotype 3); however, similar results were obtained with the comparator vaccine, a Nakayama mouse brain-derived vaccine, and the virus stock used for testing was reportedly not good (NCT00441259 results, G. Houillon personal communication). Seroprotection rates were also high in three trials among adults in non-endemic settings (e.g. 99.1% seroprotected (95% CI: 97.5-99.8) adults aged 18-65 in the US and Australia (Torresi 2010); see Table 10).

GMTs were also very high in the month following vaccination (Figure 4). Among 9-18 month-olds, GMTs were 507 (95% CI: 395-651) when PRNT was conducted with chimeric virus in Vero cells, and 198 (95% CI: 158-247) when PRNT used SA 14-14-2 in LLC-MK2 cells (Feroldi 2014; NCT01092507 results). In children, GMTs as high as 908 (95% CI: 656-1256) were generated in Korean children aged 12-24 months (Kim 2013).



**Figure 4.** Reported GMTs for chimeric vaccine (IMOJEV) from clinical trials by time since vaccination. No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

**Conclusion:** Chimeric vaccine (IMOJEV) has evidence of seroprotective neutralizing antibody titers post-immunization. This is based on an age of administration of  $\geq 9$  months.



#### 5.4.3 Long-term protection

Among children in endemic settings, four trials followed up participants for 1 year or longer. In one study, between six months and one year post-vaccination, the percent seroprotected dropped from 94.5% (95% CI: 89.4-97.6) to 88.1% (95% CI: 81.6-92.9) (Feroldi 2014). A recent study followed Thai participants vaccinated at 12-24 months for five years of age (quoted with permission from Sanofi Pasteur, data to be presented ACPID 2014). Seroprotection rates fell from 82.2% one year post-vaccination to 80.2%, 75.2%, 74.1%, and 65.6% at two, three, four, and five years post-vaccination, respectively. The corresponding GMTs were 58, 70, 61, 56, and 64 at years one, two, three, four, and five post-vaccination. Long-term protection in adults from another study was much higher. Seroprotection rates among Australia military participants aged 18-55 years were 99% (95% CI: 96-100) one month after vaccination, followed by 95% (95% CI: 87-99), 90% (95% CI: 81-96), and 94% (95% CI: 82-99) at one year, two years, and five years post-vaccination (Nasveld 2010a). However, only 46 participants (45% of the original study population) remained in the study at the final time point. In Australia and Malaysia, IMOJEV is licensed as a two-dose vaccine for the pediatric population and as a single-dose vaccine for the adult population.

Individuals given a booster dose respond rapidly with a good anamnestic response with GMTs quickly rising to levels much higher than with primary immunization. In a study among children 12-18 months in the Philippines, a booster was given two years following the first dose (Feroldi 2013). The seroprotection rate was 80% (GMT 39) just prior to the booster dose, 96% (GMT 231) seven days after the booster dose, 100% (GMT 2242) one month after the booster dose, and 99% (GMT 596) 12 months after the booster dose. Five year follow up data are pending.

In this same study, 68 participants who did not have seroprotective titers two years following primary immunization were re-vaccinated with IMOJEV. In comparing their responses to IMOJEV-naïve participants, 82.4% (95% CI: 71.2; 90.5) were seroprotected seven days after vaccination compared with 15.4% (95% CI: 5.9; 30.5) in group receiving IMOJEV as a primary immunization. The seroprotection rate in the boosted group was 100% at day 28 (95% CI: 94.7, 100.0) while it was 89.7% (95% CI: 75.8, 97.1) in the naïve group. These data suggest that although some children did not have seroprotective antibody titers two years after one dose of IMOJEV, they did have a strong anamnestic response following a second dose. Whether or not those children were protected in between the two doses is unknown.

**Conclusion:** Available immunogenicity data indicate children vaccinated at  $\geq 12$  months of age have adequate seroprotective titers at two years. One small study shows adequate seroprotective titers up to five years in adults. One study shows some evidence of declining seroprotection rates up to five years after a single dose in children. There are no vaccine effectiveness data available. Based on the data available, including long-term immunogenicity data and anamnestic booster responses in children seronegative after one dose, it is unclear whether a booster is needed for individuals living in endemic areas. It is considered acceptable for countries to introduce IMOJEV as a single dose as long as they carefully monitor for vaccine failures. More data are needed to fully assess the need for a booster dose of IMOJEV in endemic settings. Program monitoring and/or special studies should be done in different endemic settings where the level of natural boosting may vary.

#### 5.4.4 Safety

In children 12 months to 18 years IMOJEV chimeric vaccine had a safety profile comparable with licensed vaccines (hepatitis A and varicella zoster) in terms of frequency and severity of local and systemic adverse reactions (Table 11; Chokephaibulkit 2010a, Feroldi 2012, Feroldi 2013). There was lower frequency of fever, injection site erythema and swelling after the first compared to second dose. Table 9 also shows the comparability in safety profiles between CD.JEVAX and IMOJEV. IMOJEV also has a comparable safety profile to MMR vaccine when administered to children 12-18 months old in Taiwan (Huang 2014).

**Table 11.** Rates of solicited injection site reactions, systemic reactions, unsolicited AE, and SAEs among children from two studies in Thailand and the Philippines.

	IMOJEV		HEP A	
	Study 1*	Study 2**	Study 1*	Study 2**
	N=199	N=1097	N=199	N=102
<b>Children experiencing at least one:</b>	%	%	%	%
<b>Solicited injection site reaction (day 0-7)</b>	41	39.3	36	36.3
- Injection site tenderness	32	22.2	27	17.6
- Injection site erythema	23	24.4	20	25.5
- Injection site swelling	9	6.9	7	3.9
<b>Solicited systemic reaction (day 0-14)</b>	49	51.0	51	45.1
- Fever	21	20.5	21	20.6
- Vomiting	20	19.1	22	15.7
- Crying abnormal	23	18.5	20	20.6
- Drowsiness	18	18.4	15	19.6
- Appetite loss	26	25.9	29	26.5
- Irritability	28	28.6	23	27.5
<b>Unsolicited AE</b>	-	48.8	-	53.9
- Vaccine-related unsolicited adverse reactions	-	1.2	-	1.0
<b>SAEs</b>	-	3.4	-	4.9
- Vaccine-related	0	0	0	0

\*Study 1: children aged 12-24 months in Thailand (Chokephaibulkit 2010a)

\*\*Study 2: children aged 12-18 months in Thailand, Philippines (Feroldi 2012)

There are limited data in 9-12 month group to affirm the safety of the vaccine in this youngest age group. More data on the safety of IMOJEV in this age group should be generated.

In adults in two RCTs, comparable tolerability and reactogenicity with placebo and a mouse brain-derived JE vaccine were seen with the exception of local reactions (Torresi 2010). Significantly lower frequency of local adverse reactions was reported for IMOJEV than mouse brain-derived vaccine JE-VAX. The majority of adverse events was mild to moderate and resolved within a few days. Only one vaccine related serious AEFI (high-grade pyrexia) was reported within the first month of vaccination and none during a 6-month follow-up. No case of death occurred (Torresi 2010).

In addition, two serious adverse events (acute viral illness) possibly related to vaccination with IMOJEV were reported during clinical development in adults (Australian Public Assessment Report 2010). Post-marketing safety data were not available to evaluate whether there is risk of rare neurologic adverse events. The chimeric vaccine IMOJEV is based on the Yellow Fever 17D backbone, so yellow fever vaccine-associated viscerotropic disease (AVD) and acute neurotropic disease (NVD) are considered Adverse Events of Special Interest by the company and are being monitored in their

Risk Management Plans. Post-marketing surveillance for rare adverse events is important, especially for the newer products recently introduced to the market.

As IMOJEV is a live, recombinant vaccine, a variety of non-clinical and clinical studies have been undertaken to establish genetic stability, low risk of reversion to a neurotropic virus, low levels of viraemia in vaccinated subjects, lack of transmission by mosquitoes, and lack of replication in JE animal hosts (Guy 2010). Adult subjects demonstrated short duration and low titer viraemia (Monath 2003). In children, JE vaccine-naïve children had low viremia, while JE vaccine-primed children had no detectable viraemia (Chokephaibulkit 2010a).

GACVS has reviewed data on the chimeric vaccine and determined it has an acceptable safety profile (GACVS 2014).

**Conclusions:** Chimeric vaccine (IMOJEV) has an acceptable safety profile based on currently available data. Safety data in the 9-12 month age group are limited.

### **5.5 Inactivated mouse brain-derived vaccines**

Due to the shift away from mouse brain vaccines, little data have been generated on mouse brain-derived vaccines since the 2006 vaccine position paper. Per the 2006 vaccine position paper:

*In several Asian trials, primary immunization based on 2 doses given at an interval of 1–2 weeks has induced protective concentrations of neutralizing antibodies in 94–100% of children aged >1 year. Although experience from Thailand shows that JE vaccination of children aged 6–12 months may be highly efficacious as well, in most epidemiological settings primary immunization should be given at the age of 1–3 years. Given the mostly infrequent occurrence of JE in infancy and the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months. In immunogenicity studies in the USA, seroconversion occurred only in approximately 80% of adult vaccinees following an equivalent 2-dose schedule. In contrast, in US soldiers, a schedule based on vaccination on days 0, 7 and 30 resulted in 100% seroconversion. Following a booster injection approximately 1 year after the primary 2 doses, protective antibody levels have been achieved in practically all children and adults, regardless of geographical region. In people whose immunity is unlikely to be boosted by natural infection, repeated boosters are required for sustained immunity. Australian studies following the outbreak of JE in the Torres Strait demonstrated that in the majority of children the level of neutralizing antibody declines to non-protective concentrations within 6–12 months following primary immunization. About 3 years after the primary series of 3 doses, or the last booster, only 37% of adults and 24% of children had protective antibody levels.*

*In general, the mouse brain-derived JE vaccine has been considered safe, although local reactions such as tenderness, redness and swelling occur in about 20% of vaccinated subjects. A similar percentage of vaccinees may experience mild systemic symptoms, including headache, myalgia, gastrointestinal symptoms and fever. Acute disseminated encephalomyelitis (ADEM) temporally coinciding with JE immunization using the mouse brain-derived vaccine has been reported at frequencies corresponding to 1 case per 50 000–1 000 000 doses administered, but no definitive studies are available. Based on observations of a case of ADEM temporarily associated with JE vaccination, the recommendation for routine childhood JE vaccination has been withdrawn in Japan. However, the Global Advisory Committee on Vaccine Safety concluded recently that there was no*

definite evidence of an increased risk of ADEM temporally associated with JE vaccination and that there was no good reason to change current recommendations for immunization with JE vaccines. Occasionally, hypersensitivity reactions, in some cases serious generalized urticaria, facial angioedema or respiratory distress, have been reported, principally in vaccine recipients from non-endemic areas. The reported rates of such reactions in prospective and retrospective studies are usually in the range of 18–64 per 10 000 vaccinated subjects. A complicating factor is that such reactions may occur as late as 12–72 hours following immunization. Sensitization to gelatin, a vaccine stabilizer, has been suspected in some cases in Japan, but the underlying cause remains uncertain.

**Conclusions:** Ideally, mouse brain-derived vaccines should be replaced by newer generation JE vaccines. Manufacturers have been moving away from production of mouse brain-derived vaccines in favor of newer technologies. Mouse brain-derived vaccines may continue to play a role in combatting JE in some countries, but overall these products have a less favorable profile due to the increased reactogenicity compared to newer JE vaccines. In addition, inactivated mouse brain-derived vaccines may be less preferable due to variability of manufacturing, cost, and compared to some other products, number of doses required and need for repeat boosters.

### 5.6 Vaccine Interchangeability

As countries transition from the use of one product to another, or use multiple products requiring more than one dose, the potential exists for vaccinees to receive more than one product to finish out a series or for the purposes of a booster. Limited data exist on vaccine interchangeability; there have been few studies with small numbers.

**Table 12.** Overview of available data on JE vaccine interchangeability.

		Booster vaccine			
		Inactivated MB	Inactivated Vero	Live attenuated	Chimeric
Primary vaccine	Inactivated MB	NA	Erra 2012; Erra 2013; Woolpert 2012	PATH JEV04; Sohn 1999	Chokephaibulkit 2010a
	Inactivated Vero	No published data	NA	No published data	No published data
	Live attenuated	No published data	No published data	NA	No published data
	Chimeric	Monath 2003	No published data	No published data	NA

Of most relevance to endemic countries is likely inactivated mouse brain vaccine followed by vaccination with either live attenuated or chimeric vaccine. Of note, the studies of inactivated mouse brain vaccine followed by inactivated Vero cell vaccine suggested a strong anamnestic response and no serious safety signals (Erra 2012, Erra 2013, Woolpert 2012).

### 5.6.1 Inactivated mouse brain vaccine followed by live attenuated vaccine

In an open-label non-randomized single-arm trial, 294 two and five year-olds previously immunized with 2-3 doses of inactivated mouse brain vaccine in Sri Lanka were re-vaccinated with live attenuated vaccine CD.JEVAX (quoted with permission from PATH). At day 0, 98.6% (95%CI 96.6-99.6) of participants were seropositive. By day 28 post-vaccination with live attenuated vaccine, 100% (95% CI: 98.8-100) were seropositive, and at one year post vaccination, 99.7% (95% CI: 98.1-100) were seropositive. GMTs ranged from 804 (95% CI: 681-949) at day 0 to 2968 (95% CI: 2679-3289) at day 28 and 2863 (95% CI: 2518-3256) at day 365. There were no safety concerns identified in this study. Another study included 10 children in Korea who had received either two or three doses of inactivated mouse brain vaccine previously (at variable time points and number of doses) and were vaccinated with CD.JEVAX (Sohn 1999). The GMT was 3378 four weeks after re-vaccination with CD.JEVAX, more than 18-fold higher than participants who received live attenuated vaccine for the first time. This strong anamnestic response was seen regardless of whether the participant had detectable neutralizing antibodies prior to boost. No safety data specific to the children who received CD.JEVAX following inactivated mouse brain-derived vaccine were reported.

### 5.6.2 Inactivated mouse brain vaccine followed by chimeric vaccine

In a prospective, randomized open-label cross-over study in Thailand, 100 2-5 year-olds who had received 2 doses of inactivated mouse brain vaccine as part of the routine immunization program were randomized to receive one dose of chimeric JE vaccine or inactivated hepatitis A vaccine (Chokephaibulkit 2010a). Eighty-six percent of participants were seropositive at baseline. One hundred percent were seropositive 28 days post-vaccination with chimeric vaccine, with a GMT of 2634 (95% CI: 1928-3600). GMTs in previously immunized children decreased to 1055 at seven months (100% seroprotected) and 454 at 12 months (97% seroprotected). There were no vaccine-related serious adverse events and no safety concerns identified in this study. Reactogenicity following chimeric vaccine was comparable to that experienced with hepatitis A vaccine.

## 6. Consideration of other key issues

### 6.1 Recommendations for Introduction

JE vaccination should be extended to all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE transmission (e.g., presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries/regions with known JE transmission).

It is advisable that countries deciding on JE vaccine introduction have at least some minimal local data on the burden of JE disease, such as information collected through sentinel sites. More refined country-specific data are useful to identify target age groups and areas of highest risk. The latter is particularly important if a phased or only subnational vaccine introduction is considered. An absence of confirmed cases from suboptimal surveillance and case detection should not be taken as sufficient to exclude JE vaccination. Appropriate data should be available to policy makers to inform decisions about introduction, strategy, and scope of the program.

## 6.2 Age of administration and vaccine schedules

The following principles were used to identify the optimal age of administration for JE vaccination:

1. to provide protection as early as possible, taking into account local JE epidemiology;
2. to avoid interference with passively acquired maternal antibodies that can lower or impair the immune response; and
3. to take advantage of opportunities to co-administer with other vaccines rather than add additional vaccination visits

**Table 13.** Overview of currently recommended schedules and age of administration

Vaccine	Recommended schedule and age of administration based on currently available data	Supporting evidence
Inactivated Vero cell vaccine	Primary series per manufacturer's recommendations (vary by product). Generally, <ul style="list-style-type: none"><li>• ≥6 months of age in endemic settings</li><li>• ≥2 months of age in non-endemic settings</li></ul> In endemic settings, the need for a booster has not been established.	<ul style="list-style-type: none"><li>• Immunogenicity and safety data from clinical trials of IXIARO down to 2 months of age in the Philippines and US/Europe</li></ul>
Live attenuated vaccine	Single dose administered at ≥8 months of age In endemic settings, the need for a booster has not been established.	<ul style="list-style-type: none"><li>• Immunogenicity and safety data from clinical trials down to 8 months of age</li><li>• Post-marketing surveillance in China</li></ul>
Chimeric vaccine	Single dose administered at ≥9 months of age In endemic settings, the need for a booster has not been established.	<ul style="list-style-type: none"><li>• Immunogenicity and safety data from clinical trials down to 9 months of age, with limited data available in the 9-12 month age group.</li></ul>

The risk of infection will clearly differ by setting. In a metropolitan area in Manila, Philippines, where the incidence of JE would be expected to be lower than in rural settings, the seroprevalence rate jumped from 2.9% in the 1 to <3 year age group to 22.6% in the 3 to <12 year age group (Dubischar-Kastner 2012b). These data, in addition to case-based data in young children, emphasize the need for early vaccination (Country data presented at 2014 WHO Bi-Regional Meeting on JE).

## 6.3 Co-administration with other vaccines

Many countries currently co-administer JE vaccines with other vaccines for programmatic reasons despite a lack of robust data supporting safety or non-inferiority of immune responses (Table 14). The WHO measles position paper currently states that measles and JE vaccines may be co-administered at the same time but at different sites (WHO 2009).

**Table 14.** Comparison of country practices for co-administration with JE vaccines and published data on co-administration.

Co-Administered Vaccines	Inactivated Vero cell JE vaccine	Live attenuated JE vaccine	Chimeric JE vaccine
<b>M</b>		P R	
<b>MR</b>		R	
<b>MMR</b>			P
<b>OPV</b>		R	
<b>YF</b>			P
<b>Inactivated HepA</b>	P	R	
<b>Td/DT/DTP</b>		R	
<b>Influenza</b>		R	
<b>Rabies</b>	P		
<b>Rabies + Mening</b>	P		

P= Data published; R= ≥1 country reported routine co-administering, or co-administered during campaign; travelers not considered. Vaccines not listed: no indication of study or practice of co-administration with JE vaccines.

### 6.3.1 Co-administration with inactivated Vero cell vaccines

Co-administration of inactivated Vero-cell JE vaccine and hepatitis A vaccine in healthy adults showed comparable seroconversion and GMTs for all groups at 56 days post-JE and 28 days post-Hepatitis A (Kaltenböck 2009). Seroconversion for JE was between 98.2-100%. Another study in European adults demonstrated good and comparable GMTs and seroprotection for JE and rabies in JEV+PCECV+MenACWY and JEV+PCECV groups (Alberer 2014). Comparable seroprotection was seen for MenACWY + JE compared to MenACWY-alone groups. No short-term safety concerns were shown for either of these studies.

### 6.3.2 Co-administration with live attenuated vaccine

For the live attenuated vaccine, a study was conducted comparing the immunogenicity and safety of measles vaccine co-administered with CD.JEVAX in children aged 9 months in the Philippines (Gatchalian 2008, Victor 2014). At day 28 there were no significant differences between groups in both measles (86.5-91.8%) and JE seroprotection (90.5-92.1%) rates. There were no short-term safety concerns, and this conclusion was supported by GACVS. Long-term follow up from this study is ongoing (serology available only for JE due to a measles campaign that occurred in the study area). Another study in Sri Lanka also did not identify any safety concerns when measles and JE vaccine were co-administered; however, there was no control group (Wijesinghe 2014). Post-marketing surveillance in Guangdong, China (2005-2012) showed no increased sign of neurological-related events associated with co-administration of live attenuated JE vaccine with other vaccines (Liu 2014).

### 6.3.3 Co-administration with chimeric vaccine

For the chimeric JE vaccine, a study with MMR co-administration in Taiwanese children (12-18 months) demonstrated comparable immune responses for all antigens at 6 weeks (Huang 2014). At one year the JE seroprotection rate was slightly lower (seroprotection rates for measles, mumps and rubella were not significantly different between groups) in the co-administration group compared to single administration groups (88.6% vs 96.6-98.8%), however, no non-inferiority test was shown. Of the 29 children who experienced a skin and subcutaneous tissues AE (e.g. rash), 22 were in the co-

administration group (N=220). Another study of concomitant administration with yellow fever (YF) vaccine in Australian adults showed comparable YF seroconversion rates across groups (Nasveld 2010b). JE GMT was significantly decreased in the co-administration and YF/JE groups compared to JE/YF group (seroprotection 91-96% vs 100%). No short-term safety concerns were found.

#### **Conclusions:**

Data support co-administration of live attenuated JE vaccine with measles vaccine. Immunogenicity studies are needed for co-administration with MR and MMR. However, for programmatic reasons it may be considered acceptable to co-administer live attenuated JE vaccine with MR or MMR vaccines, although data are not yet available. Following the same rationale, co-administration of MMR and chimeric vaccine is acceptable although slightly lower anti-JEV GMT values, but nonetheless seroprotective, were obtained in the co-administration group at 12 months after vaccination. Immunogenicity studies, including long-term studies, are needed for co-administration of chimeric vaccine with M and MR vaccines.

Experience with inactivated mouse brain vaccines does not suggest reduced seroconversion rates or an increase in adverse events when mouse brain JE vaccine is given simultaneously with vaccines against measles, DPT and oral polio as part of the EPI program. The same is true for trials of co-administration of IXIARO with a range of vaccines given to travelers. While the possible impact of co-administration of inactivated JE vaccines with other vaccines of the childhood immunization program has not been systematically studied, co-administration of inactivated Vero cell vaccines with other vaccines for programmatic reasons seems acceptable.

Vaccine co-administration is a preferred programmatic approach. Further studies on co-administration are encouraged. Program monitoring and/or special studies are warranted to assess immunogenicity and/or effectiveness.

### **6.4 Use in special populations**

#### **6.4.1 Immunocompromised**

There are very limited data in immunocompromised persons for inactivated Vero cell, live attenuated, or chimeric JE vaccines. Four studies were conducted in Thailand with mouse brain-derived vaccine in HIV-infected persons. In the one small study of HIV-infected children not receiving anti-retroviral therapy (ART) no safety concerns were identified but the seroprotection rate was approximately half the rate in HIV-uninfected children (Rojanasuphot 1998). In the other studies in which participants were receiving ART, seroprotection was comparable to that seen in HIV-negative children; GMTs were lower, but within an acceptable range (Chokephaibulkit 2010b; Puthanakit 2007; Puthanakit 2010). Adverse events were similar between HIV-infected and HIV non-infected participants. An older study from Japan in which two doses of mouse brain-derived vaccine were given to children with neoplastic diseases demonstrated similar responses among the seven children with neoplastic diseases and the other children who were healthy or had non-neoplastic diseases (Yamada 1986). No adverse events were reported. A recent study was conducted in post-hematopoietic stem cell transplant subjects given live attenuated vaccine  $\geq 2$  years post-transplant and  $\geq 6$  months post-immunosuppressants (Pakakasama 2014, abstract only). Among the 18 children not seroprotected prior to JE vaccination, nine had seroprotective titers after one dose (only three



sustained protection for at least 12 months), seven had seroprotective titers after two doses, and two had no response.

Experience with yellow fever (YF) vaccine administered to HIV-infected persons may also inform the possible experience with chimeric JE vaccine, both because it is a live attenuated flaviviral vaccine and because the YF17D virus is the backbone for the chimeric vaccine. In a review done by GACVS in 2010, no clear evidence was available to suggest that hypothetical risk should preclude use of YF vaccine in HIV-infected persons (WHO 2011). Recent data suggest immune response wanes more rapidly in HIV-infected persons (Veit 2009). The WHO YF position paper states that YF vaccine may be offered to asymptomatic HIV-infected persons with CD4 T-cell counts  $\geq 200$  cells/mm (WHO 2013). YF vaccine is contraindicated in immunocompromised persons based on historical experience with live vaccines.

**Conclusions:** Based on indirect evidence with use of inactivated mouse brain vaccines in immunocompromised persons, inactivated Vero cell JE vaccine can be used in HIV-infected and immunocompromised persons, but the immune response may be lower than in healthy persons. Inactivated vaccines should be used preferentially over live or chimeric vaccines in immunocompromised persons. However, it is not necessary to use screening tests prior to vaccinating and it should not be a deterrent to using live or chimeric vaccines during campaigns.

#### 6.4.2 Pregnant women

There are no studies on inactivated Vero cell vaccines, live attenuated vaccine, and chimeric vaccine in pregnant women. Preclinical studies of IXIARO in pregnant rats did not show evidence of harm to the mother or foetus. According to the European Public Assessment Report, 24 pregnant women were inadvertently vaccinated in clinical studies with no untoward findings (EMA 2009).

Experience with the YF vaccine administered to pregnant women may also inform the possible experience with chimeric JE vaccine for the same reasons stated above. The WHO YF position paper recommends a risk-benefit assessment be undertaken for pregnant and lactating women but noted in areas where YF is endemic or during outbreaks the benefits of vaccination likely outweigh potential risks to the fetus (WHO 2013).

**Conclusions:** Inactivated vaccines should be used preferentially over live or chimeric vaccines in women known to be pregnant out of the same precautionary principle against using any live attenuated vaccine in pregnant women. However, it is not necessary to do pregnancy testing before JE vaccination.

#### 6.4.3 Travelers

Travelers are potentially at risk, and there are specific recommendations issued by various national authorities. Most authorities recommend vaccination for travelers going to endemic countries, particularly but not exclusively rural areas, for more than one month, or repeat travel to such areas. As noted by WHO guidelines for International Travel and Health, “the risk varies according to season, destination, duration of travel and activities. Vaccination is recommended for travelers with extensive outdoor exposure...during the transmission season” (2014).

#### 6.4.4 Health care workers

WHO defines health care workers as all persons involved in patient care such as health care professionals, residents, students, laboratory staff, administrative and service staff, as well as persons in public health acts such as field workers, epidemiologists, laboratory staff and community health workers. Health care workers at high-risk in JE-endemic areas, e.g. those involved in vector control, should be vaccinated.

#### 6.5 Vaccination strategies

JE vaccination strategies include campaigns in locally defined target groups, introduction into the routine immunization program, or a combination. Little empiric assessment of various strategies has been conducted, and mathematical modelling may help to refine the vaccination approach.

The most effective immunization strategy in JE endemic settings is a one-time campaign in the primary target population, as defined by local epidemiology (typically children <15 years of age), followed by incorporation of the JE vaccine into the routine immunization program. This approach has a greater public health impact than either strategy separately. When possible, campaigns should be scheduled outside periods of high JE disease activity to avoid any coincidental association of vaccination with encephalitis.

Some countries may have a sufficient burden of disease in the adult population to warrant vaccination of older age groups. JE vaccination does not induce any herd immunity.

There are no data documenting the impact of vaccination when initiated as a response to a JE outbreak. If an outbreak occurs, an assessment needs to be made about whether it is appropriate to implement an immediate vaccine response, including considerations such as size of outbreak, timeliness of the response, population affected, programmatic capacity, etc. Due to the need for rapid production of protective antibodies, single dose live attenuated or chimeric vaccines should be used. The use of JE vaccine during an outbreak should not deter countries from introducing JE vaccine into routine programs if they have not already done so, and occurrence of an outbreak further strengthens the case that routine immunization is needed.

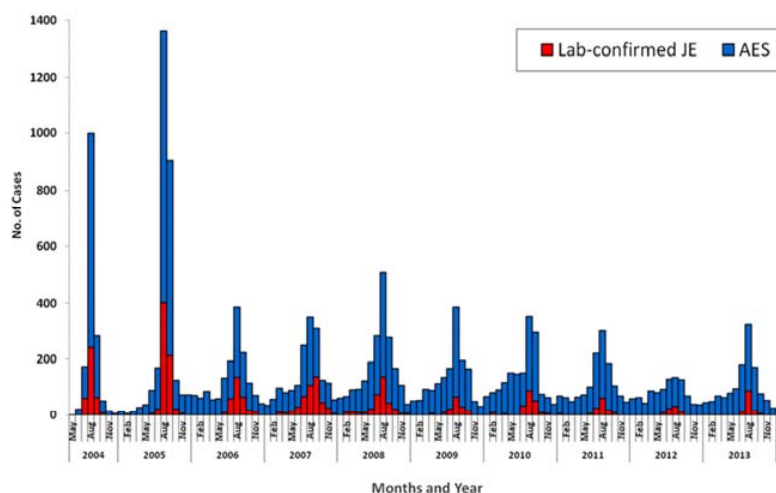
#### 6.6 Public health and economic impact

SAGE guidelines for evidence-based vaccine recommendations include considering the population impact of the vaccine and cost-effectiveness of immunization programs.

Many countries with JE surveillance systems have been able to track JE trends over time, before and after vaccination. There is clear evidence of significant impact on JE disease of population vaccination with live attenuated and inactivated mouse brain JE vaccines (Liu 2006, Upreti 2013, Zhou 2001, Chen 1992, Wong 2008, Japanese Surveillance Report 1999, Wu 1999). Disease impact studies exclusively for inactivated Vero cell vaccines and chimeric vaccines are not yet available due to the lack of widespread use; chimeric vaccine impact studies may now be possible in some of the endemic countries in which they are now being used. In Nepal, mass vaccination campaigns were conducted between 2006 and 2009 among those aged 1-15 years in some districts and among all persons  $\geq 1$  year of age in other districts, with high coverage (94% of the target population) achieved (Upreti 2013). Surveillance data from 2004-2009 were analyzed, and showed the incidence of laboratory-confirmed JE incidence following the campaigns was 1.3 per 100,000, which was 72% lower than the expected incidence of 4.6 per 100,000 had no campaigns occurred. The incidence

difference was greatest in the high-risk districts and when the vaccinated population was all individuals greater than 1 year of age. When the burden in adults is considered sufficiently high, vaccinating adults increases the impact on JE disease.

**Figure 5.** AES and lab-confirmed JE cases by month and year in Nepal (courtesy of S. Upreti).



The cost-effectiveness of JE vaccination, either when introduced directly into the routine program, or when introduced through mass campaigns followed by routine introduction, has been assessed for live attenuated, inactivated mouse brain, and inactivated PHK cell vaccines in a variety of countries (Yin 2012, Touch 2010, Liu 2008, Suraratdecha 2006, Ding 2003, Siraprapasiri 1997). The cost per case averted ranged from -\$1200 USD (live attenuated vaccine introduced into routine schedule in China; Ding 2003) to \$21,928 (inactivated mouse brain vaccine introduced through mass campaigns followed by routine in India; Suraratdecha 2006). The cost per DALY averted ranged from \$22 (live attenuated vaccine introduced into the routine program in Cambodia; Touch 2010) to \$1,247 (inactivated mouse brain vaccine introduced through mass campaigns followed by routine in India; Suraratdecha 2006).

JE vaccination, even with more expensive inactivated products requiring multiple doses, was nearly always cost-effective regardless of the vaccination strategy. One dose of live attenuated JE vaccine was typically very cost-effective by WHO criteria<sup>10</sup> or cost-saving. The cost per DALY averted was highly sensitive to the pre-vaccination incidence and the cost of the vaccine.

Gavi supports endemic countries in one-time JE vaccination campaigns for children under 15 years old, including phased campaigns until all areas have had vaccination opportunity. As part of the application to Gavi, countries must have a plan for sustaining routine immunization. This is a good strategy for public health and economic impact.

<sup>10</sup> Following the recommendations of the Commission on Macroeconomics and Health, CHOICE uses gross domestic product (GDP) as a readily available indicator to derive the following three categories of cost-effectiveness: (1) highly cost-effective (less than GDP per capita), (2) cost-effective (between one and three times GDP per capita), and (3) not cost-effective (more than three times GDP per capita). Available at: [http://www.who.int/choice/costs/CER\\_thresholds/en/](http://www.who.int/choice/costs/CER_thresholds/en/).

## **Conclusions:**

Data on the population impact of vaccination programs show significant reductions in JE cases. When high coverage is achieved in populations at risk of disease, JE in humans can be virtually eliminated while the virus remains in circulation. Due to the continued enzootic cycle of JE virus, sustained high coverage vaccination programs are critical.

Although cost-effectiveness studies are highly dependent upon parameters such as incidence of disease and vaccine price, it has been demonstrated that vaccination programs can be highly cost effective. A variety of vaccination strategies, including campaigns plus routine introduction, have been shown to be cost effective or highly cost effective. Vaccination impact studies, including demonstration of sustained low incidence of disease following a product switch, would be valuable in particular for newer vaccines.

There is a need for standardized guidance on how to approach JE vaccine assessments such as effectiveness and impact studies. This should address data source and analysis issues for using surveillance data to measure impact, data collection and analysis for observational studies to measure vaccine effectiveness, and designing surveillance and special studies to measure JE vaccine impact. There are many complexities relating to JE case diagnostics that make such studies complicated. WHO should take the lead on developing this guidance and making it available to countries and stakeholders.

### **6.7 Non-vaccine interventions**

There is little evidence to support a reduction in JE disease burden from interventions other than vaccination of humans. Other attempted strategies have included pig vaccination, environmental management for vector control, and chemical control of vectors (Erlanger 2009). Pig vaccination is limited by the high turnover in pig populations continuously throughout the year and reduced effectiveness of live attenuated vaccine in young pigs due to maternal antibodies (Igarashi 2002). It also does not affect other amplifying hosts (i.e. aquatic birds). Environmental management, although possible to reduce vector breeding along with other benefits such as saving water and reducing methane emission, is challenging, and not always feasible. It is difficult to cover all mosquito habitats with insecticides, such as rice paddies and ground pools of water, especially during the rainy season. Insecticide use, including for reasons other than JE, has promoted insecticide-resistance. Permethrin-impregnated mosquito nets were shown to provide some protection against JE in one study (Luo 1994), but several other studies showed no reduction in the risk of JE when bed nets were used (Liu 2010, Rayamajhi 2007, Phukan 2004, Lowry 1998); nonetheless bed nets may be important to reduce the risk of other vector-borne diseases. Adjunctive interventions should not divert efforts from childhood JE vaccination.

## **7. WG key conclusions and proposed recommendations**

### **7.1 Key conclusions**

- A. Japanese encephalitis is major public health problem in many countries in South East Asia and the Western Pacific.

- B. Safe and effective (immunogenic) vaccines are available.
- C. With greater access to products, including new vaccines and WHO prequalified vaccines, and with Gavi funding support for eligible countries, there are many opportunities to initiate or expand JE vaccination programs.
- D. Surveillance strengthening is needed to assess the burden of JE, inform vaccination strategies, and monitor the impact and effectiveness of JE vaccines.
- E. Assessments of the public health and economic impact of vaccination programs show significant reductions in JE cases and economic burden of JE. When high coverage is achieved in populations at risk of disease, JE disease in humans can be virtually eliminated while the virus remains in circulation.

## **7.2 Proposed JE vaccine recommendations**

1. JE vaccination should be extended to all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE transmission (i.e. presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries or regions with known JE transmission).
2. It is advisable that countries deciding on JE vaccine introduction have at least minimal local data on the burden of JE disease, such as information on confirmed cases collected through sentinel sites. More refined country-specific data are useful to identify target age groups and areas of highest risk. The latter is particularly important if a phased or only subnational vaccine introduction is considered. An absence of confirmed cases in the context of suboptimal surveillance and case detection should not be taken as sufficient to exclude the need for JE vaccination.
3. All JE-endemic countries should have at least sentinel surveillance with laboratory confirmation of JE. Acute encephalitis syndrome (AES) surveillance is an important tool for understanding all causes of encephalitis. Even in the absence of JE-confirmatory testing, reporting of AES cases can have value in demonstrating impact of vaccination programs. However, low impact of JE vaccination programs on AES may reflect the burden of non-JE causes of AES.
4. The most effective immunization strategy in JE endemic settings is a onetime campaign in the primary target population, as defined by local epidemiology (typically children <15 years of age), followed by incorporation of the JE vaccine into the routine immunization program. This approach has a greater public health impact than either strategy separately. When possible, campaigns should be scheduled outside periods of high JE disease activity. Older age groups may be considered for vaccination if the disease burden in such groups is sufficiently high.

5. Due to the continued enzootic cycle of JE virus (and thus no herd immunity), sustained high-coverage vaccination programs are critical.
6. The following vaccine dosing schedules and age of administration are recommended in **endemic settings**. For all vaccines, the need for a booster dose in endemic settings has not been established.
  - a. Inactivated Vero cell vaccine: Primary series per manufacturer's recommendations (these vary by product). Generally starting the primary series at  $\geq 6$  months of age in endemic settings
  - b. Live attenuated vaccine: Single dose administered at  $\geq 8$  months of age
  - c. Chimeric vaccine: Single dose administered at  $\geq 9$  months of age
7. Countries are strongly encouraged to conduct rigorous vaccine failure monitoring to assess the need for eventual booster doses.
8. Vaccine co-administration is a preferred programmatic approach. There are some data on co-administration of JE vaccines with some other vaccines, particularly live attenuated measles vaccine. However, many countries are already co-administering JE vaccines with vaccines not yet tested, such as combination measles-rubella vaccine. While the possible impact of co-administration of JE vaccines with measles-rubella vaccine as well as other vaccines of the childhood immunization program has not been systematically studied, co-administration for programmatic reasons seems acceptable. However, program monitoring and/or special studies are warranted to assess immunogenicity and/or effectiveness.
9. The value of reactive JE campaigns has not been studied. If an outbreak occurs in a country or region having not yet introduced JE vaccination, an assessment needs to be made about whether it is appropriate to implement an immediate vaccine response, including considerations such as size of outbreak, timeliness of the response, population affected, and programmatic capacity. Due to the need for rapid production of protective antibodies, single dose live attenuated or chimeric vaccines should be used. When outbreak response immunization is conducted, planning for routine immunization should follow.
10. Special populations:
  - a. Immunocompromised persons: Inactivated Vero cell JE vaccine can be used in HIV-infected and immunocompromised persons, but the immune response may be lower than in healthy persons. Inactivated vaccines should be used preferentially over live or chimeric vaccines in immunocompromised persons.
  - b. Pregnant women: If JE risk is sufficient to vaccinate pregnant women, inactivated vaccines should be used preferentially over live or chimeric vaccines based on the general precautionary principle against using any live attenuated vaccine in pregnant women. It is not necessary to do pregnancy testing before JE vaccination.
  - c. Travelers: JE vaccination is recommended for travelers to endemic areas with extensive outdoor exposure during the transmission season.
  - d. Health Care Workers: WHO defines health care workers as all persons involved in patient care such as health care professionals, residents, students, laboratory staff,

administrative and service staff, as well as persons in public health acts such as field workers, epidemiologists, laboratory staff and community health workers. Health care workers at high-risk in JE-endemic areas, such as those involved in vector control, should be vaccinated.

11. Adjunctive (non-vaccine) interventions, in particular vector control, should not divert efforts from childhood JE vaccination.

### **7.3 Research Priorities and Data Gaps**

*In no particular order*

- I. Long-term immunogenicity studies to inform optimal dosing schedules for long-term protection, which may vary by location (based on natural boosting or other factors).
- II. Vaccine effectiveness and impact studies (particularly for newer vaccines).
- III. Development of standardized neutralization assay reagents.
- IV. Further development of sensitive, specific, affordable commercial serological assays to ensure access to diagnostic testing in JE-endemic countries.
- V. Co-administration of live attenuated and chimeric vaccines with other live vaccines, including MR and MMR. Co-administration of any JE vaccine with other vaccines not yet studied may also be warranted.
- VI. Better description of disease severity by age, including long-term sequelae from JE disease.
- VII. Guidance on how to approach 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. WHO should take the lead on developing this guidance and making it available to countries and stakeholders.
- VIII. Development of case-investigation protocols and field tools to enable strong monitoring and assessment of vaccine failures.
- IX. The safety of live and chimeric vaccines when administered to pregnant women and immunocompromised persons is a data gap.

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## **Appendix 1. SAGE Working Group on JE Vaccines: Terms of Reference and Composition**

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of Japanese encephalitis (JE) vaccines for a SAGE review. This will lead to an update of the current (2006) JE vaccine position paper. The target date for publication of the revised vaccine position paper is 2015.

The Working Group will specifically be asked to review data relating to:

1. the global prevalence and burden of disease caused by JE, including issues relating to JE surveillance
2. the role of inactivated mouse-brain based JE vaccines in the context of other products
3. the safety, effectiveness, and immunogenicity profile of JE vaccines\*
4. the schedule and age of administration for JE vaccines
5. the duration of protection following immunization with JE vaccines
6. co-administration of JE vaccines with other vaccines
7. JE vaccination strategies to reduce disease in a country or region, including the possible utility of reactive campaigns during outbreaks
8. use of JE vaccines in special populations (e.g. immunosuppressed, pregnancy)
9. the disease impact and cost-effectiveness of JE immunization programs
10. additional critical issues that need to be considered in updating the current vaccine position paper

\*Due to the large number of available JE vaccines with limited global use, the Working Group will focus its in-depth evidence review on products with current or likely international distribution. The Working Group will also place emphasis on inactivated cell-based, live attenuated, and live chimeric vaccines.

### **Composition**

#### **SAGE Members**

- Piyanit Tharmaphornpilas (Working Group Chair), National Immunization Program, Ministry of Public Health, Thailand
- Paba Paliwadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

#### **Experts**

- Alan Barrett, Sealy Center for Vaccine Development, University of Texas Medical Branch, USA



- Susan Hills, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, USA
- Ooi Choo Huck, Sarawak Health Department, Ministry of Health, Malaysia
- Heidi Meyer, Viral Vaccines Section, Paul-Ehrlich-Institut, Germany
- Khin Saw Aye Myint, Eijkman Institute, Indonesia
- Tom Solomon, Institute of Infection and Global Health, University of Liverpool, UK
- Tomohiko Takasaki, Laboratory of Vector-Borne Viruses, National Institute of Infectious Diseases, Japan
- Shyam Upreti, Central Regional Health Directorate, Ministry of Health and Population, Nepal
- Yin Zundong, National Immunization Program, Chinese Center for Disease Control and Prevention, China

#### **WHO Secretariat**

- Joachim Hombach
- Kirsten Vannice

#### **DECLARATION OF INTERESTS**

All Working Group members completed a declaration of interests. Two members reported relevant interests. The reported relevant interests are summarized below:

##### **Susan Hills**

- Her organization (CDC) received a research grant from the Bill and Melinda Gates Foundation to investigate the impact of SA 14-14-2 JE vaccine in Asia. This interest was assessed as non-personal, specific, and financially significant\*.

##### **Piyanit Tharmaphornpilas**

- Received in 2011 a travel grant from a joint venture of the Thai Government Pharmaceutical Organization - Merieux Biological Product to attend the Re-invigorating Immunisation Policy Implementation and Success: From Parent to Partner and from Broad to Engagement. This interest was assessed as personal, non-specific and financially insignificant\*.

\* 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. Critical Policy and PICO Questions Identified by the JE WG

Theme	Policy Question	PICO Question
Effectiveness CRITICAL	What is the effectiveness of JE vaccines?	<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series of <u>inactivated Vero cell</u> -based vaccine <b>Comparator:</b> No vaccine, placebo, or other JE vaccine <b>Outcome:</b> JE disease
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series* of <u>live attenuated</u> vaccine <b>Comparator:</b> No vaccine, placebo, or other JE vaccine <b>Outcome:</b> JE disease
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series* of <u>chimeric live attenuated</u> vaccine <b>Comparator:</b> No vaccine, placebo, or other JE vaccine <b>Outcome:</b> JE disease
Safety CRITICAL	What is the risk of serious adverse events following JE vaccination?	<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Administration of <u>inactivated Vero cell</u> -based vaccine <b>Comparator:</b> No vaccine, placebo, or other vaccine <b>Outcome:</b> SAEs
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Administration of <u>live attenuated</u> vaccine <b>Comparator:</b> No vaccine, placebo, or other vaccine <b>Outcome:</b> SAEs
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Administration of <u>chimeric live attenuated</u> vaccine <b>Comparator:</b> No vaccine, placebo, or other vaccine <b>Outcome:</b> SAEs
Duration of protection CRITICAL	Is there need for a booster dose following immunization with the primary series of JE vaccination?	<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series of <u>inactivated Vero cell</u> -based vaccine received $\geq 1$ years ago <b>Comparator:</b> No vaccine, placebo, or other JE vaccine OR recipient of <u>inactivated Vero cell</u> -based vaccine $< 1$ year <b>Outcome:</b> JE disease
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series* of <u>live attenuated</u> vaccine received $\geq 1$ years ago <b>Comparator:</b> No vaccine, placebo, or other JE vaccine OR recipient of <u>live attenuated</u> vaccine $< 1$ years ago <b>Outcome:</b> JE disease
		<b>Population:</b> Immunocompetent individuals <b>Intervention:</b> Primary series* of <u>chimeric live attenuated</u> vaccine received $\geq 2$ years ago <b>Comparator:</b> No vaccine, placebo, or other JE vaccine OR recipient of <u>chimeric live attenuated</u> vaccine $< 2$ years ago <b>Outcome:</b> JE disease

\*DEFINITION: Primary series - For live attenuated/chimeric live attenuated JE vaccines, defined as one dose for all ages

### Appendix 3. Other key policy questions identified by the JE Working Group

Theme	Policy Questions
Co-Administration NON-CRITICAL	Can JE vaccines be safely and effectively co-administered with other vaccines?
Special populations NON-CRITICAL	Can JE vaccines be safely and effectively used in special populations?
Mouse brain vaccines NON-CRITICAL	What is the role of inactivated mouse brain-based JE vaccines in the context of other products?
Vaccine schedules NON-CRITICAL	What is the appropriate age of administration for JE vaccines in the routine immunization schedule?
Vaccine strategies NON-CRITICAL	What is the appropriate JE vaccine introduction strategy in an endemic country without a vaccination program?
Impact on disease NON-CRITICAL	What is the impact of JE vaccine introduction on JE disease at a country or regional level?
Cost-effectiveness NON-CRITICAL	What is the cost-effectiveness of JE vaccine introduction?
Global burden of JE NON-CRITICAL	What is the global prevalence and disease burden of JE?
At-risk population NON-CRITICAL	How should at-risk populations be defined?

**Appendix 4. Table of JE Vaccines**

Names		Manufacturers		Strain	Age (first dose)	Dose Schedule	Licensure <sup>1</sup>
Inactivated (Mouse Brain)	JenceVac	Korea: Green Cross		Nakayama	12-23 M	Primary: 3 doses (0/7-30D/>6M) Booster: Ages 6Y and 12Y	International
	JE Vaccine "Kuo Kwang"	Taiwan: Adimmune Corp		Nakayama	15-27 M	Primary: 3 doses (0/7-14D/1Y) Booster: Age 5 Y	Taiwan
	J.E. (BEIJING) – GPO	Thailand: Government Pharmaceutical Organization		Beijing-1	>= 1 Y	Primary: 2 doses (0/7-14 D) Booster: Every 1-3 Y	Thailand
	JEVAX	Vietnam: VaBiotech		Nakayama	>=1 Y	Primary: 3 doses (0/14D/1Y) Booster: Every 3 Y	Vietnam
Inactivated (Vero Cell)	JEBIK V	Japan: Biken		Beijing-1	>= 6M	Primary: 2 doses (0/6-28D) Booster: 1 Y	Japan
	ENCEVAC KD-287/ JEIMMUGEN INJ1	Japan: Kaketsuken Korea: Boryung		Beijing-1	>= 6M	Primary: 3 doses (0/7-14D/12M) Booster: Ages 6Y and 12Y	Japan, Korea
	JEVAC	China: Liaoning Chengda Biotechnolog Co		Beijing P-3	6-12M	Primary: 2 doses (0/7D) Booster: 1M-1Y	China, Cambodia
	IXIARO ICS1/JE-VC/ JESPECT	Austria: Intercell/Valneva, distributed by Novartis and bioCSL		SA 14-14-2	>=17 Y (>=2 M in US)	Primary: 2 doses (0/28D) Booster: 1 Y	US, EU, Canada, Australia, HK, Switzerland, Israel, Singapore, New Zealand, PNG, Pacific Islands
	JEEV	India: Biological E		SA 14-14-2	>=18, <=49 Y (India 1-3 years)	Primary: 2 doses (0/28D)	India, Bhutan, Pakistan, Nepal
	JENVAC	India: Bharat Biotech		Kolar Strain (JEV 821564 XY)	>=1Y	Primary: 2 doses (0/28D) Booster: >1 Y	India
Live Attenuated (PHK)	SA-14-14-2 CD JE VAX	China: Chengdu Institute of Biological Products (CDIBP)		SA 14-14-2	>=8M	Primary: 1 dose Booster: 9M-12M, or age 2Y in some countries	India, South Korea, Thailand, Nepal, Sri Lanka, DPRK, Laos, Cambodia, Burma, Malaysia, Vietnam
Live Chimeric (Vero)	IMOJIEV JE-CV/ ChimeriVax-JE	France : Sanofi pasteur		SA 14-14-2/ yellow fever 17D	>1Y	Primary: 1 dose Booster (paediatric): Age 2Y	Australia, Malaysia, Thailand, Brunei

<sup>1</sup>Not necessarily commercialized

## GRADE Table 1. What is the effectiveness of two doses (primary series) of inactivated Vero cell JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas  
**Intervention:** Two doses (primary series) of inactivated Vero cell vaccine  
**Comparison:** Placebo/No vaccination  
**Outcome :** JE disease (immunogenicity accepted)

<i>What is the effectiveness of two doses of inactivated Vero cell JE vaccine in preventing JE disease in individuals living in JE-endemic areas?</i>			
		Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		7 RCTs <sup>1</sup>
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>
		Inconsistency	None serious
		Indirectness	None serious <sup>3</sup>
		Imprecision	None serious
		Publication bias	None serious
	Factors increasing confidence	Large effect	Applicable <sup>4</sup>
		Dose-response	Not applicable
		Antagonistic bias and confounding	Not applicable
	<b>Final numerical rating of quality of evidence</b>		<b>4</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		<b>We are very confident that the true effect lies close to that of the estimate of effect on health outcome</b>
	<b>Conclusion</b>		<b>Inactivated Vero cell JE vaccines have evidence of seroprotective neutralizing antibody titers.</b>  <b>Based on a review of data on IXIARO</b>

<sup>1</sup>Clinical studies from 7 RCTs in approximately 2,890 IXIARO vaccinees provided short-term immunogenicity data. Across multiple studies in adults, high rates of seroprotection have been found one month following completion of the two-dose primary series. In the largest study of 430 adult vaccine recipients, the seroprotection rate was 98% and the GMT was 244 (Tauber 2007). Among children living in an endemic setting, there are two studies, one in India (N=24 vaccinees aged 1-3 years; Kaltenböck 2010) and one in the Philippines (N=1,411 IXIARO vaccinees aged 2 months - 17 years, 396 assessed for immunogenicity; Dubischar-Kastner 2012a). In the small Indian study, 95.7% (95% CI: 87.3-100) of vaccinees who received the age appropriate dose<sup>4</sup> were seroprotected one month following the second dose with a GMT of 201 (95% CI: 106-380). In the Philippines, the age appropriate dose (0.25ml 2 months to <3 years of age, 0.5ml 3-18 years of age) elicited the following rates of seroconversion in the 2-<6 months, 6-<12 months, 1-<3 years, 3-<12 years, and 12-<18 years age groups, respectively: 100%, 95%, 97%, 94%, and 77% (Dubischar-Kastner 2012a).

<sup>2</sup>Some RCTs assessed immunogenicity in vaccine-recipients, though not within the control group (or was a single-arm trial).

<sup>3</sup>Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>4</sup>High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.

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Tauber E, Kollaritsch H, Korinek M, Rendi-Wagner P, Jilma B, Firbas C, Schranz S, Jong E, Klingler A, Dewasthaly S, Klade CS. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet*. 2007 Dec 1;370(9602):1847-53.

## GRADE Table 2. What is the effectiveness of live attenuated JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas

**Intervention:** One dose of live attenuated JE vaccine

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** JE disease (immunogenicity accepted)

<i>What is the effectiveness of one dose of live attenuated JE vaccine in preventing JE disease in individuals living in JE-endemic areas?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>2</sup>	0
		Indirectness	None serious <sup>3</sup>	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable <sup>4,5</sup>	+1
		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			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Live attenuated JE vaccines have evidence of seroprotective neutralizing antibody titers.  <i>Based on a review of data on CD.JEVAX</i>

<sup>1</sup>Four clinical studies with 1,256 participants receiving CD.JEVAX were assessed. Seroprotection rates at 28 days post-vaccination in the Philippines study were 92.1% (95% CI: 84.3-96.7) and 90.6 (95% CI: 85.3-94.4); the latter result was in the group administered measles vaccine one month prior (Victor 2014). The seroprotection rate was 97.3% (95% CI: 93.1-99.2) for the live attenuated vaccine when used as a control in a chimeric JE vaccine RCT in children aged 9 months to 18 years in Thailand (Feroldi 2014). In a similar study in children 12-24 months in Korea, the seroprotection rate was 99.1% (Kim 2013).

<sup>2</sup>In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)(Zaman 2014). Two lots were not equivalent with a seroprotection rate difference of -4.33 (-11.94-3.31). No clinical consequences have been established and it was determined not to downgrade.

<sup>3</sup>Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>4</sup>High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.

<sup>5</sup>Two effectiveness studies were done in the near-term after vaccination. A case control study in Nepal estimated vaccine effectiveness to be 99.3% (95% CI: 94.9-100) in the one week to one month time period post-vaccination (Bista 2001). A second case-control study in India estimated vaccine effectiveness to be 94.5% (95% CI: 81.5-98.9) six months following vaccination (Kumar 2009).



## Reference List

### **Clinical Studies in Endemic Settings**

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Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS, Luby SP, Rahman M, Hills S, Bhardwaj M, Flores J. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. *Vaccine*. 2014 Sep 18 (epub ahead of print).

### **Vaccine Effectiveness Studies (<12 months post-vaccination)**

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### GRADE Table 3. What is the effectiveness of chimeric JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas

**Intervention:** One dose of chimeric JE vaccine

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** JE disease (immunogenicity accepted)

<i>Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		10 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>2</sup>	0
		Indirectness	None serious <sup>3</sup>	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable <sup>4</sup>	+1
		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			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Chimeric JE vaccines have evidence of seroprotective neutralizing antibody titers.  <i>Based on a review of data on IMOJEV</i>

<sup>1</sup>Includes approximately 3,750 IMOJEV recipients in endemic and non-endemic settings. High seroprotection rates one month post-vaccination (no simultaneous vaccination) were reported. In the lowest age group (9-18 months), the seroprotection rate was estimated at 99.3% (95% CI: 96.2-100.0) (Feroldi 2014<sup>1</sup>). Similar results were found in Korea (Kim 2013) among 12-24 month-olds (seroprotection 100%, 95% CI: NR) and in Thailand and the Philippines among 12-18 month-olds (seroprotection 95.0%, 95% CI: 93.3-96.3) (Feroldi 2012). Among 36-42 month-olds, 89.7% (95% CI: 75.8-97.1) were seroprotected one month post vaccination. Lower seroprotection rates were found with some serological assays (all genotype 3 challenge viruses) in a small study in India (e.g., against Nakayama strain and Indian strains) (NCT00441259 results). Seroprotection rates were also high in three trials among adults in non-endemic settings (e.g. 99.1% seroprotected (95% CI: 97.5-99.8) adults aged 18-65 in the US and Australia (Torresi 2010); see Table 10.

<sup>2</sup>Lower GMTs and rates of seroconversion were seen in one small study using Nakayama strain (NCT00441259). It was communicated that the virus stock was not good (G. Houillon, personal communication). Similar results were obtained in the same study in participants vaccinated with Nakayama-based inactivated mouse brain-derived vaccine, and no downgrade was applied.

<sup>3</sup>Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>4</sup>High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.

## Reference List

### Clinical Studies in Endemic Settings

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Clinical Trials Data:

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GRADE Table 4. Is there need for a booster dose following immunization with the primary series of **inactivated Vero cell JE vaccine** in individuals living in JE-endemic areas?

**Population** : Immunocompetent individuals living in JE-endemic areas

**Intervention**: Two doses (primary series) of inactivated Vero cell vaccine administered  $\geq 12$  months previously

**Comparison**: Placebo/No vaccination/other JE vaccine

**Outcome** : JE disease (immunogenicity accepted)

<i>Is there need for a booster dose following immunization with the primary series of inactivated Vero cell JE vaccine in individuals living in JE-endemic areas?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious <sup>3,4</sup>	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable <sup>5</sup>	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			Our confidence in the estimate of the effect on the health outcome is limited.
	Conclusion			<p>A primary series of inactivated Vero cell JE vaccines administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least three years after the primary immunization.</p> <p><i>Based on a review of data on IXIARO</i></p>

<sup>1</sup>Five clinical studies following participants 12 months post-primary series, 2 years, or 3 years are available, limiting the full assessment of long-term protection. Data in adults from non-endemic settings suggest a decline in seroprotection rates and GMTs in the 24 months following primary immunization. One study in Austria, Germany, and Romania found seroprotection rates dropped from 99% (95% CI: 96.1-99.7) at one month following the primary series to 82% two years later and 84.9% (95% CI: 78.3-89.7) three years later (Schuller 2008a; CDC 2011); however, these results were obtained from a study population among which some had previously been exposed or vaccinated against Tick-Borne Encephalitis (TBE). Another study in Germany and Northern Ireland (without TBE) found seroprotection rates dropped from 97.3% (95% CI: 94.4-100.0) to 48.3% (95% CI: 39.4-57.3) (Schuller 2009; Dubischar-Kastner 2010a). A booster dose is indicated  $>12$  months after the primary series in non-endemic settings for longer protection. There are limited data in children and in endemic settings. In a study in the Philippines among children aged 2 months – 16 years, the seroprotection rate among 150 children at 3 years was 90%. The GMT decreased between month 2 and month 7, but then was relatively stable through the 3 years of follow up (49-52). (Dubischar-Kastner 2014 and unpublished, quoted with permission from Valneva)

<sup>2</sup>The limited duration of follow up (three years post primary series) of participants in endemic areas (300 children ages 2 months to 17 years) limits the ability to assess the duration of protection in these settings.

<sup>3</sup>Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>4</sup>Data are available from one endemic country (Philippines), with only 150 participants. Other data from adults in non-endemic settings is less applicable (not downgraded twice, as the small population and limited duration of follow up was downgraded under study design).

<sup>5</sup>Data from one study in the Philippines do support a high level (>80%) of effectiveness, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. However, due to the other reasons for downgrading, it was not felt appropriate to upgrade.

## Reference List

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**GRADE Table 5. Is there a need for a booster dose following immunization with one dose of live attenuated JE vaccine in individuals living in JE-endemic areas?**

**Population :** Immunocompetent individuals living in JE-endemic areas

**Intervention:** One dose of live attenuated JE vaccine administered  $\geq 12$  months previously

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** JE disease (immunogenicity accepted)

<i>Is there a need for a booster dose following immunization with one dose of live attenuated JE vaccine in individuals living in JE-endemic areas?</i>				
			Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		2 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>2</sup>	0
		Indirectness	None serious <sup>3</sup>	-2
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable <sup>4</sup>	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>3</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>			<b>We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome</b>
	<b>Conclusion</b>			<p><b>A single dose of live attenuated JE vaccine administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least three years after immunization.</b></p> <p><i>Based on a review of data on CD.JEVAX</i></p>

<sup>1</sup>Two clinical studies are available with data on participants 12 months after vaccination, and for one of these studies, 2 years and 3 years after vaccination. A study from the Philippines measured immunogenicity of a single dose (and no other vaccine administered for at least 28 days) for three years (NCT00412516 results). Among 8 month-olds administered a single dose of live attenuated vaccine, seroprotection was measured at 90.4% (95% CI: 81.9-95.8), 81.1% (95% CI: 71.5-88.6), and 79.3% (69.3-87.2) at 1 year, 2 years, and 3 years post vaccination. Among 10 month-olds, the corresponding seroprotection rates were 86.1% (95% CI: 80.6-90.6), 80.7% (95% CI: 74.6-85.9), and 81.9% (95% CI: 75.8-87.0). These figures are consistent with 12-month immunogenicity results from a study of Thai children aged 9-12 months (Feroldi 2014).

<sup>2</sup>In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)(Zaman 2014). Two lots were not equivalent with a

seroprotection rate difference of -4.33 (-11.94-3.31). It is not known whether the long-term seroprotection rates and effectiveness of the GMP vaccine will be consistent with those seen in studies of the non-GMP vaccine.

<sup>3</sup>Study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>4</sup> High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. Although data for three years is only based on one study, it is supported by three effectiveness studies done at one year or greater after vaccination. A case control study in Nepal estimated vaccine effectiveness to be 95.5% (95% CI: 90.1-99.2) one year following vaccination (Ohrr 2005). A second case-control study in Nepal estimated vaccine effectiveness to be 96.2% (95% CI: 73.1-99.9) five years following vaccination (Tandan 2007). A case control study done in China in the 1990s estimated vaccine effectiveness to be 80% (95% CI: 44-93) up to 14 years after vaccination with a single dose.

## Reference List

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Tandan JB, Ohrr H, Sohn YM, Yoksan S, Ji M, Nam CM, Halstead SB. Single dose of SA 14-14-2 vaccine provides long-term protection against Japanese encephalitis: a case-control study in Nepalese children 5 years after immunization. *Vaccine*. 2007 Jun 28;25(27):5041-5.



**GRADE Table 6. Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?**

**Population :** Immunocompetent individuals living in JE-endemic areas

**Intervention:** One dose of chimeric JE vaccine administered  $\geq 12$  months previously

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** JE disease (immunogenicity accepted)

<i>Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?</i>				
			Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		6 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>	-1
		Inconsistency	None serious <sup>3</sup>	0
		Indirectness	None serious <sup>4</sup>	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable <sup>5</sup>	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>2</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>			<b>Our confidence in the estimate of the effect on the health outcome is limited.</b>
	<b>Conclusion</b>			<b>A single dose of chimeric JE vaccine administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least five years after immunization.</b>  <b>Based on a review of data on IMOJEV</b>

<sup>1</sup>Six clinical studies with data for nearly 2000 subjects provides immunogenicity data for IMOJEV vaccinees at 12 months or longer following vaccination. Among children in endemic settings, four trials followed up participants for 1 year or longer. In one study, between six months and one year post-vaccination, the percent seroprotected dropped from 94.5% (95% CI: 89.4-97.6) to 88.1% (95% CI: 81.6-92.9) (Feroldi 2014<sup>1</sup>). A recent study followed 200 Thai participants vaccinated at 12-24 months for five years (quoted with permission from Sanofi Pasteur, data to be presented at ACPID 2014). Seroprotection rates fell from 80.2% one year post-vaccination to 80.2%, 75.2%, 74.1%, and 65.6% at two, three, four, and five years post-vaccination, respectively. Long-term protection in adults from another study was much higher. Seroprotection rates among Australia military participants aged 18-55 years were 99% (95% CI: 96-100) one month after vaccination, followed by 95% (95% CI: 87-99), 90% (95% CI: 81-96), and 94% (95% CI: 82-99) at one year, two years, and five years post-vaccination (Nasveld 2010a). However, only 46 participants (45% of the original study population) remained in the study at the final time point.

<sup>2</sup>Data are only available from 2 studies with follow-up to 5 years, and there are no effectiveness data, limiting the ability to fully assess long-term protection.

<sup>3</sup>Immunogenicity was higher over time in adults compared with children; there may be heterogeneity in the duration of protection by age.

<sup>4</sup>RCT outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

<sup>5</sup>Due to the lower seroprotection rates reported in children in endemic settings, the small number of studies, and the lack of supporting effectiveness studies, no upgrade was applied.

## Reference List

### RCTs

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Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, Boaz M, Hutagalung Y, Bouckennooghe A, Feroldi E. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. *Vaccine*. 2014 Mar 12. pii: S0264-410X(14)00312-0.

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Clinical Trials Data:

<http://clinicaltrials.gov/ct2/show/results/NCT01092507>

<http://clinicaltrials.gov/ct2/show/results/NCT00441259>

## GRADE Table 7. What is the risk of serious adverse events following vaccination with inactivated Vero cell JE vaccine?

**Population :** Immunocompetent individuals

**Intervention:** Two doses (primary series) of inactivated Vero cell vaccine

**Comparison:** Placebo/No vaccination/Other JE vaccine

**Outcome :** Serious adverse events

<i>What is the risk of serious adverse events following vaccination with inactivated Vero cell JE vaccine?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		11 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>	-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			We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Inactivated Vero cell JE vaccine has an acceptable safety profile.  Based on a review of data on IXIARO

<sup>1</sup>Two pooled analyses of 7 clinical studies (N=3558 vaccinated with IXIARO) and 10 clinical studies (N=4,043 vaccinated with IXIARO) have been published. In adults there was comparable tolerability and reactogenicity with placebo (adjuvant alone) and mouse brain-derived JE vaccine except for local reactions. A significantly lower frequency of severe local reactions was reported for IXIARO compared to mouse brain-derived JE vaccine. In a clinical trial of children aged  $\geq 2$  months to  $< 1$  year in the Philippines, a similar percentage of participants receiving IXIARO (N=131) or Prevnar (N=64) experienced solicited (58.0% vs. 59.4%), unsolicited (72.5% vs. 65.6%), and serious (0% vs. 1.6%) adverse events up to Day 56 after the first vaccination (European Public Assessment Report 2013).

<sup>2</sup> This vaccine has had limited use outside of clinical trials. Post-marketing data are published for the first 12 months of use (Schuller 2011). The ability to detect less common serious adverse events is limited.

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## GRADE Table 8. What is the risk of serious adverse events following vaccination with the live attenuated JE vaccine?

**Population :** Immunocompetent individuals

**Intervention:** One dose of live attenuated JE vaccine

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** Serious adverse events

<i>What is the risk of serious adverse events following vaccination with the live attenuated JE vaccine?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4 RCTs <sup>1,2</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None 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			4
Summary of Findings	Statement on quality of evidence			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			<p>Live attenuated JE vaccine has an acceptable safety profile.</p> <p><i>Based on a review of data on CD.JEVAX</i></p>

<sup>1</sup>Four clinical studies of 1,256 participants contributed to the safety assessment. In children 9 months to 6 years, live attenuated SA 14-14-2 had moderately higher frequency and severity of local and systemic adverse reactions, including fever, compared to chimeric vaccine (Feroldi 2014; Kim 2013). No vaccine-related serious adverse reactions or deaths were reported in RCTs (up to 7 months follow up) except for two cases of pyrexia in children aged 12-23 months.

<sup>2</sup>Post-marketing surveillance has also been done. Based on 23 million doses distributed between 2005-2012, 1426 adverse events were reported (61 per million doses), although this is an underestimate as is typical in particular with developing passive surveillance systems. Case reports were also reviewed, as was an observational study.

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## GRADE Table 9. What is the risk of serious adverse events following vaccination with the chimeric JE vaccine?

**Population :** Immunocompetent individuals living in JE-endemic areas

**Intervention:** One dose of chimeric JE vaccine

**Comparison:** Placebo/No vaccination/other JE vaccine

**Outcome :** Serious adverse events

<i>What is the risk of serious adverse events following vaccination with the chimeric JE vaccine?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		10 RCTs <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>	-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			We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Chimeric JE vaccine has an acceptable safety profile.  Based on a review of data on IMOJEV

<sup>1</sup>10 RCTs contributing approximately 4,000 participants contributed safety data. In children 12 months to 18 years IMOJEV chimeric vaccine had a safety profile comparable with licensed vaccines (Hepatitis A and varicella zoster) in terms of frequency and severity of local and systemic adverse reactions (Chokephaibulkit 2010, Feroldi 2012, Feroldi 2013). There was lower frequency of fever, injection site erythema and swelling after the first compared to second dose. Table 9 also shows the comparability in safety profiles between CD.JEVAX and IMOJEV. IMOJEV also has a comparable safety profile to MMR vaccine when administered to children 12-18 months in Taiwan (Huang 2014). In adults in two RCTs, comparable tolerability and reactogenicity with placebo and a mouse brain-derived JE vaccine were seen with the exception of local reactions (Torresi 2010). Significantly lower frequency of local adverse reactions was reported for IMOJEV than mouse brain-derived vaccine JE-VAX. The majority of adverse events was mild to moderate and resolved within a few days. Only one vaccine related serious AEFI (Pyrexia) was reported within the first month of vaccination and none during a 6-month follow-up. No case of death occurred (Torresi 2010). In addition, two serious adverse events (acute viral illness) possibly related to vaccination with IMOJEV were reported during clinical development in adults (Australian Public Assessment Report 2010).

<sup>2</sup>This vaccine has had limited use outside of clinical trials. The ability to detect less common serious adverse events is limited.

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# Meningococcal A conjugate vaccine roll-out in the African meningitis belt

## Summary update

*prepared by the Meningitis Vaccine Project & partners*

SAGE, October 2014

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### Background

Over the last century sub-Saharan Africa has been plagued by repeated epidemics of meningococcal meningitis. Almost all of the major outbreaks have been caused by group A *Neisseria meningitidis*. Reactive immunizations with polysaccharide vaccines have been used for the last 30 years but have not succeeded in controlling the problem. After the disastrous 1996–1997 epidemic with more than 250,000 cases and 25,000 deaths, there arose renewed interest in developing a preventive strategy based on new meningococcal conjugate vaccines.

In June 2001, the Bill & Melinda Gates Foundation provided core funding for the establishment of the Meningitis Vaccine Project (MVP), a partnership between PATH and the World Health Organization (WHO), with the goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure, and widespread introduction of meningococcal conjugate vaccines. A monovalent group A meningococcal (MenA) conjugate vaccine, MenAfriVac, a registered trademark of the Serum Institute of India, was developed through the MVP. The vaccine was licensed, for use in individuals aged 1 to 29 years, in 2009 and prequalified by WHO in 2010.

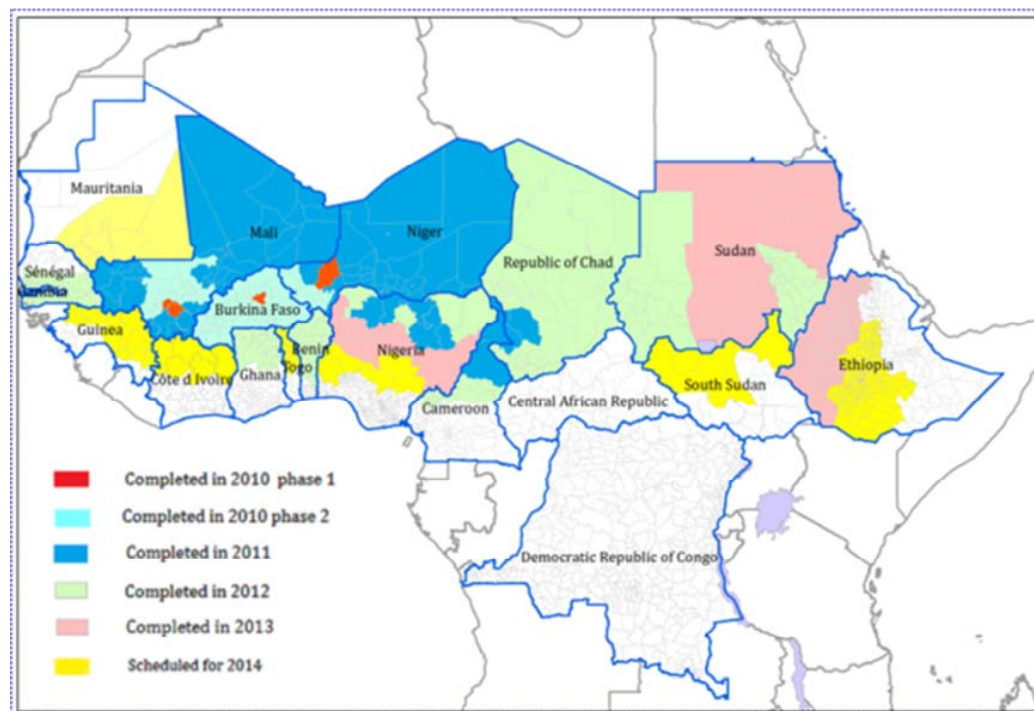
Comprehensive mass immunization campaigns of 1- to 29-year olds with a single dose of MenAfriVac have been a cornerstone of the MenA conjugate vaccine introduction plan. This strategy aims to strongly and immediately protect individuals directly and reduce bacterial carriage and transmission, and thereby rapidly reduce overall disease-related morbidity and mortality rates within the community. As large population groups are immunized within a short period of time, the public health benefits of immunization should be rapidly visible and considerable. Following the initial mass vaccination campaigns, countries will have the option of protecting new birth cohorts through routine immunization, catch-up campaigns, or a mixed approach so that population protection is maintained in the long term against the deadly and devastating meningitis A epidemics. The introduction strategy of the MenA conjugate vaccine was presented as an investment case to the GAVI Alliance Board in June 2008. The GAVI Alliance and Fund Boards approved the strategy of the Meningitis Investment Case committing to support the initial mass preventive campaigns, surveillance, and the launch of introduction into routine immunization in 26 countries of the African meningitis belt. Furthermore, resources were set aside to fund a meningitis vaccine stockpile for emergency outbreaks. The financial sustainability plan, as set forth in the investment case, assumed that countries would be able to mobilize donor funds and health system funds to provide increasing country support to routine immunization. All the 26 countries are expected to have received support for preventive mass immunization campaigns and introduced MenAfriVac by 2016 with high coverage of the target population aged 1 to 29 years.

## Summary of progress

As at 30 September 2014, 17/26 countries have or are in the process of implementing MenA preventive campaigns, as illustrated in Figure 1.

- Over 153 million persons living in 12 countries of the meningitis belt have received one dose of MenAfriVac since the vaccine was first introduced in Africa in 2010, with high overall vaccine coverage, ranging from 93% to 105% (administrative coverage) or 90% to 98% (survey assessed coverage), except in some areas in Northern Nigeria and in Northern Chad with overall administrative coverage reaching 77% to 79%. National campaigns have been completed in 10 countries (Benin, Burkina Faso, Cameroun, Chad, Ghana, Mali, Niger, Senegal, Sudan and The Gambia) and are ongoing in two countries (Ethiopia and Nigeria).
- In 2014 and/or early 2015, two countries will pursue their campaign (fourth and last campaign in Nigeria; second campaign in Ethiopia) and five new countries are expected to launch their first national campaign (Côte d'Ivoire, Guinea, Mauritania, South Sudan and Togo).
- The remaining nine countries are planning to conduct campaigns, immunizing their 1 to 29 year-olds at-risk population in 2015-2016 (Burundi, Central African Republic, Democratic Republic of Congo, Guinea Bissau, Eritrea, Kenya, Rwanda, Tanzania and Uganda), with the expectation of over 250 million persons immunized throughout the 26 belt countries by the end of 2016.

**Figure1. MenAfriVac roll-out in the African meningitis belt from 2010 to 2014**



# Modelling long-term vaccination strategies with MenAfriVac® in the African meningitis belt

Executive summary prepared for SAGE, October 2014\*

## Introduction

The introduction of MenAfriVac® in mass campaigns targeting 1-29 year olds across countries of the African meningitis belt has successfully reduced meningitis incidence and carriage due to *Neisseria meningitidis* group A (NmA) <sup>1-3</sup>. Policy makers now need to consider which subsequent vaccination strategies to recommend in order to sustain population protection in the long term. The overall aim of this project is to develop and apply mathematical models of NmA transmission and disease to investigate the optimal future use of MenAfriVac® to inform these decisions.

Models have become an important tool for immunisation policy makers. They allow a wide range of immunisation strategies to be explored and the uncertainties underlying both model structure and model parameters can be examined. Transmission dynamic models allow the direct and indirect (herd immunity/protection) effects of vaccination programmes to be measured. Only two transmission dynamic models of NmA in the African meningitis belt have been published to date <sup>4 5</sup>. Here, we build on our previous work<sup>4, 6</sup> and utilise recently available evidence from Africa to investigate appropriate policy options for the sustained use of MenAfriVac®.

## Methods

### *Epidemiology of NmA*

A model should be able to capture the key features of the epidemiology of NmA in the African meningitis belt. There are periodic but irregular epidemics of meningococcal meningitis in the meningitis belt which vary in magnitude<sup>7</sup>. Meningitis incidence is highly seasonal; epidemics occur in the dry season and die out with the onset of the rains<sup>7</sup>. Meningococci are spread through respiratory droplets and usually infection results in a period of asymptomatic carriage with disease being a relatively rare event; thus any model attempting to capture the transmission dynamics of meningococci must essentially include the carrier state. Our previous work<sup>4</sup> showed that the complex and irregular timing of epidemics could be explained by the interaction of temporary immunity conferred by carriage of the bacteria together with seasonal changes in the transmissibility of infection. The inclusion of 'natural' immunity following carriage is further supported by studies showing high seroprevalence to NmA<sup>8</sup> before MenAfriVac® introduction. The risk of NmA disease varies by age, affecting mainly children and being uncommon in older adults<sup>9</sup>; carriage prevalence also varies by age so an appropriate model must include age-structuring.

### *Model structure and parameters*

We developed a compartmental model that divides the population into the following states; (1) susceptible, (2) carrier of NmA, (3) disease due to NmA, (4) immune, and in vaccinated populations a mirror of these four states: (5) vaccinated susceptible, (6) vaccinated carrier, etc. The population is further structured into 19 age groups; 0 to <3 months, 3 to <9 months, 9 to <12 months, 1 to 4 years, 5 to 9 years for those aged < 10 years, with 5 year age groups to age 80 years subsequently and continuous ageing between groups. We included seasonal forcing of the transmission and invasion rates using a sinusoidal function with annual stochastic variation to reflect climatic<sup>10</sup> or other external variability.

We considered a range of vaccination strategies, starting five or ten years after initial vaccine introduction, including routine Expanded Programme on Immunization (EPI) immunisation, periodic mass campaigns and EPI plus catch-up immunisation of children born since the initial mass campaigns. Vaccination was implemented in different ways according to the strategy used. For mass vaccination, we assumed that

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vaccination occurred as a discrete event at one point in time. Routine immunisation was implemented as a continuous event, with individuals being vaccinated at 3, 9 or 12 months of age according to the schedule considered. Vaccinated individuals have some protection against both carriage and disease, so that vaccination resulted in both direct and indirect protection.

Model parameters were based on the available literature wherever possible. It was necessary to estimate several parameters, using available data and model fitting techniques to inform these estimates.

The model was coded and run using R-3.1.0, using package deSolve to perform the numerical integration of differential equations. The time step was 1 day. The model was run for 40 years after the initial mass vaccination campaign. For each vaccination strategy the average of 300 simulations was taken and the distribution of the results explored. The model was reviewed by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) in September 2014 (cf. Reports from other Advisory Committees on Immunization: IVIR-AC, session 3 for information, SAGE October 2014). Full details of the model structure are available on request.

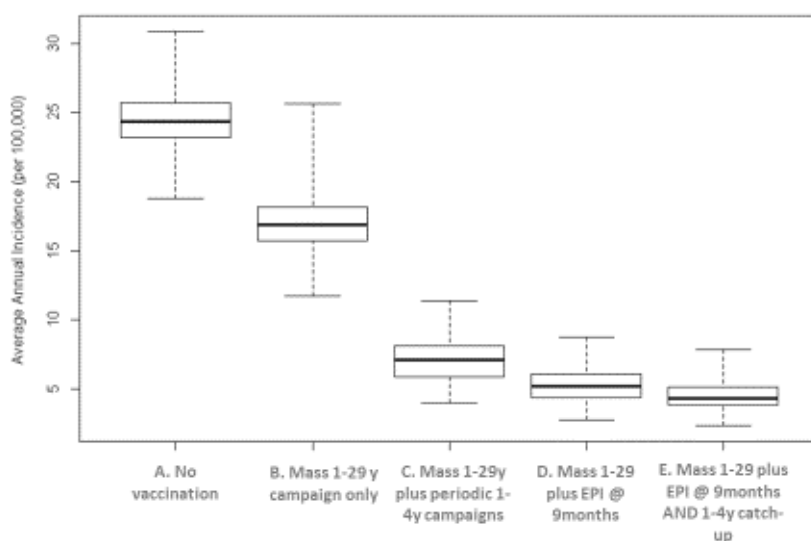
## Results

This model was able to capture the typical annual incidence of meningitis in the pre-vaccine era, with irregular epidemics of varying size.

Following initial mass vaccination of 1-29 year olds at high uptake, disease control was excellent in the short term. With no subsequent immunisation, the model predicted a strong resurgence in disease incidence approximately 15 years after vaccine introduction, assuming an average of 10 years of protection by vaccination. With a shorter duration of protection, disease incidence increased more quickly (e.g. after around 10 years assuming 5 years vaccine protection).

Several long-term immunisation strategies were considered and all were effective in maintaining control of disease (figure, options C, D, E). There was considerable overlap in the distribution of results, but routine EPI immunisation at 9 months of age (D) resulted in lower average annual incidence than regular mass campaigns of 1-4 year olds (C), provided EPI coverage was above ~60%. The strategy with the lowest overall average annual incidence and longest time to resurgence was introduction into EPI at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated 1-4 year olds (E).

*Figure: Box plot to show the median, inter-quartile range and full range of the predicted annual incidence per 100,000 for different immunisation strategies in the 40 years following vaccine introduction from 300 model simulations*



## Discussion

We developed a model of NmA transmission and disease that was able to adequately describe the epidemiology observed in the African meningitis belt. We simulated the initial mass vaccination campaigns and predicted a period of very low incidence for at least ten years following these mass campaigns, even when assuming a short duration of protection of around 5 years. The indirect effects of the vaccine were clearly important in maintaining this low incidence post-introduction; we assumed a high degree of protection against carriage, consistent with the observed data<sup>1,3</sup>. Of the long-term immunisation strategies, we predicted that a 'combination' strategy of routine EPI vaccination after 5 years together with a catch-up campaign targeting children aged 1-4 years born after the initial campaigns was the most effective.

Our conclusions are different to another model of MenAfriVac<sup>®</sup> vaccination, which suggested that periodic mass campaigns were superior to routine EPI. Although there are potentially important differences in model structures and implementation, this is probably largely because the duration of protection they assumed was much greater (essentially lifelong) for children immunised in campaigns than through EPI, whereas we assumed that protection in 1-4 year olds would be similar to those immunised at the age of 9 months, based on data from MVP (Meningitis Vaccine Project) MenAfriVac<sup>®</sup> trials (<http://www.meningvax.org/research-development.php>).

Our model structure was based upon extensive previous work that used a range of deterministic models, to explore the importance of seasonality and immunity following colonisation<sup>4</sup>. As such, we feel we have good understanding of the underlying system dynamics. We extended our previous model to incorporate vaccination, age structuring and stochastic variation in seasonal forcing (to capture unknown external forces including for example dust or humidity conditions<sup>11</sup>).

Some model parameters were known, others could be inferred or estimated from existing data and in some cases where parameters were unknown a plausible range was defined. More information on a range of parameters would be desirable, including the duration of temporary immunity following carriage, contact patterns and age-specific duration of vaccine protection; the latter being a particularly influential in determining the relative impact of different immunisation strategies. Our work would also benefit from greater exploration of structural and parameter uncertainty; this is planned for the future.

Acknowledging the strengths and weaknesses of our approach, these results can be used to inform policy recommendations for long term vaccination strategies with MenAfriVac<sup>®</sup>.

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# Results from the MenA conjugate vaccine (PsA-TT) randomized controlled trials in infants and young children

## Executive summary

*prepared by the Meningitis Vaccine Project & partners*  
SAGE, October 2014

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### Background and vaccine development rationale

To overcome the limited immunogenicity of the meningococcal group A (MenA) polysaccharide (Ps) vaccine, the protein conjugation technology was applied to the development of MenAfriVac® (Serum Institute of India Ltd.). The MenA Ps is covalently conjugated to a protein, which acts as an immunologic carrier. MenAfriVac is a purified MenA polysaccharide tetanus toxoid (TT) conjugated vaccine (10 µg of conjugate per dose). In December 2009, Drug Controller General of India (DCGI), the Indian National Regulatory Agency, granted MenAfriVac a Marketing Authorization (MA) and WHO prequalification was obtained on 23 June 2010.

Efficacy assessment was based on serological data showing that MenAfriVac induces superior functional immune responses, both in terms of post vaccination serum bactericidal antibody (SBA) levels and induction of immunological memory, when compared to meningococcal A Ps containing vaccines. MenAfriVac's current indication is active immunization of individuals aged 1 to 29 years against invasive meningococcal disease caused by *Neisseria meningitidis* group A.

From December 2010, MenAfriVac was introduced in Africa (first in Burkina Faso, Mali and Niger) with mass vaccination in the age group of 1-29 years old. One year after vaccine introduction, experience from Burkina Faso provided early evidence that mass vaccination was associated with a significantly reduced risk of meningitis in the targeted population, as well as among the unvaccinated age groups (less than 1 year and over 29 years of age) suggesting vaccine induced herd protection [1]. The data indicate a virtual disappearance of group A meningococci and the lowest number of acute meningitis cases in the past 15 years in Burkina Faso. This latter finding is consistent with the disappearance of *N. meningitidis* group A carriage among both vaccinated and unvaccinated individuals in Burkina Faso within one year of vaccination implementation [2]. The phased introduction of MenAfriVac in Chad just prior to the 2012 epidemic provided the opportunity to assess the effectiveness of the vaccine by comparing incidence rates of meningitis in vaccinated and unvaccinated areas over the same observation period (2.48/100,000 versus 43.8/100,000) indicating a 94% reduction in crude incidence rate. Furthermore, a 98% decrease in the prevalence of MenA carriage was shown in all age groups living in one vaccinated area, as compared to recent pre-vaccination time period [3]. Adverse events following immunization (AEFIs) were monitored in approximately 11 million MenAfriVac vaccinees in Burkina Faso in 2010, through both countrywide enhanced passive and sentinel active surveillance. The observations did not indicate any outstanding safety issue [4]. Safety reports periodically updated after administration of more than 153 million doses have confirmed the reactogenicity and safety profile of MenAfriVac. Altogether these observations indicate an acceptable safety profile, high vaccine efficacy and establishment of herd protection against MenA disease of MenAfriVac. Introduction of MenAfriVac for mass vaccination in the age group of 1-29 year old has now been implemented in 12 African countries of the meningitis belt since December 2010, with the expectation to control group A meningococcal disease.

Although MenAfriVac is highly efficacious, MenA epidemics are likely to return in countries where mass vaccination have been introduced because the susceptible population, mainly the new birth cohorts, will increase yearly. It will therefore be critical to ensure that population immunity is sustained following the initial mass vaccination in the age group of 1-29 year old. Maintaining population immunity could then be achieved either through repeated periodic mass immunization campaigns that would target the age group of 1-4 year old, or through routine vaccination of infants. With this latter approach in mind, two options, which could be considered for the incorporation of MenAfriVac into the Expanded Programme on Immunization (EPI) schedule depending on the age of vaccination, have been evaluated in the studies presented here.

- Option 1: When immunization starts in early infancy two doses of MenAfriVac are administered: one dose at age 14 weeks (with PENTA3 and OPV) and a second dose at age 9 months (with Measles and Yellow Fever vaccines, and possibly Rubella vaccine).

- Option 2: When administration starts later, one dose of MenAfriVac is administered at age 9-12 months (with Measles and Yellow Fever vaccines, possibly Rubella vaccine), followed if deemed necessary by a 2<sup>nd</sup> dose at age 15-18 months.

Whereas the antigenic content of MenAfriVac, i.e. 10 µg polysaccharide A conjugated to tetanus toxoid (PsA-TT) was initially selected in line with other meningococcal conjugate vaccines licensed at time of its development, dose ranging studies were conducted to define the infant dosage. Indeed, clinical trials were designed to define the optimal dosage and immunization schedules that would fit within the EPI in infants living in the African meningitis belt. Because of the very high demonstrated immunogenicity of MenAfriVac in 12-23 month old children [5], and the likelihood that more than one dose might be required for effective immunization of the youngest infants, it seemed appropriate to assess reduced antigenic content. Further, the risk of immunological interference with co-administration of vaccines is unpredictable and occurs most frequently in early life. These concerns are thus related to both the need to co-administer a range of antigens simultaneously to infants and a relatively immature immune system of recipients [6]. Furthermore, consideration was given to the clinical experience with other conjugated vaccines; including an investigational group A and C meningococcal conjugate vaccine [7]. Finally, these considerations are also consistent with existing meningococcal conjugate vaccines that contain oligo- or polysaccharides quantity less than 10 µg.

Hence, two studies (PsA-TT-004 and PsA-TT-007) were conducted to evaluate reduced antigenic contents of the vaccine compared to MenAfriVac, - 5 µg and 2.5 µg polysaccharide A conjugated to tetanus toxoid, in one trial carried out in the younger age group (14 weeks) and - 5 µg polysaccharide A conjugated to tetanus toxoid, in the other trial conducted in 9 month old infants, when given according to the proposed immunization schemes fitting in the EPI schedule.

The safety and immunogenicity data support the use of MenAfriVac, 5µg dosage, for active immunization for the protection against invasive meningococcal disease caused by *Neisseria meningitidis* group A in young children from the age of 3 months to 24 months.

## Overview of clinical immunogenicity/efficacy and safety studies

For the purpose of the present indication variation, the clinical development plan of the MenAfriVac 5 µg conjugate vaccine included two additional clinical studies, conducted between November 2008 and September 2013, in the intended target age population, living in two countries of the African meningitis belt: a phase II dose ranging study (PsA-TT-004) conducted in healthy infants and toddlers in Ghana and a phase III study (PsA-TT-007) also conducted in healthy infants and toddlers in Mali. A detailed description of these two studies is presented in Table 1. In both double-blind randomized controlled studies, the reference group received the 10 µg dosage (MenAfriVac). Two additional dosages, 5 µg and 2.5 µg (in study PsA-TT-004), or one additional dosage, 5 µg (in study PsA-TT-007), were assessed. Study vaccines were concomitantly given with EPI and rubella

vaccines. A control group in each of the studies received only EPI vaccines [8]. A total of 2700 subjects were enrolled and randomized and 2698 were vaccinated in the two clinical studies.

The studies were designed to assess safety and immunogenicity of different antigen amounts of PsA-TT vaccine and different schedules before 2 years of age. In addition, both studies assessed the ability of PsA-TT to induce immune memory and to evaluate the safety and immunogenicity of concomitantly administered EPI and rubella vaccines in this age group. The phase II study (PsATT-004) also evaluated the antibody persistence till 36 months of age. On the average subjects were followed up for at least 7 months in study PsA-TT-007 and for 30 months in study PsA-TT-004 since enrolment.

The evaluation of the efficacy of the PsA-TT 5 µg vaccine was based on its ability to induce levels of bactericidal antibodies non-inferior to those induced by MenAfriVac, the reference licensed PsA-TT 10 µg vaccine [9]. The field experience with use of MenAfriVac in countries of the African meningitis belt has since 2010 provided compelling evidence that the vaccine prevents meningococcal invasive disease as well as infection. This confirms experience with other licensed meningococcal vaccines for which data indicate that the presence of induced serum capsular bactericidal antibodies (SBA) correlates to protection and, therefore, can be considered a valid surrogate marker of protection [10]. A primary criterion in determining noninferior immunogenicity of the lower dosages of vaccine in comparison with immunogenicity of the reference 10 µg vaccine dosage was the percentage of vaccinees having a fourfold or greater response in bactericidal antibody in relation to the baseline values [11]. The antibody assays used to evaluate immunogenicity were standardized to yield reproducible data and fully validated. The functional antibody titer in human sera to MenA was measured with a serum bactericidal antibody assay using baby rabbit complement (rSBA) [12].

The primary serological assay used to assess the immunogenicity of the PsA-TT vaccine was thus a validated rSBA to measure functional antibody activity in human sera to group A *Nm*. This is consistent with the World Health Organization (WHO) recommendation for the evaluation of meningococcal polysaccharide and conjugate vaccines [9]. The primary endpoint in study PsA-TT-004 was the percentage of subjects who showed a seroconversion for MenA antibodies measured by rSBA assay, i.e. a 4-fold or higher response in post-immunization serum MenA rSBA antibody titer with respect to pre-immunization serum MenA rSBA antibody titer, at 28 days after each vaccine dose. An almost identical endpoint, the percentage of subjects who showed a seroconversion for MenA antibodies measured by rSBA assay at 28 days after the last vaccine dose, was one of the primary endpoints in study PsA-TT-007. A co-primary endpoint, geometric mean titer (GMT) of MenA antibody titers measured by rSBA assay at 28 days after the last vaccine dose, is included in the study PsA-TT -007.

The main secondary immunogenicity endpoints in the clinical studies included: (1) for MenA antibodies measured by rSBA: percentage of subjects reaching a threshold of 1:128 for MenA rSBA antibody titer and geometric mean titer (GMT); (2) for MenA capsular polysaccharide antibodies measured by ELISA [13]: percentage of subjects who showed a seroconversion for MenA IgG ELISA concentrations, i.e. a 4-fold or higher response in post-immunization MenA IgG ELISA concentration with respect to pre-immunization concentration; percentage of subjects reaching a threshold of 2 µg/ml for MenA IgG ELISA concentrations and geometric mean concentration (GMC). For immune response to EPI antigens, percentage of subjects with specific IgG concentration or neutralizing antibody titer above predefined discriminatory thresholds and GMC/GMT for each of the specific IgG concentration or neutralizing antibody titer.



**Table 1** Overview of clinical immunogenicity/efficacy and safety studies

Study ID Phase	Number of Study Centers, Locations	Study start Study end Total enrollment/ goal	Design Control type	Dose, Route	Study & Control Vaccines	#Subjects by arm	Study objective	Duration	Gender F/M Median age at first vaccination (Range)	Primary endpoint(s)	# subjects with at least 1 dose (2 doses) PsA-TT 10µg PsA-TT 5µg PsA-TT 2.5µg
PsA-TT-004 II	1, Ghana	November 2008 to May 2012 1200/1200	Randomized double-blind control dose- ranging	1 or 2 doses of different PsA-TT dosages  IM	PsA-TT 10 µg PsA-TT 5 µg PsA-TT 2.5 µg  EPI vaccines	200 per group	Safety and immunogenicity, concomitant administration with EPI vaccines, immune persistence	33 months	597/601*, 14 weeks (min-max, 13-18 weeks)	4-fold or higher response in rSBA titers**	579 (192)  200 (191)  200 (194)
PsA-TT 007 III	1, Mali	March 2012 to September 2013 1500/1500	Randomized double-blind control dose- ranging	1 or 2 doses of different PsA-TT dosages  IM	PsA-TT 10µg PsA-TT 5µg  EPI vaccines	300 per group	Safety and immunogenicity, concomitant administration with EPI vaccines	7 to 10 months	725/775, 9 months (min-max, 9- 13 months)	4-fold or higher response in rSBA titers and rSBA geometric mean titers (GMT)***	600 (280)  600 (279)

\* 2 volunteers noted not to be qualified before vaccination

\*\* Sero-conversion from baseline just prior to vaccination to 28 days after vaccination with two doses

\*\*\* Sero-conversion from baseline just prior to vaccination to 28 days after vaccination, GMT ratio 28 days after last vaccination

## Clinical trials

Both clinical studies, PsA-TT-004 and PsA-TT-007, were conducted in accordance with the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) regulations and guidelines, and all applicable regulatory and ethical requirements.

### STUDY PsA-TT-004

The study was conducted in Navrongo, Ghana from November 2008 to May 2012 (Principal Investigator: Dr. Abraham Hodgson, Navrongo Health Research Centre, Ghana Health Services, Navrongo, Ghana).

The primary objective was to demonstrate that the MenAfriVac 5 µg vaccine and the 2.5 µg PsA-TT vaccine elicited antibody responses that showed non-inferiority to those achieved by the 10 µg PsA-TT vaccine, i.e. MenAfriVac, 28 days after each dose. Hence, this study includes a double-blind, randomized, and controlled comparison of the immunogenicity and the safety of three different dosages of MenAfriVac (group 1A), MenAfriVac 5 µg (group 1B), and 2.5 µg PsA-TT (group 1C) - when administered to healthy infants in a two dose schedule at 14 weeks and 9 months of age. In addition, the safety and immunogenicity of one dose of MenAfriVac when given at 9 months (group 2) or at 12 months (group 3) of age were also evaluated. Group 4 received only the recommended EPI vaccines, i.e. OPV and DTwPHBVHib at 14 weeks of age, Measles and Yellow Fever vaccines at 9 months of age, and DTwPHBVHib at 12 months of age. PsA-TT immunogenicity data were obtained before and 28 days after each dose of PsA-TT and up to the age of 24 and 36 months, i.e. 18 to 27 months after the last PsA-TT dose depending on the study group. The immunogenicity of concomitantly administered vaccines - OPV, DTwPHBVHib, Measles and Yellow Fever according to the EPI, was also measured one month after vaccination.

The study was powered to demonstrate non-inferiority of the MenA rSBA antibody response elicited by MenAfriVac 5 µg and the 2.5 µg dosage of PsA-TT to that of MenAfriVac. The percentage of vaccinees with a 4-fold or higher response in rSBA titer compared to baseline was used as primary immunogenicity endpoint and the upper limit of the 97.5% confidence interval of the difference in response rates between MenAfriVac group (group 1A) and lower dosage group (group 1B or group 1C) was set to be less than 10% (a predefined non-inferiority margin) in order to claim non-inferiority of lower dosage of PsA-TT to MenAfriVac [14;15]. Differences in response rates that are within 10% are unlikely to represent a medically significant change in vaccine efficacy. Such predefined margin of non-inferiority has generally been considered acceptable for the purpose of evaluation of other conjugate vaccines recently licensed [16;17]. Under the assumptions of a response rate of 90% for MenAfriVac in group 1A, power set at 80% and one-sided alpha risk at 0.0125, the required sample size for the evaluable immunogenicity population was 188 per study group.

Twelve hundreds (1200) infants aged 14 to 18 weeks whose medical history did not show any obvious health problem and who had been fully vaccinated according to the local EPI schedule were randomly allocated to one of six groups: 1A, 1B, 1C, 2, 3 and 4 (200 each). Overall 157 subjects (13.1%) were discontinued between the age of 14 weeks (visit 1) and 36 months (visit 11). Discontinuation was predominantly due to lost to follow up (29.9%), out-migration (26.8%), protocol violation (21.7%) and deaths (11.5%). The per protocol population for immunogenicity evaluation 28 days after the second dose at 9 months of age comprised of 180 infants in group 1A, 184 infants in group 1B and 185 individuals in group 1C providing a power higher than 80% to the primary statistical analysis with extremely high percentages of subjects with a seroconversion 28 days after the second dose. A total of 1043 subjects completed the last visit at the age of 3 years (visit 11). They were distributed in the 6 groups as follows: 176 in group 1A, 178 in group 1B, 169 in group 1C, 171 in group 2, 181 in group 3 and 168 in group 4. These figures indicate a high completion rate for a trial lasting 33 months and an acceptable balance among the study groups.

At time of enrollment, there were no medically relevant differences in demographic and clinical criteria. Baseline rSBA GMTs were very low, ranging from 2.04 (group 1C) to 2.29 (group 1B) in the overall group 1. Although the slight variation reached statistical significance, baseline rSBA levels can be considered comparable.

#### Analysis of immunogenicity data

Per protocol evaluable population was the primary data set for the evaluation of immunogenicity data. Of note, the analysis in the ITT population yielded similar results.

Following the first dose at 14 weeks of age, the percentages of infants with a seroconversion (defined as at least a 4-fold response in MenA rSBA antibody titers 28 days after vaccination with respect to baseline) were high in all groups: 93.9% (95% CI 89.3 - 96.9), 94.1% (95% CI 89.7 - 97.0), and 96.7% (95% CI 93.0 - 98.8) in groups 1A, 1B, and 1C, respectively. The differences (and 97.5% CI) in percentage of subjects with a seroconversion were -0.2% (-6.3 - 5.7) between Groups 1A and 1B and -2.9% (-8.6 - 2.4) between groups 1A and 1C. Following the second dose at 9 months of age, infants with a seroconversion in relation to baseline were: 99.4% (95% CI 96.8 - 100.0), 99.4% (95% CI 96.8 - 100.0), and 99.4% (95% CI 96.9 - 100.0) in groups 1A, 1B, and 1C, respectively. The differences (and 97.5% CI) in percentage of subjects with a seroconversion were -0.0% (-3.4 - 3.3) between groups 1A and 1B and -0.0% (-3.4 - 3.2) between groups 1A and 1C. Hence relating to the primary study objective, non-inferiority of MenAfriVac 5 µg and 2.5 µg PsA-TT vaccine to MenAfriVac was demonstrated after the first dose given at 14 weeks of age (window 14 to 18 weeks) and after the second dose at 9 months of age (window 9 to 12 months).

There was no difference among the three study groups with respect to the secondary endpoints of the MenA rSBA response, i.e. the percentage achieving an antibody titer  $\geq 1:128$  and GMTs after the first and second dose. One month after the second dose, GMTs of MenA rSBA titer were 4932.68 (95% CI 4239.02 - 5739.86), 5048.63 (95% CI 4429.28 - 5754.59), and 4238.04 (95% CI 3560.38 - 5044.67) in Groups 1A, 1B and 1C, respectively, indicating very high antibody levels compared to the controls, 3.25 (95% CI 2.57 - 4.12) in group 4. They were also higher than levels achieved by one dose of MenAfriVac given at 9 months of age to naïve infants of group 2, 2845.72 (95% CI 2346.96 - 3450.47), demonstrating the priming effect of the first dose given at 14 weeks. In group 3, one dose of MenAfriVac at 12-18 months of age (median 15 months) induced a high GMT of MenA rSBA antibody titer, 3196.90 (95% CI 2667.08 - 3831.97). Comparison of GMTs of MenA rSBA antibody titer achieved one month after one dose of MenAfriVac in groups 1A, 2 and 3 indicates an age related increase, which is likely attesting to the maturation of the infant immune system.

The design of the study provides data on the persistence of antibody until the age of 24 months (i.e. 12 to 15 months after last dose in groups 1 and 2) and until the age of 36 months (i.e. 18 to 27 months after the last dose in groups 1 and 2). High levels of MenA rSBA antibody were maintained until the age 36 months. Whereas antibody levels dropped substantially during the first 12-15 month time period after the last PsA-TT vaccine dose, the percentages of subjects with MenA rSBA antibody titer  $\geq 1:128$  remained high: 85.0% (95% CI 78.7 - 90.1), 86.8% (95% CI 80.8 - 91.4), 87.8% (95% CI 81.8 - 92.4), 82.4% (95% CI 75.8 - 87.8), 92.5% (95% CI 87.6 - 96.0) in groups 1A, 1B, 1C, 2, and 3, respectively vs. 47.9% (95% CI 40.1 - 55.8) in the control group 4. Furthermore, GMTs are indicative of long-term seroprotection in all vaccinated groups. At the age of 24 months, GMTs for MenA rSBA antibodies were: 343.73 (95% CI 256.02 - 461.50), 419.53 (95% CI 309.45 - 568.78), 480.55 (95% CI 358.05 - 644.96), 369.50 (95% CI 261.00 - 523.10) and 790.40 (95% CI 593.85 - 1052.01) in groups 1A, 1B, 1C, 2, and 3, respectively vs. 30.57 (95% CI 19.60 - 47.67) in the control group 4. There were no further decrease in antibody levels between 24 and 36 months of age. At the age of 36 months, the percentages of subjects with MenA rSBA antibody titer  $\geq 1:128$  remained high: 81.7% (95% CI 74.9 - 87.3), 88.1% (95% CI 82.2 - 92.6), 87.3% (95% CI 81.0 - 92.0), 88.1% (95% CI 82.1 - 92.7), 91.2% (95% CI 85.9 - 95.0) in groups 1A, 1B, 1C, 2, and 3, respectively vs. 69.9% (95% CI 62.0 - 76.9) in control Group 4. GMTs for MenA rSBA antibodies were: 355.97 (95% CI 242.22 - 523.13), 553.75 (95% CI 402.75 - 761.37), 483.44 (95% CI 333.75 - 700.28), 488.17 (95% CI 344.25 - 692.26) and 812.75 (95% CI 597.86 - 1104.87) in groups 1A, 1B, 1C, 2, and 3, respectively and 139.28 (95% CI 88.57 - 219.01) in control group 4. Gradually increasing MenArSBA antibody levels were noted among controls from the age of 10 months to 36 months. Such an observation may be the result of

encountering group A meningococcus, other meningococcal serogroups, other *Neisseria* species such as *N. lactamica* which may play a role in the development of immunity to meningococcus, or cross reacting enteric bacteria or moieties [18-20]. At age of 24 months, the differences (and 97.5% CI) in percentage of subjects with a seroconversion were 0.1% (-7.7 - 7.8) between Groups 1A and 1B and -2.4% (-10.0 - 5.0) between Groups 1A and 1C. At age of 36 months, the differences (and 97.5% CI) in percentage of subjects with a seroconversion were -8.5% (-17.4 - 0.0) between groups 1A and 1B and -4.5% (-13.9 - 4.9) between groups 1A and 1C. Non-inferiority of MenAfriVac 5µg and the 2.5 µg dosage to MenAfriVac was demonstrated at the ages of 24 and 36 months, in terms of the immune response expressed as percentage of subjects with a seroconversion. The conclusion was confirmed by percentage of subjects with MenA rSBA titer  $\geq 1:128$  or GMT of MenA rSBA antibodies at the ages of 24 and 36 months.

#### Analysis of reactogenicity and safety data

Safety evaluation included monitoring of immediate reactions within one hour of vaccination, solicited reactions and AEs during a time window of 4 days, as the majority of local and systemic reactions occur usually within 2 days of vaccination, and AEs for four weeks after each vaccination. Serious adverse events were recorded during the entire study duration. All safety evaluations were performed on the ITT population (there was no instance of wrong treatment assignment).

#### ***Immediate reactions***

There were no immediate local reactions noted at the site of PsA-TT injection for any dose given at 14 weeks, 9 months or 12 months of age. Immediate mild and transient systemic reactions were recorded in 3 subjects following concomitant vaccinations with Measles and Yellow fever at 9 months of age [1 subject in Group 1B, 2 subjects in pooled Control Group (Groups 3 and 4)] and following vaccination with DTwPHBVHib only at 12 months of age in one subject in group 1A, one subject in group 1B, and one subject in group 4, but none after concomitant vaccination with PsA-TT 10 µg in group 3.

#### ***Solicited local reactions***

Local reactions at the site of injection of PsA-TT at 14 weeks of age were predominantly mild and transient tenderness. Induration were less frequent, lasted a little longer and never reached 50 mm of diameter. Local reactions were noted in 11.5%, 8.0% and 12.5% of subjects at the site of PsA-TT injection for groups 1A, 1B and 1C, respectively, whereas higher rates were observed at the DTwPHBVHib injection site (23.0% of subjects in group 1B to 30.5% in group 1C). Local reactions at the site of PsA-TT injection were less common after the second dose of PsA-TT given at 9 months of age, with frequencies of 4.7%, 3.7% and 2.1% of subjects for groups 1A, 1B and 1C, respectively, suggesting a trend for a dosage related increase in local reactions. Local reactions at the site of PsA-TT injection were less frequent in naïve subjects receiving a first dose of MenAfriVac (Group 2). Mild and transient tenderness was the most common reaction and no induration reached 50 mm of diameter. Local reactions at the site of PsA-TT injection after a first dose of MenAfriVac given at 12 months of age were noted in 8.9% of group 3 subjects whereas higher rates were noted at the DTwPHBVHib injection site (28.4%) in the same group. Mild and transit tenderness was the most frequent reaction and no induration reached 20 mm of diameter. Altogether these observations indicate that local reactions at the injection site of PsA-TT are mainly mild and transient and do not increase after the second dose. The data also suggest that concomitant administration of DTwPHBVHib which is more reactogenic may influence reporting of local reactions at the PsA-TT site.

#### ***Solicited systemic reactions***

After the first PsA-TT dose given simultaneously with DTwPHBVHib, similar rates of systemic reactions were reported in 12.5% of subjects in group 1A, 11.0% of subjects in group 1B and 14.0% of subjects in group 1C and 9.9% of subjects in the pooled control group (pooled group of groups 2, 3, and 4). Systemic reactions were predominantly mild and transient. The most common systemic reactions were diarrhea (ranging 6.5% in group 1B to 8.0% in group 1C), persistent crying (ranging from 2.5% in groups 1A and 1B to 3.0% in group 1C), loss of appetite (ranging from 1.0% in group 1B to 2.5% in group 1A), and vomiting (ranging from 0.5% in group 1B to 2.0% in group 1C). All fevers were  $\leq 38.9^{\circ}\text{C}$ . After the second dose given simultaneously with Measles and Yellow Fever, similar rates of systemic reactions were reported in 4.1% of subjects in group 1A, 6.3% in group 1B and 3.1% of group 1C, and 4.4% in the pooled control group (pooled group of groups 3 and 4).

Systemic reactions were predominantly mild and transient. Among the group 1, the most common systemic reactions were diarrhea (ranging 0.5% in group 1C to 4.2% in group 1B), fever (ranging from 1.0% in group 1A to 2.1% in groups 1B and 1C), and vomiting (ranging from 0% in group 1C to 1.0% in group 1B). All fevers were  $\leq 39.9^{\circ}\text{C}$ . Rate of systemic reactions in group 2 (first dose of MenAfriVac administered with Measles and Yellow Fever vaccines) was 6.9%.

#### ***Adverse events within 28 days of dose 1***

Adverse events (including local and systemic reactions ongoing beyond Day 4) within 28 days of the first vaccination given at 14 weeks of age occurred with similar frequency and were reported in 42.0% of subjects, 42.5%, 46.0% and 39.6% in groups 1A, 1B, 1C and the pooled control group (pooled group of groups 2, 3, and 4), respectively. The AEs, other than persisting reactions, were reported in 35.0% of subjects, 35.0%, 35.0% and 31.3% of groups 1A, 1B, 1C and the pooled control group, respectively. The most commonly reported adverse events were gastroenteritis occurring in 13.4% of subjects, induration predominantly at the DTwPHBVHiB injection site that did not resolve by Day 4 or that began after Day 4 (11.5%), respiratory tract infection (11.2%) and malaria (8.3%). The percentages of infants reporting each specific event were similar among study groups. All related AEs were local or systemic reactions ongoing beyond Day 4, or with onset after Day 4.

#### ***Adverse events within 28 days of dose 2***

Rates of adverse events (including local and systemic reactions ongoing beyond Day 4) within 28 days of vaccination given at 9 months were similar and reported in 46.6% of subjects, 41.4%, 45.4%, 40.2% and 46.4% in groups 1A, 1B, 1C, 2 and the pooled control group (pooled group of groups 3 and 4), respectively. The most commonly reported adverse events were malaria occurring in 20.8% of subjects, respiratory tract infection (18.0%) and gastroenteritis (11.0%). The percentages of infants reporting each specific event were similar among study groups, with the exception of on-going systemic reactions, mainly diarrhea, that were more frequent in the pooled PsA-TT group than in the pooled control group, 4.8% versus 1.4%. Overall, adverse events were transient and of mild or moderate intensity in most of the cases, and unrelated to any vaccine except for solicited post-immunization reactions ongoing (or occurring) beyond Day 4. The rates of AEs, other than on-going reactions, occurring within 28 days of vaccination increased with age at vaccination: overall percentages were 33.1 % of subjects after vaccination at 14 weeks of age, 43% after vaccination at 9 months of age and 49.2% after vaccination at 12 months of age. Infections and infestations were largely the predominating causes of AEs within 28 days of vaccination, including gastroenteritis, malaria and respiratory tract infections. The increasing rates of malaria and to a lesser extent of respiratory tract infections, with age contributed to these observations.

#### ***Serious adverse events (SAEs) and deaths***

Overall, there were 408 serious adverse events reported in the study. Most of them (89.0%) were due to infective causes, 5.9% from blood and lymphatic disorders, 2.7% from injuries and poisoning, and 2.4% from other causes including respiratory, gastrointestinal, congenital, metabolic, nervous, general, and ear and labyrinth disorders. Among the SAEs classified as “Infections and infestations”, severe malaria and gastroenteritis of moderate intensity were most commonly reported. Three cases of meningitis were reported during study period, two were due to *N. meningitidis* group W135 (one each in group 1C and group 1A) and one (group 1A) due to an unspecified pathogen. SAEs with onset within 28 days of the first (14 weeks of age), second (9 months of age) and third vaccination (12 months of age) were 11, 22 and 9 cases (2 cases with day of onset beyond 28 days after the third vaccination were included due to late follow-up visit), respectively and were not found to occur at significantly different rates among the PsA-TT groups and the pooled control groups. They were all considered unrelated to study vaccines except the 2 following cases which were one case of febrile seizure that occurred on day 0 and resolved within 24 hours (group 3 after concomitant vaccination of MenAfriVac and DTwPHBVHiB) and one case of facial oedema with onset on the day of vaccination and resolving within 48 hours (group 1A after concomitant vaccination of the second dose of MenAfriVac and DTwPHBVHiB). Twenty subjects died during the entire study period. Eighteen (90%) died of infective causes, and one each died of malnutrition and foreign body aspiration. None of the 20 deaths was assessed related to the study vaccine.

## STUDY PsA-TT-007

The study was conducted in Bamako (Mali) from March 2012 to September 2013 (Principal Investigator: Professor Samba Sow, Centre pour le Développement des Vaccins, CVD-Mali, Ministry of Health, Bamako, Mali).

The primary objective of study PsA-TT-007 was to compare 28 days after the last vaccination of PsA-TT the immunogenicity of two PsA-TT vaccine dosages, MenAfriVac 5µg and MenAfriVac, when administered in a one-dose schedule at 9 months of age or a two-dose schedule at 9 and 15 months of age, in order to determine the optimal dosage and schedule fitting in routine immunization sessions, in co-administration with EPI vaccines (Measles, Yellow Fever and Rubella vaccines). In this double-blind, randomized, and controlled study, healthy infants aged 9 months were randomly allocated to one of the following groups to receive:

- Group 1: Two doses of PsA-TT vaccine concomitantly with Measles and Yellow Fever vaccines at 9 months of age and with combined Measles-Rubella vaccines at 15 months of age, with Group 1A: MenAfriVac® and Group 1B: MenAfriVac 5µg;
- Group 2: One single dose of PsA-TT vaccine concomitantly with Measles and Yellow Fever vaccines at 9 months of age and one dose of combined Measles-Rubella vaccines at 15 months of age, with Group 1A: MenAfriVac® and Group 1B: MenAfriVac 5µg;
- Group 3: One dose of Measles and Yellow Fever vaccines at 9 months of age and one of combined Measles-Rubella vaccines at 15 months of age (control group).

The five-group design allowed the evaluation of two different formulations (MenAfriVac 5 µg and MenAfriVac) and the relevance of a booster dose (two-dose schedule with MenAfriVac 5µg and MenAfriVac). Furthermore, the safety profile of the study vaccine given concomitantly with the recommended EPI vaccines was assessed in reference to controls (group 3), as well as possible immunological interferences due to simultaneous administration.

The study was powered to demonstrate non-inferiority of the MenA rSBA antibody response elicited by the two-dose schedule with MenAfriVac 5µg (group 1B), one-dose of MenAfriVac (group 2A) or one-dose of MenAfriVac 5µg (group 2B) to the immune response elicited by the two-dose schedule with MenAfriVac (group 1A). Two primary endpoints (percentage of vaccinees with a 4-fold or higher response in MenA rSBA titer compared to baseline and MenA rSBA GMTs determined 28 days after the last vaccine dose) were used. Non-inferiority was declared if the upper 98.3% confidence bound of the difference in percentage of the 4-fold responders between relevant study groups was less than 10% as in study PsA-TT-004 *and* if the upper 98.3% confidence bound of the GMT ratio was less than 1.5, an additional stringent criterion. Under the assumptions of a seroconversion rate of 90% for MenAfriVac group 1A, power set at 90% and one-sided alpha risk at 0.0083, the required sample size for the evaluable immunogenicity population was 265 per study group. This estimated sample size provided a power of 97% to detect a non-inferiority margin of 1.5 for GMT ratio using a one-sided, two-sample t-test, at one-sided significance level of 0.0083 and assuming the standard deviation of log<sub>2</sub>-transformed titers was 1.58 (based on the results of the infant study PsA-TT-004 performed in Ghana).

Fifteen hundreds (1500) infants aged 9 to 12 months, whose medical history did not show any obvious health problem and who had been fully vaccinated according to the local EPI schedule, were randomly allocated to one of the 5 study groups, 1A, 1B, 2A, 2B and 3 (300 each). Overall 111 subjects (7.4%) were discontinued between the age of 9 (visit 1) and 15 months (visit 6). Discontinuation was predominantly due to consent withdrawal (73.9%) and out-migration (18%). Deaths were the cause of 3.6% discontinuations. A total of 1389 subjects completed the study until visit 6. They were distributed in the 5 groups as follows: 278 in group 1A, 278 in group 1B, 280 in group 2A, 277 in group 2B and 276 in group 3. These figures indicate a high completion rate with an acceptable balance among the study groups.

At time of enrollment, there were no medically relevant differences in demographic (except for distribution of sex) and clinical criteria among the 5 groups. Baseline rSBA GMTs were very low and similar across study groups.

### Analysis of immunogenicity data

Per protocol evaluable population was the primary data set for the evaluation of immunogenicity data. Of note, the analysis in the ITT population yielded similar results.

Relating to the primary study objective, high percentages of subjects developed a 4-fold or higher response in MenA rSBA titer 28 days after the last dose of PsA-TT vaccine with respect to baseline in all groups: 100% (95% CI 98.9 - 100.0), 99.6% (95% CI 97.9 - 100.0), 98.6% (95% CI 96.4 - 99.6), and 97.2% (95% CI 94.5 - 98.8) in groups 1A, 1B, 2A, and 2B, respectively. The difference (and 98.3% CI) in seroconversion rates was: 0.4% (-1.8 - 2.8) between group 1A and group 1B, 1.4% (-0.8 - 4.4) between group 1A and group 2A and 2.8% (0.6 - 6.3) between group 1A and group 2B. GMTs of MenA rSBA titers measured 28 days after the last dose of PsA-TT vaccine were 12108.3 (95% CI 10960.6 - 13376.2), 11095.9 (95% CI 9901.4 - 12434.4), 4883.1 (4244.2 - 5618.1), and 4167.3 (95% CI 3508.2 - 4950.3) in groups 1A, 1B, 2A, and 2B, respectively; GMTs in groups 1A and 1B in which subjects received two doses of PsA-TT vaccine were more than twice the GMTs in groups 2A and 2B in which subjects received only one dose of PsA-TT vaccine. The GMT ratios (and 98.3% CI) of group 1A versus group 1B, group 1A versus group 2A, and group 1A versus group 2B were: 1.1 (0.9 - 1.3), 2.5 (2.0 - 3.1), and 2.9 (2.3 - 3.7), respectively. Thus, non-inferiority of MenAfriVac 5µg (group 1B) administered in a two-dose schedule to MenAfriVac administered in a two-dose schedule was demonstrated. As the second dose of PsA-TT induced a substantial increase in antibody levels, non-inferiority of the one-dose schedule could not be demonstrated for the GMT endpoint, despite high antibody levels achieved 28 days after one dose given at 9 months of age. Nonetheless, one dose schedule, no matter with what PsA-TT dosage (10 µg or 5 µg), was non-inferior to MenAfriVac administered in a two-dose schedule when the seroconversion endpoint is considered.

The study design allows also comparing the immune responses induced by MenAfriVac 5µg with those to MenAfriVac after a first dose given at 9 months of age. Pooled MenAfriVac 5µg group (pooled group of groups 1B and 2B) was non-inferior to the pooled MenAfriVac group (pooled group of groups 1A and 2A) based on the percentages of subjects with a 4-fold or higher response in MenA rSBA antibody titer one month after vaccination with respect to baseline, 97.3% (95% CI 95.6 - 98.5) in the pooled MenAfriVac 5µg group versus 98.2% (95% CI 96.8 - 99.1) in the pooled MenAfriVac group with a difference of 0.9% (98.3% CI -1.3 - 3.3) between the pooled MenAfriVac group and the pooled MenAfriVac 5µg group. When considering the other MenA rSBA related endpoints, -percentage of subjects with MenA rSBA titer  $\geq 1:8$  and percentage of subjects with MenA rSBA titer  $\geq 1:128$  one month after vaccination, statistically significant differences were noted in favor of MenAfriVac. Of note the differences were numerically minimal and high proportions of subjects achieved these threshold, -for instance, the percentage of subjects with MenA rSBA titer  $\geq 1:128$  were 99.5% (95% CI 98.5 - 99.9) in the pooled MenAfriVac group and 97.9% (95% CI 96.3 - 98.9) in the pooled 5µg-dosage group. A similar trend was found for GMT of MenA rSBA titers. The ratio of GMTs of the pooled MenAfriVac group versus the pooled 5 µg group after adjusting baseline titer, sex, and visit was 1.3 (95%CI 1.1 - 1.5). One month after the first dose given at 9 months, the reverse cumulative distribution (RCD) curves of MenA rSBA titers for groups 1A, 1B, 2A and 2B are clearly shifted to the right compared to that among controls (group 3), and do not exhibit any actual decrease before the value of 1:512. These differences between MenAfriVac 5µg and MenAfriVac were not persisting 7 months after one dose. The MenAfriVac 5µg group (2B) was non-inferior to the MenAfriVac group (2A) based on the percentage with a 4-fold or higher response in MenA rSBA antibody titer 7 months after one dose with respect to baseline, 95.8% (95% CI 92.6 - 97.9) in group 2B versus 96.9% (95% CI 94.0 - 98.7) in group 2A with a difference of 1.1% (98.3% CI -3.2 - 5.6) between groups 2A and 2B. Similar GMTs of MenA rSBA titers were observed in group 2A (2195.6 (95% CI 1810.6 - 2662.5)) and 2B (2382.7 (95% CI 1951.9 - 2908.6)) 7 months after one dose and the ratio of GMTs of group 2A versus group 2B was 1.0 (95% CI 0.8 - 1.3) after adjusting for baseline titer, sex, and visit. Other endpoints, -percentage of subjects with MenA rSBA titer  $\geq 1:8$  and percentage of subjects with MenA rSBA titer  $\geq 1:128$  were not different between the two groups seven months after vaccination; the percentage of subjects with MenA rSBA titer  $\geq 1:128$  were 96.9% (95% CI 94.0 - 98.7) in group 2A and 96.6% (95% CI 93.6 - 98.4) in group 2B.

### Analysis of reactogenicity and safety data

Safety evaluation included monitoring of immediate reactions within 30 minutes of vaccination, solicited reactions and AEs during a time window of 4 days as the majority of local and systemic reactions occur usually within 2 days of vaccination and AEs for four weeks after each vaccination. Serious adverse events were recorded during the entire study duration. All safety evaluations were performed on the ITT population (there was no instance of wrong treatment assignment).

#### ***Immediate reactions***

There were neither any immediate local reactions noted at the site of PsA-TT injection nor any immediate systemic reactions for any dose given at 9 months or 15 months of age.

#### ***Solicited local reactions***

Local reactions at the injection site of PsA-TT given at 9 months of age were rare (<1%), mild and transient (resolving within 2 days) tenderness. Local reactions were similarly uncommon (<1%), mild and transient at the Yellow Fever and Measles injection sites. There were no local reactions after the second dose of PsA-TT given at 15 months of age, except one case of mild and transient tenderness in group 1B reported at the site of PsA-TT injection. Altogether these observations indicate that local reactions at the injection site of PsA-TT are rare, mild and transient and do not increase after the second dose.

#### ***Solicited systemic reactions***

After the first PsA-TT vaccine dose given simultaneously with Yellow Fever and Measles vaccines, systemic reactions were reported in 16.7% , 18.3%, 19.0% , 19.0% and 17.0% of subjects in groups 1A, 1B, 2A, 2B and 3 (control). There was no statistically significant difference between the pooled MenAfriVac group (pooled group of groups 1A and 2A) and the pooled MenAfriVac 5µg group (pooled group of groups 1B and 2B) and between each pooled PsA-TT group and the control group 3. Systemic reactions were generally mild and no reaction was rated grade 3 (severe). The most common systemic reactions were diarrhea (ranging 9.0% in group 1B to 13.3% in group 2B), vomiting (ranging from 4.7% in group 3 to 7.0% in group 1A) and fever (ranging from 3.7% in groups 2B and 3 to 5.3% in group 1B). After the second PsA-TT vaccine dose given simultaneously with Measles-Rubella vaccine, systemic reactions were reported in 6.4% of vaccinees. Rates of systemic reactions were 3.9% of subjects in group 1A, 7.9% in group 1B, 8.9% in group 2A, and 5.7% in group 2B and control group 3 and not statistically different between groups 1A and 1B and between each of groups 1A and 1B and pooled control group (pooled group of groups 2A, 2B and). Systemic reactions were predominantly mild and transient. The most common systemic reactions were diarrhea (ranging 1.8% in group 1A to 5.7% in groups 1B and 2A). All other systemic reactions were reported in similar proportions among groups in less than 3% of subjects in each group.

#### ***Adverse events within 28 days of dose 1***

Rates of adverse events (including systemic reactions ongoing beyond Day 4) within 28 days of the first vaccination were similar: 63.3%, 67.3%, 65.7%, 68.3% and 63.0% of subjects in groups 1A, 1B, 2A, 2B, and the control group 3, respectively. “Infections and infestations” in the system organ class (SOC) analysis were observed in 50.0%, 55.0%, 53.0% and 54.3% of subjects in groups 1A, 1B, 2A and 2B, respectively and for 51.3% of subjects in control group 3 and were mainly bronchitis, gastroenteritis, diarrhoea infectious, and pharyngitis. “Gastrointestinal disorders”, mainly diarrhoea, were reported by 14.7 % of subjects and “respiratory, thoracic and mediastinal disorders” by 11.9%. The percentages of infants reporting each specific event were similar among study groups. All related AEs were systemic reactions, mainly diarrhoea, ongoing beyond Day 4. There were no statistically significant differences in percentage of subjects with related AEs between study groups compared.

#### ***Adverse events within 28 days of dose 2***

Adverse events (including systemic reactions ongoing beyond Day 4) within 28 days of vaccination at 15 months of age were occurring with similar rates in the five study groups - 42.5% of subjects in group 1A, 38.0% in group 1B, 35.6% in group 2A, 40.1% in group 2B and 40.9% in group 3. “Infections and infestations” were largely the most common SOC category noted in the five groups: 36.1% of subjects in group 1A, 31.2% in group 1B, and 30.6%, 33.3% and 33.7% of the subjects in groups 2A, 2B and 3, respectively. They were mainly bronchitis, rhinitis and pharyngitis. Overall, the



proportions of subjects reporting each specific event were similar among each of the study groups. All related AEs were systemic reactions ongoing beyond Day 4 and there were no statistically significant differences in the rate of related AEs between study groups compared. All adverse events resolved without sequelae.

#### ***Serious adverse events (SAEs) and deaths***

Overall, 42 serious adverse event were reported during the entire study period and occurred with similar proportions in the five study groups for each follow up period (i.e. within 28 days of each vaccination and during the interval between the 2 doses). Ten out of the 42 SAEs occurred within 28 days after the first vaccination, six out of the 42 SAEs occurred within 28 days after the second vaccination, and most of them (81%) were infections and infestations according to SOC. Most of the SAEs were resolving within 7 days without sequelae and all were considered unrelated to study vaccines. Four subjects died during the study period. Three died from gastroenteritis and one from injury. None of the 4 deaths was related to the study vaccine.

### **IMMUNOGENICITY OF CONCOMITANTLY ADMINISTERED VACCINES IN STUDIES PsA-TT-004 AND -007**

In both studies, potential interference in the immune response to the EPI vaccines administered concomitantly with PsA-TT vaccine was assessed by examining non-inferiority of immune responses to EPI antigens in PsA-TT groups in which subjects received EPI and PsA-TT vaccines simultaneously to the immune responses in subjects receiving these EPI vaccines alone. Primary immunogenicity endpoints for each vaccine antigen were the percentage of subjects achieving predefined antibody concentrations or titers one month after vaccination. If the upper bound of the 95% CI of the difference in percentages of subjects achieving the predetermined threshold for a given EPI vaccine between the control group (receiving only the EPI vaccine) and a specific study group (receiving simultaneous administration of PsA-TT and the EPI vaccine) was less than 10% (pre-specified non-inferiority margin), the comparator was considered non-inferior to the control. In both studies, the size of the study allowed a number of sera tested for the immunogenicity of EPI vaccines to provide a power over 90% to demonstrate non-inferiority for pair wise comparison between a study group and the respective control, with an assumed response rate of 95% at the predefined threshold for a given EPI antigen.

The non-inferiority of each of PsA-TT groups (EPI with PsA-TT) to the relevant control group (EPI alone) was demonstrated for most of pairwise comparisons in the two studies, in terms of response rate of subjects with immune response to a given EPI antigen reaching predefined threshold. For study PsA-TT-004, the few exceptions relate to the percentages of subjects with *B. pertussis* specific IgG concentration  $\geq 11$  IU/ml which were much lower (40.7% - 47.5% ) than the expected response rate of 95% one month after the third DTwPHBVHib dose in all study groups and for which non-inferiority of three PsA-TT groups (groups 1A, 1B, 1C) to the control group was not demonstrated, percentages of subjects with anti-PRP IgG concentration  $\geq 1$   $\mu$ g/ml one month after the third DTwPHBVHib dose for which non-inferiority of group 1C to the control group was not shown, percentages of subjects with Measles-specific IgG concentration  $> 11$  DU for which non-inferiority of groups 1B and 2 to the control group 4 was not shown and percentages of subjects with Yellow Fever neutralizing antibody titer  $\geq 1:8$  one month after vaccination at 9 months of age which were less (69.9% - 79.4%) than the expected response rate in all groups and for which non-inferiority of groups 1C and 2 to group 4 was not demonstrated. Although non-inferiority was not shown, there were no statistically significant differences in GMTs or GMCs for any of these 4 EPI vaccine antigens one month after vaccination after adjusting age, sex, and pre-dose concentration (or titer): GMCs of *B. Pertussis* specific IgG concentrations ranged from 8.0 to 9.1; GMCs of anti-PRP IgG concentration were from 2.5 to 3.2; GMCs of Measles-specific IgG concentrations were from 13.0 to 13.8; GMTs of Yellow Fever neutralizing antibody titer ranged from 12.5 to 16.7 one month after vaccination. Overall, the percentages of subjects with immune response achieving a predefined threshold were similar across study groups. In study PsA-TT-007, non-inferiority of group 2A to the control group 3 was not demonstrated for the percentage of subjects with Yellow Fever neutralizing antibody titer  $\geq 1:8$  one

month after vaccination at 9 months of age. The percentages were high, ranging from 94.8% to 98.3% and GMTs were similar, ranging from 29.8 to 34.5 one month after vaccination. Noteworthy, antibody measurement for Yellow Fever antigen was performed in only approximately 20% of samples. In study PsA-TT-004, co-administration of MenAfriVac or MenAfriVac 5µg did not interfere with the tetanus antitoxin nor the PRP antibody response (induced by the tetanus toxoid Hib conjugate as in Zilbrix), which indicates the absence of carrier epitopic suppression. Study PsA-TT-007 provides evidence that the carrier protein in MenAfriVac or MenAfriVac 5µg elicited tetanus antitoxin antibody.

The immunogenicity of rotavirus and pneumococcal conjugate vaccines which might be simultaneously given with MenAfriVac 5µg has not been formally evaluated in these two studies. Based on the clinical experience with co-administration of Prevenar13 and NeisVac, a meningococcal group C polysaccharide tetanus toxoid conjugated vaccine (10 µg of conjugate per dose), there were no immunological interference as the immunogenicity of the 2 vaccines, Prevenar13 and NeisVac, was not altered. Therefore, it is reasonable to expect similar findings for MenAfriVac 5µg [21;22]. Published data on the concomitant administration of Rotarix with Meningitec, a meningococcal group C polysaccharide CRM<sub>197</sub> conjugated vaccine, and other recommended infant vaccines and that of Rotateq with NeisVac and other recommended infant vaccines does not provide evidence of any immunological interference[23;24].

## Discussion

The clinical studies PsA-TT-004 and PsA-TT-007 address issues related to the potential use of MenAfriVac 5 µg when incorporated into the EPI to maintain population immunity. One (“9 months of age”) and two (“14 weeks and 9 months of age”, and “9 and 15 months of age”) immunization schedules fitting EPI sessions were evaluated.

### *Safety of MenAfriVac 5 µg*

A total of 3315 doses of PsA-TT vaccine were administered in the two studies, including 1651 doses of MenAfriVac, 1270 doses of MenAfriVac 5µg and 394 doses of 2.5 µg PsA-TT. Eleven hundred and seventy nine (1179) and 472 infants received a first and second dose of MenAfriVac, respectively whereas 800 and 470 infants received a first and second dose of MenAfriVac 5µg.

The reactogenicity profile of PsA-TT concomitant with EPI vaccines in infants aged between 14 weeks and 9 months at time of immunization was shown to be similar to that of concomitantly given EPI vaccines. Local reactions at injection sites of PsA-TT and EPI vaccines were predominantly mild and transient. Local reactions at the site of PsA-TT injection were observed in less than 11% of infants. There were no significant increases in systemic reactions due to concomitant vaccination of PsA-TT compared to the EPI vaccines administered alone. No clinically significant differences in the frequency or severity of AEs within 28 days of vaccination were observed among infants receiving PsA-TT simultaneously with the EPI vaccines compared to EPI vaccines alone, indicating a comparable safety profile. In general, reported AEs within 28 days of vaccination corresponded to symptoms associated with medical conditions occurring commonly in subjects of the same age as subjects included in both studies and living in meningitis belt countries. AEs that were considered related to study vaccine were essentially post-immunization reactions ongoing beyond day 4 (mostly induration and gastrointestinal disorders). Overall, reported serious adverse events (SAEs) were not statistically different among study groups at any time during the vaccination series and follow-up observation period. By far, the most frequently reported SAEs were infections and infestations according to SOC. Overall, the safety database shows a comparable safety profile for MenAfriVac 5µg and MenAfriVac when co-administered with the recommended EPI vaccines and does not reveal any signals for a specific adverse event to occur in excess.

Nonetheless, there are limitations to the safety database. The safety of PsA-TT has only been evaluated in healthy infants and the size of the database may be too small to detect rare AEs that would occur at a frequency lower than 0.5%. However, the clinical experience with more than 150 million doses of MenAfriVac administered has clearly shown that MenAfriVac has an acceptable safety profile. In both studies, MenAfriVac was used as comparator which provides added confidence as to the safety profile of MenAfriVac 5µg. Furthermore, it is biologically not plausible that the reduced antigenic content, in the same vaccine formulation considered here, would be associated a different safety profile. Therefore, the usual pharmacovigilance programme will allow to assess whether any AEs, that were too rare to be observed in studies PsA-TT-004 and PsA-TT-007, are associated with MenAfriVac 5µg when used in routine EPI practice.

#### *Immunogenicity of MenAfriVac 5 µg*

Immunogenicity data in infants, aged from 14 weeks (study PsA-TT-004) to 9 months (study PsA-TT-007) at time of first vaccination, indicate that MenAfriVac 5µg elicits functional immune responses that are similar to those induced by MenAfriVac. In both studies, non-inferiority of MenAfriVac 5µg to MenAfriVac was demonstrated in terms of the primary immunogenicity endpoint for subjects with a seroconversion in MenA rSBA antibody titer. Specifically, with respect to percentage of subjects with a 4-fold or higher response in MenA rSBA antibody titer with respect to baseline, non-inferiority of MenAfriVac 5 µg administered at 14 weeks and 9 months of age to MenAfriVac administered at 14 weeks and 9 months of age, concomitantly with EPI vaccines, was demonstrated at 28 days after the second dose up to 24 to 27 months after the second dose in study PsA-TT-004; non-inferiority of MenAfriVac 5µg administered in 9 months of age or administered in 9 months and 15 months of age to MenAfriVac administered in 9 months and 15 months of age, concomitantly with EPI vaccines was established at 28 days of the last vaccine dose in study PsA-TT-007.

Findings in study PsA-TT-004 indicate that a schedule consisting of 2 doses of MenAfriVac 5µg given at 14 weeks and 9 months of age was highly immunogenic. One month after the second dose, GMT of MenA rSBA titers was high (5048.6) for MenAfriVac 5µg and significantly greater than that achieved by a single dose of MenAfriVac at 9 months, indicating that the first dose of MenAfriVac 5µg is effectively priming the immune system. MenA rSBA antibody titers  $\geq 1/128$  were persisting in 88.1% of subjects in the 5µg group at the age of 36 months. In study PsA-TT 007, a co-primary endpoint related to MenA rSBA GMTs was added to assess non-inferiority of alternative schedule and dosage of PsA-TT vaccine to MenAfriVac administered in a two-dose schedule. For this endpoint, the alternative schedule and dosage of PsA-TT can be claimed to be non-inferior to MenAfriVac administered in a two-dose schedule if the 98.3% upper confidence bound of GMT ratio of the alternative schedule and dosage group versus the MenAfriVac group is less than 1.5 at 28 days after the last dose of MenAfriVac, which appears to be a very stringent requirement. Based on this criterion only, two-dose schedule of MenAfriVac 5µg was non-inferior to two-dose schedule of MenAfriVac, but one-dose schedule given at 9 months of age for both MenAfriVac and MenAfriVac 5 µg was not shown non-inferior to two-dose schedule of MenAfriVac given at 9 months and 15 months of age. This is due to the strong antibody increase induced by a second dose of PsA-TT resulting in high MenA rSBA GMTs that were greater than 11,000 for both MenAfriVac and MenAfriVac 5µg. However, such high GMT level may not persist very long. According to one of the pre-licensure studies for MenAfriVac conducted in toddlers (study PsA-TT-002) [5], GMT was 10037.4 at 28 days after two doses of MenAfriVac given at 12 to 23 months of age for the first dose and 10 months later for the second dose, but 14 months after the second dose of MenAfriVac, GMT decreased to 2720.8, which indicated a substantial decline of antibody titers for MenAfriVac within about a year. Even though based on GMT, non-inferiority of the one-dose schedule of PsA-TT with either 10 µg or 5 µg to the two-dose schedule of MenAfriVac was not demonstrated, high MenArSBA titers were already achieved following one dose of PsA-TT given at 9 months of age; GMTs at 28 days after the single dose of PsA-TT were 4883.1 and 4167.3 for the one-dose schedule of MenAfriVac and MenAfriVac 5µg, respectively. Seven months after the single dose, MenArSBA titers remained high: GMTs were 2195.6 and 2382.7 for the one-dose schedule of MenAfriVac and MenAfriVac 5µg, respectively and they were not significantly different from each other after adjusting for baseline titer, sex, and visit.

Antibody persistence depending on PsA-TT dosage, schedule and age at vaccination was modelled using a longitudinal mixed model analysis. The analysis was based on MenA rSBA antibody data from studies PsA-TT-004 and -007 presented here, and from the earlier study PsA-TT-002 where MenAfriVac was administered to toddlers and antibody persistence was evaluated up to 4.25 to 5 years after vaccination. The MenAfriVac 5µg vaccine was shown to have an immune response profile over time at least as good as that of MenAfriVac, whether administered in a one-or- two-dose schedule. Based on the immune response profile over an extended period of time of the MenAfriVac vaccine when given in a one-dose or two-dose schedule, it is reasonable to predict that the trajectory of immune response of the MenAfriVac 5µg vaccine will follow a similar trend and that a single dose of MenAfriVac 5µg vaccine given from age 9 months onwards will induce sustained antibody levels over time. It is therefore highly probable that MenAfriVac 5µg would be as effective as MenAfriVac to prevent group A meningococcal disease in infants when given as a two dose schedule at the age of 14 weeks and 9 months, or as one dose schedule given from the age of 9 months.

WHO recommendations on measles vaccination include the administration of a second dose of measles vaccine at 15 to 18 months of age in regions where measles transmission is on-going. This provides an opportunity for MenAfriVac vaccination which justifies considering extending the age indication up to 24 months for MenAfriVac 5µg. A review of immunogenicity data indicate an age related increase in MenAfriVac induced MenArSBA antibody levels from 14 weeks to 18-23 months of age. Since MenAfriVac 5µg demonstrated non inferiority to MenAfriVac at 14 weeks and at 9 months, it is reasonable to project non inferiority up to the age of 24 months. Hence the data support that MenAfriVac 5µg is indicated for: “active immunization for the protection against invasive meningococcal disease caused by *N. meningitidis* serogroup A in young children aged 3 to 24 months”, with the following proposed immunization schedules

- From 14 weeks of age, two dose schedule with an interval of at least three months
- From 9 months of age, one dose

#### *Concomitant vaccination*

Data from both studies have shown that concomitant administration of MenAfriVac or MenAfriVac 5µg, does not affect the safety profile and the immunogenicity of routinely recommended infant vaccines in the EPI. The immunogenicity profile of all EPI vaccine antigens that were evaluated in these two studies exhibited mostly non-inferior immune responses induced by EPI vaccines co-administered with PsA-TT vaccine compared to the immune responses induced by EPI vaccines alone. Failure to show non-inferiority in some instances were partly due to either lower than expected response rates at the predefined threshold considered for a given antigen or smaller than required number of tested sera. Overall, compared with EPI vaccines administered alone, the percentages of responders and geometric mean levels of vaccine induced antibodies were similar for all EPI antigens when MenAfriVac and PsA-TT vaccines were given concomitantly. These data support that MenAfriVac 5µg vaccine can be safely and effectively given concomitantly with the other EPI vaccines as recommended. This would greatly ease the programmatic challenges related to adding immunization of infants or toddlers against group A meningococcal disease.

## **Conclusion**

The two clinical studies provided convincing evidence that MenAfriVac 5 µg is well tolerated and safe. MenAfriVac 5µg would provide a substantial benefit given its demonstrated ability to elicit sustained functional immune responses in infants from the age of 14 weeks that are non- inferior to the immune responses induced by MenAfriVac which has proven highly effective. Clinical data allow its routine use within recommended EPI. The benefit-to-risk ratio of MenAfriVac 5µg appears to be highly favourable. Monitoring disease caused by group A *N. meningitidis* in countries where routine infant immunisation with MenAfriVac 5µg is implemented will confirm as to whether its impact is associated with sustained population immunity and whether changes in immunisation recommendations such as booster doses would be needed.

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World Health  
Organization

Organisation mondiale de la Santé

# Weekly epidemiological record Relevé épidémiologique hebdomadaire

18 NOVEMBER 2011, 86th YEAR / 18 NOVEMBRE 2011, 86<sup>e</sup> ANNÉE

No. 47, 2011, 86, 521–540

<http://www.who.int/wer>

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## Meningococcal vaccines: WHO position paper, November 2011

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 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 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 manufacturers, the medical community, the scientific media and the public.

This document incorporates the most recent developments in the field of meningococcal vaccines to guide the introduction and use of meningococcal vaccines in national immunization schedules. It replaces the position paper published in the *Weekly Epidemiological Record* in October 2002.

Recommendations on the use of meningococcal vaccines were discussed by SAGE at its meeting in April 2011. Evidence presented at the meeting can be accessed at <http://www.who.int/immunization/sage/previous/en/index.html>.

## Note de synthèse: position de l'OMS sur les vaccins antiméningococciques, novembre 2011

Conformément à son mandat, qui est de fournir des orientations aux Etats Membres sur les questions relatives aux politiques de santé, l'OMS publie régulièrement des notes de synthèse actualisées sur les vaccins et les associations vaccinales contre les maladies ayant des répercussions internationales en santé publique. Ces notes traitent principalement de l'utilisation des vaccins dans les programmes de vaccination à grande échelle; elles récapitulent l'essentiel des informations générales sur les maladies et les vaccins et présentent en conclusion la position actuelle de l'OMS concernant leur utilisation dans le monde.

Ces notes ont été examinées par des spécialistes à l'OMS et à l'extérieur, et sont passées en revue et approuvées par le Groupe stratégique consultatif d'experts de l'OMS sur la vaccination (SAGE) (<http://www.who.int/immunization/sage/fr/index.html>). Elles sont principalement destinées aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination. Elles peuvent également être utiles aux organismes internationaux de financement, aux fabricants de vaccins, au monde médical, aux médias scientifiques et au grand public.

Le présent document incorpore les développements les plus récents survenus dans le domaine des vaccins antiméningococciques afin de fournir des informations utiles pour l'introduction et l'utilisation des vaccins antiméningococciques dans les calendriers nationaux de vaccination. Il remplace la note de synthèse publiée en octobre 2002 dans le *Relevé épidémiologique hebdomadaire*.

Les recommandations relatives à l'utilisation des vaccins antiméningococciques ont été évoquées par le SAGE lors de sa réunion d'avril 2011. On peut accéder aux données présentées lors de la réunion en consultant la page suivante: <http://www.who.int/immunization/sage/previous/en/index.html>.

WORLD HEALTH  
ORGANIZATION  
Geneva

ORGANISATION MONDIALE  
DE LA SANTÉ  
Genève

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

11.2011  
ISSN 0049-8114  
Printed in Switzerland

In this paper, footnotes provide a limited number of core references; summaries of these references can be found at <http://www.who.int/immunization/documents/positionpapers/en/index.html>. Grading tables which assess the quality of scientific evidence in support of key recommendations are also available through this link and are referenced in the position paper.

## Introduction

### Epidemiology

In most countries, *Neisseria meningitidis* (the meningococcus) is recognized as a leading cause of meningitis and fulminant septicaemia and a significant public health problem. However, surveillance data from many countries, particularly in Asia, are incomplete or lacking and there is currently no reliable global burden estimate.

The majority of invasive meningococcal infections are caused by organisms expressing one of the serogroup A, B, C, X, W135 or Y capsular polysaccharides.<sup>1</sup> Meningococci of these serogroups have the potential to cause both endemic disease and outbreaks, but their relative prevalence varies considerably with time and geographic location. In the African meningitis belt, which is considered to have the highest annual incidence of meningococcal disease in the world (see below), serogroup A has been the most important cause of disease, although outbreaks caused by serogroups C and W135, and most recently by serogroup X, have also occurred. In Europe, the incidence of meningococcal disease ranges from 0.2 to 14 cases per 100 000 population and the majority of cases are caused by serogroup B strains, particularly in countries which have introduced serogroup C meningococcal conjugate vaccines. A similar pattern is reported from Australia and New Zealand. In the Americas, the incidence of meningococcal disease is in the range of 0.3 to 4 cases per 100 000 population. In the United States, the majority of cases are caused by serogroups B, C and Y, and serogroup W135 is very rare. In Latin America serogroups B and C cause the majority of cases. Limited data suggests that in Asia, most meningococcal disease is caused by meningococci belonging to serogroup A or C.<sup>2</sup>

*Neisseria* species, which usually reside asymptomatically in the human nasopharynx, are easily transmitted to close contacts by respiratory droplets. Nasopharyngeal carriage of potentially pathogenic *N. meningitidis* has been reported in 4%–35% of healthy adults. In particular, high carriage rates have been found in relatively confined populations such as college students and army recruits.<sup>3</sup>

<sup>1</sup> Stephens D S. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium *Neisseria meningitidis*. *Vaccine*, 2009, 27 (Suppl. 2):B71–77.

<sup>2</sup> Harrison L H. Global epidemiology of meningococcal disease. *Vaccine*, 2009, 27 (Suppl. 2):B51–63.

<sup>3</sup> *Background paper on meningococcal vaccines*, WHO Strategic Advisory Group of Experts on Immunization, 2011. Geneva, World Health Organization, 2011 ([http://www.who.int/immunization/sage/1\\_mening\\_background\\_document\\_v5\\_3\\_apr\\_2011.pdf](http://www.who.int/immunization/sage/1_mening_background_document_v5_3_apr_2011.pdf), accessed November 2011).

Dans le présent article, les notes de bas de page fournissent un nombre limité de références de base; on peut trouver les résumés de ces références à l'adresse suivante: <http://www.who.int/immunization/documents/positionpapers/fr/index.html>. Les tableaux de notation qui évaluent la qualité des données scientifiques sur lesquelles reposent les principales recommandations sont également disponibles par ce lien et sont référencés dans la note de synthèse.

## Introduction

### Épidémiologie

Dans la plupart des pays, *Neisseria meningitidis* (nom scientifique du méningocoque) est une cause majeure de méningite et de septicémie foudroyante, ainsi qu'un problème important de santé publique. Toutefois, les données de la surveillance de nombreux pays, en particulier en Asie, sont incomplètes ou manquantes et on ne dispose pas actuellement d'une estimation fiable de la charge de morbidité mondiale de cette maladie.

La majorité des infections à méningocoques sont provoquées par des germes exprimant l'un des polysides capsulaires des sérogroupes A, B, C, X, W135 ou Y.<sup>1</sup> Les méningocoques appartenant à ces sérogroupes sont potentiellement à l'origine de la forme endémique de la maladie et de flambées, mais leur prévalence varie considérablement en fonction du temps et du lieu géographique. Dans la ceinture africaine de la méningite, qui est considérée comme ayant l'incidence annuelle de la méningococcie la plus élevée au monde (voir plus bas), le séro-groupe A a été la cause de maladie la plus importante, même si des flambées provoquées par les sérogroupes C et W135, et plus récemment par le séro-groupe X, ont également sévi. En Europe, l'incidence de la méningococcie se situe entre 0,2 et 14 cas pour 100 000 habitants et la majorité d'entre eux sont dus à des souches appartenant au séro-groupe B, en particulier dans les pays qui ont introduit les vaccins antiméningococciques conjugués contre le séro-groupe C. Un schéma analogue est rapporté en Australie et en Nouvelle-Zélande. Dans les Amériques, l'incidence de la méningococcie se situe entre 0,3 et 4 cas pour 100 000 habitants. Aux États-Unis, la majorité des cas sont dus aux sérogroupes B, C et Y, et le séro-groupe W135 y est très rare. En Amérique latine, les sérogroupes B et C sont à l'origine de la majorité des cas. Des données limitées laissent à penser qu'en Asie la plupart des cas de méningococcie seraient dus à des méningocoques appartenant au séro-groupe A ou C.<sup>2</sup>

Les *Neisseria*, qui sont habituellement présentes dans le rhinopharynx de l'homme de manière asymptomatique, se transmettent facilement à l'entourage des malades par les gouttelettes respiratoires. Le portage rhinopharyngé de *N. meningitidis* potentiellement pathogène a été rapporté chez 4 à 35% des adultes en bonne santé. Des taux de portage élevés ont en particulier été trouvés dans des populations relativement confinées telles que les étudiants des campus et les recrues de l'armée.<sup>3</sup>

<sup>1</sup> Stephens D S. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium *Neisseria meningitidis*. *Vaccine*, 2009, 27 (Suppl. 2):B71–77.

<sup>2</sup> Harrison L H. Global epidemiology of meningococcal disease. *Vaccine*, 2009, 27 (Suppl. 2):B51–63.

<sup>3</sup> *Document d'information sur les vaccins antiméningococciques*, Groupe stratégique consultatif d'experts (SAGE) sur la vaccination, 2011. Genève, Organisation mondiale de la Santé, 2011 ([http://www.who.int/immunization/sage/1\\_mening\\_background\\_document\\_v5\\_3\\_apr\\_2011.pdf](http://www.who.int/immunization/sage/1_mening_background_document_v5_3_apr_2011.pdf), consulté en novembre 2011). [Document disponible uniquement en langue anglaise.]



Although meningococcal disease frequently occurs as scattered, apparently unrelated cases or in small outbreaks, in some regions this endemic situation may alternate with devastating, unpredictable epidemics. This is the case in the African meningitis belt, which is the region in sub-Saharan Africa stretching from Senegal in the west to Ethiopia in the east.<sup>4</sup> This region is inhabited by around 300 million people. During the dry season, from December to June, the incidence of meningococcal disease peaks and occasionally reaches rates of up to 1000 cases per 100 000 inhabitants, as occurred during the explosive epidemics in 1996 and 2000–2001.<sup>5</sup> During the 2006–2007 epidemic season, 53 438 suspected cases and 3816 deaths were reported to WHO from 15 African countries.<sup>6</sup> Outbreaks following the Hajj pilgrimage to Mecca illustrate how high levels of transmission of *N. meningitidis* can occur under crowded conditions. In 1987, there was a Hajj-associated outbreak caused by serogroup A, and in 2001 by serogroup W135. The latter pathogen was carried back to regions as far apart as China and Latin America.<sup>5</sup>

Endemic disease occurs primarily in children and adolescents, with highest attack rates in infants aged 3–12 months, whereas in meningococcal epidemics, rates may rise in older children and young adults. Crowding is an important risk factor; tobacco smoke, asplenia, HIV infection, and travel to epidemic areas are associated with an increased risk for meningococcal disease. Host genetic factors predisposing to meningococcal infection include deficiencies in terminal complement components.<sup>3</sup>

In the African meningitis belt, the WHO definition of a meningococcal epidemic is >100 cases/100 000 population/year. In endemic countries, incidences of >10 cases, 2–10 cases, and <2 cases per 100 000 population and year characterize high, moderate, and low endemicity, respectively. An outbreak outside the meningitis belt may be defined as a substantial increase in invasive meningococcal disease in a defined population above that which is expected by place and time.<sup>3</sup>

#### Etiological agent

*N. meningitidis* is a gram-negative diplococcal bacterium which causes disease only in humans. It is classified into 12 serogroups (A, B, C, 29E, H, I, K, L, W135, X, Y and Z) based on the structure of the polysaccharide capsule. Further classification is based on class 1 outer membrane proteins (PorA), class 2 or 3 (PorB) outer membrane proteins, and lipopoly(oligo)saccharide structure, respectively.<sup>1</sup> Capsule switching between serogroups has reportedly arisen in several geographic

Bien que la méningococcie apparaisse fréquemment sous la forme de cas dispersés apparemment sans aucun lien les uns avec les autres, ou sous la forme de petites flambées dans certaines régions, cette situation d'endémie peut alterner avec des épidémies dévastatrices et imprévisibles. C'est le cas dans la ceinture africaine de la méningite, qui est la région d'Afrique subsaharienne s'étendant du Sénégal dans l'ouest jusqu'à l'Éthiopie dans l'est.<sup>4</sup> Cette région compte environ 300 millions d'habitants. Au cours de la saison sèche, du mois de décembre au mois de juin, l'incidence de la méningococcie est maximum et atteint parfois des taux allant jusqu'à 1000 cas pour 100 000 habitants, comme cela a été le cas au cours des épidémies explosives de 1996 et de 2000–2001.<sup>5</sup> Au cours de la saison épidémique 2006–2007, 53 438 cas présumés et 3816 décès ont été notifiés à l'OMS par 15 pays africains.<sup>6</sup> Les flambées faisant suite au pèlerinage du Hadj à La Mecque illustrent la façon dont des taux de transmission élevés de *N. meningitidis* peuvent voir le jour dans des situations de surpeuplement. En 1987, il y a eu une flambée associée au Hadj provoquée par le sérotype A et en 2001, une autre due au sérotype W135. Ce dernier germe a été ramené dans des régions aussi éloignées les unes des autres que la Chine et l'Amérique latine.<sup>5</sup>

Sous sa forme endémique, la maladie touche principalement les enfants et les adolescents, les taux d'atteinte les plus élevés étant relevés chez les enfants âgés de 3 à 12 mois, alors que lors des épidémies de méningococcie ces taux peuvent augmenter chez les enfants plus âgés et les jeunes adultes. La promiscuité est un facteur de risque important; le tabagisme, l'asplénie, l'infection à VIH et les voyages dans les zones épidémiques sont associés à un risque accru de méningococcie. Les facteurs génétiques liés à l'hôte prédisposant à la méningococcie sont les déficits en composants terminaux du complément.<sup>3</sup>

Dans la ceinture africaine de la méningite, la définition OMS de l'épidémie de méningococcie est la suivante: >100 cas/100 000 habitants/an. Dans les pays d'endémie, des incidences >10 cas, de 2 à 10 cas et <2 cas pour 100 000 habitants et par an caractérisent respectivement une endémie forte, modérée et faible. On peut définir une flambée survenant en dehors de la ceinture de la méningite comme une augmentation importante de la méningococcie invasive dans une population donnée, au-dessus de ce à quoi on pourrait s'attendre dans cet endroit et à ce moment-là.<sup>3</sup>

#### Agent étiologique

*N. meningitidis* est un diplocoque à Gram négatif qui ne provoque une maladie que chez l'homme. Sa classification comporte 12 sérogroupes (A, B, C, 29E, H, I, K, L, W135, X, Y et Z) basés sur la structure de la capsule polysaccharidique. Une autre classification est basée sur les protéines de la membrane externe appartenant aux classes 1 (PorA), 2 ou 3 (PorB) et sur la structure lipopoly(oligo)saccharidique.<sup>1</sup> Des substitutions de capsules entre sérogroupes se seraient produites dans plusieurs zones géographiques par recombinaison in vivo au cours d'un

<sup>4</sup> Molesworth A M et al. Where is the meningitis belt? Defining an area at risk of epidemic meningitis in Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2002, 96:242–249.

<sup>5</sup> Al-Tawfiq J A et al. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *Journal of travel medicine*, 2010, 17 (Suppl.): 3–8.

<sup>6</sup> SAGE meeting, 6–9 November 2007. Update on epidemiological situation and supply of meningococcal vaccine. Geneva, World Health Organization, 2007 ([http://www.who.int/immunization/sage/previous\\_november2007/en/](http://www.who.int/immunization/sage/previous_november2007/en/), accessed November 2011).

<sup>4</sup> Molesworth A M et al. Where is the meningitis belt? Defining an area at risk of epidemic meningitis in Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2002, 96:242–249.

<sup>5</sup> Al-Tawfiq J A et al. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *Journal of travel medicine*, 2010, 17 (Suppl.): 3–8.

<sup>6</sup> Réunion du SAGE, 6–9 novembre 2007. Le point sur la situation épidémiologique et l'approvisionnement en vaccin antiméningococcique. Genève, Organisation mondiale de la Santé, 2007 ([http://www.who.int/immunization/sage/previous\\_november2007/en/](http://www.who.int/immunization/sage/previous_november2007/en/), consulté en novembre 2011). [Document disponible uniquement en langue anglaise.]



areas through in vivo recombination during nasopharyngeal co-carriage, and further evolution and adaptation occurs through incorporation of DNA from other commensal pathogens and phages.<sup>3</sup>

Although meningococcal strains usually reside harmlessly in the nasopharynx, transition from asymptomatic carriage to invasive disease may occur owing to a number of factors, including differences in the genetic composition and capsule structure of pathogenic and non-pathogenic strains. Isolates from carriers may be capsulated or non-capsulated, whereas blood and CSF isolates are invariably capsulated.<sup>1</sup>

#### Pathogenesis

The first step in the pathogenesis of meningococcal disease is attachment of the organism through surface pili to non-ciliated columnar epithelial cells of the nasopharynx. Following attachment, meningococci proliferate on the endothelial cell surface and form microcolonies. The bacteria may then cross mucosal surfaces, enter the bloodstream and produce a systemic infection. Once access to the bloodstream is obtained, meningococci may multiply rapidly to high levels. This pathogen may also translocate across the blood-meningeal barrier to infect the meninges and cause meningitis. In the blood, meningococci produce a strong inflammatory response with activation of the complement and coagulation cascades. A lipo-oligosaccharide (LOS), which is a key inducer of cellular inflammatory responses, is essential in causing meningococcal disease. LOS-induced secretion of various cytokines (e.g. IL-6 and TNF- $\alpha$ ), as well as chemokines, reactive oxygen species, and nitric oxide, leads to endothelial damage and capillary leakage, with a potential for subsequent necrosis of peripheral tissues and multiple organ failure. LOS levels correlate with mortality rates seen in meningococcal disease.<sup>1</sup> Polymorphisms in the genes coding for some of the components of these pathways have been shown to be involved in the susceptibility, severity, and outcome of meningococcal disease.<sup>3</sup>

#### Clinical features

Symptoms of invasive meningococcal disease (IMD) usually occur 1–4 days after infection. Besides meningitis and septicæmia, meningococci occasionally cause arthritis, myocarditis, pericarditis and endophthalmitis. Signs and symptoms of IMD in infants and young children include fever, poor feeding, irritability, lethargy, nausea, vomiting, diarrhoea, photophobia and convulsions. The characteristic feature of meningococcal septicæmia is a hemorrhagic (petechial or purpuric) rash that does not blanch under pressure. Signs of meningitis in older children and adults include neck rigidity, photophobia and altered mental status, whereas in infants non-specific presentation with fever, poor feeding and lethargy is common.

Most untreated cases of meningococcal meningitis and/or septicæmia are fatal. Even with appropriate care up

portage rhinopharyngé concomitant, et d'autres phénomènes d'évolution et d'adaptation se produisent par l'incorporation d'ADN provenant d'autres germes pathogènes commensaux et phages.<sup>3</sup>

Bien que les souches de méningocoques colonisent habituellement le rhinopharynx sans dommage, la transition entre le portage asymptomatique et la maladie invasive peut se produire en raison d'un certain nombre de facteurs, notamment de différences dans la composition génétique et la structure de la capsule des souches pathogènes et non pathogènes. Les isoléments effectués chez des porteurs peuvent être ou non encapsulés, tandis que les isoléments réalisés à partir du sang ou du LCR sont invariablement encapsulés.<sup>1</sup>

#### Pathogénie

La première étape de la pathogénie de la méningococcie est l'attachement des méningocoques aux cellules épithéliales en colonnes non ciliées du rhinopharynx par l'intermédiaire des pili situés à leur surface. Suite à cet attachement, les méningocoques prolifèrent sur la surface cellulaire endothéliale et forment des microcolonies. Les bactéries peuvent ensuite franchir les surfaces muqueuses, pénétrer dans la circulation sanguine et provoquer une infection générale. Une fois obtenu l'accès vers la circulation sanguine, les méningocoques peuvent se multiplier rapidement et atteindre des concentrations élevées. Ce germe pathogène peut également traverser la barrière hémato encéphalique pour infecter les meninges et provoquer une méningite. Dans le sang, les méningocoques provoquent une forte réponse inflammatoire avec activation du complément et réaction en cascade de la coagulation. Un lipo-oligosaccharide (LOS), inducteur essentiel des réponses inflammatoires cellulaires, est indispensable pour provoquer la méningococcie. La sécrétion de diverses cytokines (par exemple IL-6 et TNF- $\alpha$ ), de chimiokines, d'une forme réactive de l'oxygène et d'oxyde nitrique induite par le LOS conduit à des lésions endothéliales et à des fuites capillaires pouvant entraîner une nécrose ultérieure des tissus périphériques et une défaillance polyviscérale. Les concentrations de LOS sont corrélées avec les taux de mortalité observés dans la méningococcie.<sup>1</sup> On a montré que les polymorphismes des gènes codants pour certains des éléments de ces mécanismes invasifs étaient impliqués dans la sensibilité à la méningococcie, dans la gravité et l'issue de cette dernière.<sup>3</sup>

#### Caractéristiques cliniques

Les symptômes d'une méningococcie invasive débutent en général 1 à 4 jours après l'infection. En dehors d'une méningite et d'une septicémie, les méningocoques provoquent parfois une arthrite, une myocardite, une péricardite ou une endophthalmie. Les signes et symptômes de méningococcie chez le nourrisson et le jeune enfant sont les suivants: fièvre, perte de l'appétit, irritabilité, léthargie, nausées, vomissements, diarrhée, photophobie et convulsions. Le signe caractéristique de la septicémie à méningocoques est un rash (pétéchial ou purpurique) hémorragique qui ne s'efface pas à la pression. Les signes de méningite chez les enfants plus âgés et les adultes sont les suivants: raideur de la nuque, photophobie et altération de l'état mental, tandis que chez le nourrisson un tableau non spécifique avec fièvre, perte de l'appétit et léthargie est courant.

La plupart des cas de méningite et/ou de septicémie à méningocoques non traités sont mortels. Même avec des soins appro-

to 10% of patients die, typically within 24–48 hours of the onset of symptoms. In the meningitis belt of Africa, fatality from MenA disease has been estimated at 10–15%, although higher rates have been seen in some settings.<sup>7</sup> Approximately 10% to 20% of survivors of meningococcal meningitis are left with permanent sequelae such as mental retardation, deafness, epilepsy, or other neurological disorders.<sup>8</sup>

#### Naturally acquired immunity

Bactericidal antibodies develop in response to nasopharyngeal carriage of *N. meningitidis* and >10–14 days after nasopharyngeal colonization, development of meningococcal disease becomes highly unlikely.<sup>1</sup> The antibody response to carriage is not limited to the strain that is being carried, but can also extend to heterologous strains of pathogenic meningococci (groups A, B, C) with subsequent development of specific IgG, IgM and IgA antibodies.<sup>9</sup> This response may last for several months after the carried strains can no longer be detected. However, it is not clear whether nasopharyngeal carriage leads to immunological memory. Also, although specific antibodies are generally protective, this immunity is not absolute; meningococcal disease can occur in individuals with pre-existing antibody titres that are generally considered protective.<sup>10</sup>

In neonates, immunity to systemic meningococcal infection is conferred by the passive transfer of IgG antibodies from mother to fetus; in preterm infants, this transfer is suboptimal. In infancy, the peak incidence of meningococcal disease occurs when serum bactericidal antibody titres are low, and in adulthood the decreasing incidence of disease is correlated with increasing titres of such antibody.<sup>9</sup>

#### Diagnosis

The gold standard for diagnosis of invasive meningococcal disease is isolation of *N. meningitidis* from normally sterile body fluids – mainly blood or cerebrospinal fluid (CSF) – or from purpuric skin lesion scrapings. Since meningococci can be a component of normal nasopharyngeal flora, their isolation from this site does not definitively confirm a clinical diagnosis of IMD. When parenteral antibiotic treatment is initiated, the isolation rate of meningococci from blood culture drops from 50% to <5%, and the likelihood of CSF positivity by culture or microscopy is also rapidly reduced. Methods based on rapid polymerase chain reaction (PCR) can complement standard laboratory procedures as they are less affected by prior antibiotic therapy and these methods are being used increasingly.<sup>3</sup>

priés, on enregistre jusqu'à 10% de décès, habituellement dans les 24 à 48 heures suivant l'apparition des symptômes. Dans la ceinture africaine de la méningite, la mortalité de la méningococcie A a été estimée à 10%-15%, bien que des taux plus élevés aient été observés dans certains endroits.<sup>7</sup> Près de 10% à 20% des patients qui survivent à une méningite à méningocoques présentent des séquelles permanentes telles qu'une arriération mentale, une surdité, une épilepsie ou d'autres troubles neurologiques.<sup>8</sup>

#### Immunité acquise naturelle

Des anticorps bactéricides sont fabriqués en réponse au portage rhinopharyngé (*N. meningitidis*) et >10-14 jours après la colonisation rhinopharyngée, il est très peu probable qu'apparaisse une méningococcie.<sup>1</sup> La réponse en anticorps au portage n'est pas limitée à la souche portée, mais peut également s'étendre aux souches hétérologues de méningocoques pathogènes (groupes A, B, C), avec production ultérieure d'IgG, d'IgM et d'IgA spécifiques.<sup>9</sup> Cette réponse peut perdurer pendant plusieurs mois après que les souches portées ne peuvent plus être détectées. Toutefois, on ne sait pas si le portage rhinopharyngé entraîne une mémoire immunologique. De plus, si les anticorps spécifiques sont en général protecteurs, cette immunité n'est pas absolue; une méningococcie peut se déclarer chez des sujets présentant des titres d'anticorps préexistants généralement considérés comme protecteurs.<sup>10</sup>

Chez le nouveau-né, l'immunité contre une méningococcie systémique est conférée par le transfert passif des IgG de la mère au fœtus; chez le nourrisson né avant terme ce transfert est suboptimal. Au cours de la petite enfance, le pic de l'incidence de la méningococcie se produit lorsque les titres d'anticorps bactéricides sériques sont faibles et à l'âge adulte, la baisse de l'incidence de la maladie est corrélée avec l'augmentation de ces titres d'anticorps.<sup>9</sup>

#### Diagnostic

L'étalon or du diagnostic de la méningococcie invasive est l'isolement de *N. meningitidis* dans des liquides organiques normalement stériles – principalement le sang ou le liquide céphalo-rachidien (LCR) – ou par grattage de lésions cutanées purpuriques. Comme les méningocoques peuvent être une composante de la flore rhinopharyngée normale, leur isolement à cet endroit-là ne confirme pas définitivement un diagnostic clinique de méningococcie. Lorsqu'on démarre un traitement antibiotique par voie parentérale, le taux d'isolement de méningocoques dans les hémocultures chute, passant de 50% à <5%, et la probabilité que le LCR soit positif en culture ou à l'examen microscopique est également rapidement abaissée. Des méthodes basées sur la PCR rapide peuvent compléter les méthodes de laboratoire standard, car elles sont moins perturbées par un traitement antibiotique antérieur et elles sont de ce fait de plus en plus utilisées.<sup>3</sup>

<sup>7</sup> Greenwood B et al. Mortality from meningococcal disease during an epidemic in the Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1987, 81: 536–538.

<sup>8</sup> Ramakrishnan M et al. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Medicine*, 2009, 7:47.

<sup>9</sup> *The immunological basis for immunization series: module 15 – meningococcal disease*. Geneva, World Health Organization, 2010. (Available from [http://whqlibdoc.who.int/publications/2010/9789241599849\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599849_eng.pdf)).

<sup>10</sup> Greenwood B M et al. Factors influencing susceptibility to meningococcal disease during an epidemic in the Gambia, West Africa. *The Journal of Infection*, 1987, 14:167–184.

<sup>7</sup> Greenwood B et al. Mortality from meningococcal disease during an epidemic in the Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1987, 81: 536–538.

<sup>8</sup> Ramakrishnan M et al. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Medicine*, 2009, 7:47.

<sup>9</sup> *The immunological basis for immunization series: module 15 – meningococcal disease*. Genève, Organisation mondiale de la Santé, 2010. (Disponible sur [http://whqlibdoc.who.int/publications/2010/9789241599849\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599849_eng.pdf).) [Document disponible uniquement en langue anglaise.]

<sup>10</sup> Greenwood B M et al. Factors influencing susceptibility to meningococcal disease during an epidemic in the Gambia, West Africa. *The Journal of Infection*, 1987, 14:167–184.

Standard procedures to differentiate cultured *N. meningitidis* from related *Neisseria* species include testing for oxidase and the capacity to ferment selected carbohydrates. Where laboratory facilities are limited and rapid diagnosis essential, the latex agglutination test may be used. Although this test is less sensitive than PCR, it has a high specificity along with ease of performance when conducted by experienced laboratory technicians.<sup>11</sup> Multilocus sequence typing is now used to identify major invasive lineages of the pathogen during outbreaks and epidemics.<sup>12</sup>

#### Treatment

Empiric therapy with cefotaxime or ceftriaxone should be started while awaiting confirmation of diagnosis. Once the diagnosis is confirmed, treatment can be changed to intravenous penicillin G. Alternatively, ceftriaxone may be used for the entire duration of therapy owing to ease of dosing and reports of decreased susceptibility to penicillin in several countries. A single dose of long-acting chloramphenicol or ceftriaxone is used for the treatment of epidemic meningococcal meningitis in sub-Saharan Africa.<sup>3, 13</sup> In certain developing countries where penicillin resistance is high, such as Viet Nam, intramuscularly administered chloramphenicol is the standard treatment for *N. meningitidis*, but emerging resistance to this drug is a cause for concern.<sup>3</sup>

Septicaemic shock and raised intracranial pressure in meningitis are particular problems in the management of meningococcal disease. In addition to antibiotics, intensive care measures are required. WHO guidelines for diagnosing and managing meningitis have recently been published.<sup>13</sup>

Close contacts of a patient with invasive meningococcal disease are at increased risk of secondary disease. Antibiotics are effective in preventing additional cases through eradicating carriage of the invasive strain. Most secondary cases occur within the first 72 hours after presentation of the index case; risk of secondary disease decreases to near baseline by 10–14 days. Close contacts include household, child care, and preschool contacts. In outbreaks involving limited populations, those with direct, prolonged contact with a case of meningococcal disease may also be offered clearance treatment. Ideally, where indicated, treatment should be started within 24 hours of identification of the index case. Antibiotics effective for this purpose include rifampicin, ciprofloxacin, ceftriaxone or azithromycin.<sup>14</sup>

Les méthodes standard permettant de distinguer les *N. meningitidis* cultivées des espèces de *Neisseria* apparentées comprennent la recherche d'oxydase et la capacité à fermenter certains glucides. Lorsque les installations de laboratoire sont limitées et qu'un diagnostic rapide est essentiel, l'épreuve d'agglutination au latex peut être utilisée. Bien qu'elle soit moins sensible que la PCR, elle est hautement spécifique et facile à mettre en œuvre lorsqu'elle est pratiquée par des techniciens de laboratoire expérimentés.<sup>11</sup> Le typage séquentiel multilocus est désormais utilisé pour identifier les principales lignées invasives de ce germe au cours des flambées et des épidémies.<sup>12</sup>

#### Traitement

Un traitement empirique par le céfotaxime ou la ceftriaxone doit être démarré en attendant la confirmation du diagnostic. Une fois celui-ci confirmé, on peut passer à un traitement à la pénicilline G par voie intraveineuse. Sinon, il est possible d'utiliser la ceftriaxone pour toute la durée du traitement étant donné sa facilité d'administration et le fait qu'on a rapporté une sensibilité moindre à la pénicilline dans plusieurs pays. Une dose unique de chloramphénicol ou de ceftriaxone à action prolongée est employée pour le traitement de la méningite à méningocoques épidémique en Afrique subsaharienne.<sup>3, 13</sup> Dans certains pays en développement où la résistance à la pénicilline est élevée, comme le Viet Nam, le chloramphénicol administré par voie intramusculaire est le traitement standard de l'infection à *N. meningitidis*, mais l'émergence d'une résistance à ce médicament suscite des préoccupations.<sup>3</sup>

Le choc septicémique et l'élévation de la pression intracrânienne en cas de méningite sont des problèmes particuliers au cours de la prise en charge de la méningococcie. Des soins intensifs sont nécessaires en plus des antibiotiques. Des lignes directrices OMS relatives au diagnostic et à la prise en charge de la méningite ont récemment été publiées.<sup>13</sup>

L'entourage d'un patient présentant une méningococcie invasive est exposé à un risque accru de maladie secondaire. Les antibiotiques sont efficaces pour prévenir l'apparition d'autres cas car ils éradiquent le portage de la souche invasive. La plupart des cas secondaires se produisent dans les 72 heures suivant la déclaration du cas initial; le risque diminue ensuite jusqu'à une valeur proche du niveau de départ en 10 à 14 jours. Dans l'entourage figurent les personnes vivant dans le ménage, celles s'occupant des enfants et les contacts d'âge préscolaire. Lors des flambées sévissant dans des populations limitées, on peut également offrir un traitement bactéricide à tous ceux qui ont eu un contact direct et prolongé avec un cas de méningococcie. L'idéal est de commencer le traitement, lorsqu'il est indiqué, dans les 24 heures suivant l'identification du cas initial. Les antibiotiques efficaces à cette fin sont la rifampicine, la ciprofloxacin, la ceftriaxone ou l'azithromycine.<sup>14</sup>

<sup>11</sup> Bronská E et al. Invasive meningococcal disease and latex agglutination test—is it still beneficial for diagnosis? *Folia Microbiologica (Praha)*, 2005, 50:453–456.

<sup>12</sup> Jolley KA et al. Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS microbiology reviews*, 2007, 3:89–96.

<sup>13</sup> *Managing meningitis epidemics in Africa*. Geneva, World Health Organization, 2010 (WHO/HSE/GAR/ERI/2010.4). (Also available at [http://whqlibdoc.who.int/hq/2010/WHO\\_HSE\\_GAR\\_ERI\\_2010.4\\_eng.pdf](http://whqlibdoc.who.int/hq/2010/WHO_HSE_GAR_ERI_2010.4_eng.pdf)).

<sup>14</sup> Zelmanovici Trestioreanu A et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Systemic Review*, 2011, CD004785.

<sup>11</sup> Bronská E et al. Invasive meningococcal disease and latex agglutination test—is it still beneficial for diagnosis? *Folia Microbiologica (Praha)*, 2005, 50:453–456.

<sup>12</sup> Jolley KA et al. Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS microbiology reviews*, 2007, 3:89–96.

<sup>13</sup> *Gestion des épidémies de méningite en Afrique*. Genève, Organisation mondiale de la Santé, 2010 (WHO/HSE/GAR/ERI/2010.4). (Egalement disponible sur [http://whqlibdoc.who.int/hq/2010/WHO\\_HSE\\_GAR\\_ERI\\_2010.4\\_fre.pdf](http://whqlibdoc.who.int/hq/2010/WHO_HSE_GAR_ERI_2010.4_fre.pdf)).

<sup>14</sup> Zelmanovici Trestioreanu A et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Systemic Review*, 2011, CD004785.

## Meningococcal vaccines

Currently available meningococcal vaccines include polysaccharide vaccines and polysaccharide-protein conjugate vaccines. Although purified capsular polysaccharide antigens elicit protective antibody responses, conjugate vaccines are more immunogenic and also induce immunological memory. Both polysaccharide and conjugate vaccines are available against meningococci of serogroups A, C, W135 and Y.

Serogroup B vaccines are based on protein (outer membrane vesicles) extracted from selected outbreak strains. Strain-specific serogroup B vaccines have been used successfully in some countries to limit outbreaks, but they are not widely available.

No vaccine is available against disease caused by serogroup X meningococci.

Meningococcal vaccines should be stored at 2–8°C. Most meningococcal polysaccharide vaccines are recommended for subcutaneous injection whereas conjugated meningococcal vaccines are administered by deep intramuscular injection, preferably in the deltoid muscle (or in the anterolateral aspect of the upper thigh in individuals <12 months of age). The vaccines must not be administered intravenously, and must not be mixed with other vaccines in the same syringe. In general, meningococcal vaccines can be administered simultaneously with other vaccines, provided separate sites of injection are used. Detailed information on the individual vaccines is offered by the manufacturers in package leaflets.

WHO has developed a set of quality requirements for the production and control of meningococcal group A and C polysaccharide vaccines<sup>15</sup> and protein conjugate vaccines.<sup>16, 17</sup>

Due to the relatively low incidence of meningococcal disease, pre-licensure clinical efficacy studies may not be feasible. Meningococcal polysaccharide and protein conjugate vaccines are licensed based on evidence of an immune response in vaccinated subjects using serum bactericidal activity (SBA) as the immunologic correlate of protection. In a prospective study of new US army recruits, a strong correlation was observed between development of MenC disease and anti-MenC hSBA titres of  $\leq 1:4$  (a SBA test using human complement). Also, in studies on sera from unvaccinated sub-

## Vaccins antiméningococciques

Les vaccins antiméningococciques actuellement disponibles comprennent les vaccins polysidiques et les vaccins polysidiques conjugués. Bien que les antigènes polysidiques capsulaires purifiés provoquent des réponses en anticorps protecteurs, les vaccins conjugués sont plus immunogènes et induisent également une mémoire immunologique. Des vaccins polysidiques et des vaccins conjugués sont disponibles contre les méningocoques des sérogroupes A, C, W135 et Y.

Les vaccins contre le sérogruppe B sont préparés à partir d'une protéine (vésicules de la membrane externe) extraite de certaines souches à l'origine de flambées. Des vaccins contre le sérogruppe B spécifiques de souche ont été utilisés avec succès dans certains pays pour limiter les flambées mais ils ne sont pas largement disponibles.

On ne dispose d'aucun vaccin contre la maladie causée par les méningocoques appartenant au sérogruppe X.

Les vaccins antiméningococciques doivent être conservés entre 2°C et 8°C. La plupart des vaccins polysidiques sont recommandés en injection sous-cutanée, tandis que les vaccins conjugués sont administrés par injection intramusculaire profonde, de préférence dans le deltoïde (ou sur la face antérolatérale de la cuisse chez les sujets âgés de <12 mois). Ces vaccins ne doivent pas être administrés par voie intraveineuse et ne doivent pas être mélangés avec d'autres vaccins dans la même seringue. En général, ils peuvent être administrés simultanément avec d'autres vaccins pour autant qu'on utilise des points d'injection séparés. Des informations détaillées concernant chaque vaccin figurent dans les notices d'emballage des fabricants.

L'OMS a élaboré une série de normes de qualité relatives à la production et au contrôle des vaccins polysidiques contre les groupes A et C<sup>15</sup> et des vaccins conjugués.<sup>16, 17</sup>

En raison de l'incidence relativement faible de la méningococcie, des études d'efficacité clinique avant homologation peuvent ne pas être réalisables. Les vaccins antiméningococciques polysidiques et conjugués reçoivent une autorisation de mise sur le marché basée sur la preuve d'une réponse immunitaire chez les sujets vaccinés, en se servant de l'activité bactéricide du sérum (ABS) comme indicateur immunologique de protection. Dans une étude prospective réalisée chez de nouvelles recrues de l'armée des États-Unis, on a observé une forte corrélation entre l'apparition d'une méningococcie C (MenC) et le titre d'activité bactéricide anti MenC hABS  $\leq 1:4$  (test utilisant du complément

<sup>15</sup> Requirements for meningococcal polysaccharide vaccine (Amendment 1999). In: *WHO Expert Committee on Biological Standardization. Fiftyth report*. Geneva, World Health Organization, 2002, Annex 2 (WHO Technical Report Series, No. 904). (Available at [http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/WHO\\_TRS\\_904\\_Amendment1999\\_meningA2.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/WHO_TRS_904_Amendment1999_meningA2.pdf).)

<sup>16</sup> Recommendations for the production and control of group C meningococcal conjugate vaccines (Addendum 2003). In: *WHO Expert Committee on Biological Standardization. Fifty-third report*. Geneva, World Health Organization, 2004, Annex 3 (WHO Technical Report Series, No. 926). (Available at [http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/Annex%203%20\(90-94\)TRS-926meningC2003.Pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/Annex%203%20(90-94)TRS-926meningC2003.Pdf).)

<sup>17</sup> Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines (WHO/BS/06.2041). In: *WHO Expert Committee on Biological Standardization*. Geneva, World Health Organization, 2006 (<http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/MenA%20Final%20BS204102.Nov.06.pdf>, accessed November 2011).

<sup>15</sup> Requirements for meningococcal polysaccharide vaccine (Amendment 1999). In: *WHO Expert Committee on Biological Standardization. Fiftyth report*. Genève, Organisation mondiale de la Santé, 2002, Annexe 2 (Série de rapports techniques de l'OMS, No 904). (Disponible sur [http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/WHO\\_TRS\\_904\\_Amendment1999\\_meningA2.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/WHO_TRS_904_Amendment1999_meningA2.pdf).) [Document disponible uniquement en langue anglaise.]

<sup>16</sup> Recommendations for the production and control of group C meningococcal conjugate vaccines (Addendum 2003). In: *WHO Expert Committee on Biological Standardization. Fifty-third report*. Genève, Organisation mondiale de la Santé, 2002, Annexe 2 (Série de rapports techniques de l'OMS, No 926) (Disponible sur [http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/Annex%203%20\(90-94\)TRS926meningC2003.Pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/Annex%203%20(90-94)TRS926meningC2003.Pdf).) [Document disponible uniquement en langue anglaise.]

<sup>17</sup> Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines (WHO/BS/06.2041). In: *WHO Expert Committee on Biological Standardization*. Genève, Organisation mondiale de la Santé, 2006 (<http://www.who.int/biologicals/publications/trs/areas/vaccines/meningococcal/MenA%20Final%20BS204102.Nov.06.pdf>, consulté en novembre 2011). [Document disponible uniquement en langue anglaise.]



jects, hSBA titres seem to correlate with clinical protection against group A, B or C meningococcal disease.<sup>18</sup> Immunological studies on serogroup C infection showed that anti-meningococcal titres of  $\geq 1:8$  in rSBA tests (SBA test using rabbit complement) reliably predict protection against serogroup C disease.<sup>19</sup> Titres of  $\geq 1:4$  in hSBA or  $\geq 1:8$  in rSBA are commonly accepted as correlates of protection also against meningococci of other serogroups, for example as criteria for vaccine licensure.<sup>3</sup> So far, however, the correlations of these titres with protection against group A, W or Y meningococcal disease have not been adequately studied in clinical trials.

Recent studies on vaccine failures following immunization with MenC conjugate vaccines in the United Kingdom suggest that persistence of specific antibodies may be a more appropriate correlate of long-term protection than the ability to generate a booster response on exposure to the antigen.<sup>20</sup>

#### Polysaccharide vaccines

Internationally marketed meningococcal polysaccharide vaccines are based on purified, heat-stable, lyophilized capsular polysaccharides from meningococci of the respective serogroup. They are available in bivalent (A, C), trivalent (A, C, W135), and quadrivalent (A, C, W135, Y) formulations. The vaccines contain 50 µg of each of the individual polysaccharides. No adjuvants are included. Only one manufacturer produces multidose vials that contain thiomersal as a preservative. Meningococcal polysaccharide vaccines are administered as a single dose to persons  $\geq 2$  years old; most of these vaccines are given subcutaneously.

Adverse reactions to polysaccharide meningococcal vaccines are usually mild; the most frequent reaction is 1–2 days of pain and redness at the site of injection, which occur in 4%–56% of vaccine recipients. Transient fever is reported in <5% of recipients, most commonly in infants. The rate of systemic allergic reactions (e.g. urticaria, wheezing, rash) is estimated at <0.1/100 000 vaccine doses and anaphylaxis has been documented in <0.1/100 000 vaccine recipients. Neurologic reactions (e.g., seizures, anaesthesias, and paraesthesias) have also been observed infrequently.<sup>9</sup> With the exception of previous severe allergic reaction to any component of these vaccines, there are no contraindications to their use, including for vaccination of pregnant women and immunodeficient individuals.

The immunogenicity and clinical efficacy of serogroup A and serogroup C meningococcal polysaccharide vaccines are well established. A Cochrane review

humain). De plus, dans des études effectuées sur les sérums de sujets non vaccinés, les titres du hABS semblent être corrélés avec la protection clinique contre la méningococcie des groupes A, B ou C.<sup>18</sup> Des études immunologiques sur l'infection par le séro-groupe C ont montré que des titres d'anticorps antiméningococques  $\geq 1:8$  dans les tests de mise en évidence du IABS (test utilisant du complément de lapin) permettent de prévoir de manière fiable la protection contre la maladie due au séro-groupe C.<sup>19</sup> Des titres  $\geq 1:4$  dans les tests du hABS ou  $\geq 1:8$  dans les tests du IABS sont communément acceptés aussi comme indicateurs de protection contre des méningocoques appartenant à d'autres sérogroupes, par exemple comme critères d'homologation d'un vaccin.<sup>3</sup> Cependant, jusqu'ici, les corrélations que ces titres ont montré avec la protection contre les groupes A, W ou Y n'ont pas été suffisamment étudiées dans des essais cliniques.

Des études récentes menées sur les échecs vaccinaux enregistrés suite à la vaccination par les vaccins conjugués MenC au Royaume-Uni laissent à penser que la persistance d'anticorps spécifiques peut être un indicateur plus approprié de la protection à long terme que l'aptitude à générer une réaction anamnétique lors de l'exposition à l'antigène.<sup>20</sup>

#### Vaccins polyosidiques

Les vaccins antiméningococciques polyosidiques présents sur le marché international sont préparés à partir de polyosides capsulaires purifiés, thermostables et lyophilisés, issus des sérogroupes correspondants. Ils sont disponibles en formulations bivalentes (A, C), trivalentes (A, C, W135) et quadrivalentes (A, C, W135, Y). Ces vaccins renferment 50 µg de chacun des polyosides. Il n'y a aucun adjuvant. Un seul fabricant produit des flacons multidoses qui renferment du thiomersal comme conservateur. Les vaccins antiméningococciques polyosidiques sont administrés en une dose unique aux sujets âgés de  $\geq 2$  ans; la plupart le sont par voie sous-cutanée.

Les réactions indésirables à ces vaccins sont généralement bénignes; la réaction la plus fréquente est une douleur et une rougeur durant 1 ou 2 jours au point d'injection, qui se produit chez 4%–56% des vaccinés. Une fièvre transitoire est signalée chez <5% des vaccinés, le plus souvent chez les nourrissons. La fréquence des réactions allergiques systémiques (urticaire, respiration sifflante, rash cutané) est, selon les estimations, <0,1/100 000 doses de vaccin et des réactions anaphylactiques ont été documentées chez <0,1/100 000 vaccinés. Des réactions neurologiques (convulsions, anesthésies et paresthésies) ont peu souvent été observées aussi.<sup>9</sup> A l'exception d'une réaction allergique antérieure grave à l'un des constituants de ces vaccins, il n'y a pas de contre-indication à leur utilisation, notamment chez la femme enceinte et les sujets immunodéfi-cients.

L'immunogénicité et l'efficacité clinique des vaccins antiméningococciques polyosidiques contre le séro-groupe A et le séro-groupe C sont bien établies. Une revue Cochrane des études

<sup>18</sup> Goldschneider I et al. Human immunity to the meningococcus. I. The role of humoral antibodies. *Journal of Experimental Medicine*, 1969, 129:1307–1326.

<sup>19</sup> Borrow R et al. Meningococcal surrogates of protection—serum bactericidal antibody activity. *Vaccine*, 2005, 23:2222–2227.

<sup>20</sup> Auckland C. Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. *The Journal of infectious diseases*, 2006, 194:1745–1752.

<sup>18</sup> Goldschneider I et al. Human immunity to the meningococcus. I. The role of humoral antibodies. *Journal of Experimental Medicine*, 1969, 129:1307–1326.

<sup>19</sup> Borrow R et al. Meningococcal surrogates of protection—serum bactericidal antibody activity. *Vaccine*, 2005, 23:2222–2227.

<sup>20</sup> Auckland C. Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. *The Journal of infectious diseases*, 2006, 194:1745–1752.

of immunogenicity studies<sup>21</sup> showed that group A polysaccharide vaccines have documented short-term efficacy levels of 85%–100% both in children aged  $\geq 2$  years and in adults. Although serogroup A polysaccharide may induce an antibody response in infants as young as 3 months, a response comparable to that occurring in adults is not achieved until age 4–5 years. The serogroup C component is poorly immunogenic among recipients aged <18–24 months and hypo-responsiveness to repeated doses of serogroup C polysaccharide vaccine has been demonstrated in infants and adults, especially if doses are repeated more than once. Serogroups W135 and Y polysaccharides are safe and immunogenic among adults and children aged  $>2$  years.<sup>9</sup>

When different serogroups of meningococcal polysaccharide are administered together as bivalent, trivalent or quadrivalent vaccines, independent group-specific immune responses are obtained.

The high protective effectiveness of meningococcal polysaccharide vaccines is demonstrated in studies on immunization of closed populations of adults at high risk for disease, including household contacts of affected individuals and military recruits.<sup>22, 23</sup> Such vaccines are also used successfully in outbreak control,<sup>24</sup> but they do not seem to have any significant impact on meningococcal carriage in the nasopharynx.<sup>25, 26</sup>

After a single dose of the vaccine in children  $<4$  years of age the levels of specific antibodies as well as clinical protection decline rapidly over the first 2–3 years, whereas in school children and adults, a single dose of groups A and C polysaccharide vaccine provides protection for at least 3 years.<sup>9</sup> After 3–5 years, one booster dose may be given to persons considered to be at continued risk of exposure including health workers.

Exploring the possible use of reduced vaccine doses in case of vaccine shortage,<sup>6</sup> a trial that included non-immune volunteers in Uganda demonstrated non-inferiority for 1/5 doses versus full doses for serogroups A, W135, and Y, but not for serogroup C.<sup>27</sup>

Although some countries such as China, Saudi Arabia and Syria have used meningococcal polysaccharide vaccines in their routine vaccination programmes, these

d'immunogénicité<sup>21</sup> a montré que les vaccins polysidiques contre le groupe A ont des degrés d'efficacité à court terme documentés de 85% à 100%, aussi bien chez les enfants âgés de  $\geq 2$  ans que chez les adultes. Bien que le polyside du sérotype A puisse induire une réponse en anticorps chez des nourrissons dès l'âge de 3 mois, une réponse comparable à celle observée chez l'adulte n'est pas atteinte avant l'âge de 4 à 5 ans. La composante anti-sérogroupe C est peu immunogène avant l'âge de 18 à 24 mois et l'on a mis en évidence une faible réponse à des doses répétées de vaccin polysidique antisérogroupe C chez les nourrissons et les adultes, surtout si les doses sont répétées plusieurs fois. Les polysides des sérotypes W135 et Y sont sûrs et immunogènes chez l'adulte et l'enfant âgé de  $>2$  ans.<sup>9</sup>

Lorsqu'on administre ensemble les polysides antiméningococciques de différents sérotypes sous forme de vaccins bivalents, trivalents ou quadrivalents, on obtient des réponses immunitaires spécifiques de groupe indépendantes.

L'efficacité protectrice élevée des vaccins antiméningococciques polysidiques est démontrée par des études sur la vaccination de populations fermées d'adultes exposés à un risque élevé de maladie, notamment les contacts familiaux des sujets touchés et les recrues de l'armée.<sup>22, 23</sup> Ces vaccins sont également utilisés avec succès pour lutter contre les flambées,<sup>24</sup> mais ils ne semblent pas avoir un effet important sur le portage du méningocoque dans le rhinopharynx.<sup>25, 26</sup>

Après une dose unique de vaccin chez l'enfant de  $<4$  ans, les concentrations d'anticorps spécifiques et la protection clinique diminuent rapidement au cours des 2 à 3 premières années, tandis que chez les enfants d'âge scolaire et les adultes, une dose unique d'un vaccin polysidique contre les sérotypes A et C assure une protection pendant au moins 3 ans.<sup>9</sup> Au bout de 3 à 5 ans, un rappel peut être administré aux personnes considérées comme étant exposées en permanence au risque, notamment les agents de santé.

En explorant les possibilités d'utilisation de doses vaccinales réduites en cas de pénurie de vaccins,<sup>6</sup> un essai portant sur des volontaires non immuns en Ouganda a mis en évidence la non-infériorité de doses divisées par 5 par rapport aux doses complètes pour les sérotypes A, W135 et Y, mais pas pour le sérotype C.<sup>27</sup>

Bien que certains pays comme l'Arabie saoudite, la Chine et la Syrie, aient utilisé des vaccins antiméningococciques polysidiques dans leurs programmes de vaccination systématique, ces

<sup>21</sup> Patel M et al. Polysaccharide vaccines for preventing serogroup A meningococcal meningitis. *Cochrane database of systematic reviews*, 2005: CD001093.

<sup>22</sup> Greenwood BM et al. Prevention of secondary cases of meningococcal disease in household contacts by vaccination. *British medical journal*, 1978, 1:1317–1319.

<sup>23</sup> Biselli R et al. Dramatic reduction of meningococcal meningitis among military recruits in Italy after introduction of specific vaccination. *Vaccine*, 1993, 11: 578–581.

<sup>24</sup> Rosenstein N et al. Efficacy of meningococcal vaccine and barriers to vaccination. *JAMA: + the journal of the American Medical Association*, 1998, 279:435–439.

<sup>25</sup> Dellicour S, Greenwood BM. Impact of meningococcal vaccination on pharyngeal carriage of meningococci. *Tropical Medicine and International Health*, 2007, 12:1409–1421.

<sup>26</sup> Grading of scientific evidence – Table I (effect of meningococcal vaccines on mucosal carriage). Available at [http://www.who.int/entity/immunization/meningococcal\\_grad\\_carriage.pdf](http://www.who.int/entity/immunization/meningococcal_grad_carriage.pdf).

<sup>27</sup> Guerin P et al. Immunogenicity of fractional doses of tetravalent a/C/Y/W135 meningococcal polysaccharide vaccine: results from a randomized non-inferiority controlled trial in Uganda. *PLoS Neglected Tropical Diseases*, 2008, 2: e342.

<sup>21</sup> Patel M et al. Polysaccharide vaccines for preventing serogroup A meningococcal meningitis. *Cochrane database of systematic reviews*, 2005: CD001093.

<sup>22</sup> Greenwood BM et al. Prevention of secondary cases of meningococcal disease in household contacts by vaccination. *British medical journal*, 1978, 1:1317–1319.

<sup>23</sup> Biselli R et al. Dramatic reduction of meningococcal meningitis among military recruits in Italy after introduction of specific vaccination. *Vaccine*, 1993, 11: 578–581.

<sup>24</sup> Rosenstein N et al. Efficacy of meningococcal vaccine and barriers to vaccination. *JAMA: + the journal of the American Medical Association*, 1998, 279:435–439.

<sup>25</sup> Dellicour S, Greenwood BM. Impact of meningococcal vaccination on pharyngeal carriage of meningococci. *Tropical Medicine and International Health*, 2007, 12:1409–1421.

<sup>26</sup> Cotation des preuves scientifiques – Tableau I (effet des vaccins antiméningococciques sur le portage rhinopharyngé). Disponible sur [http://www.who.int/entity/immunization/meningococcal\\_grad\\_carriage.pdf](http://www.who.int/entity/immunization/meningococcal_grad_carriage.pdf).

<sup>27</sup> Guerin P et al. Immunogenicity of fractional doses of tetravalent a/C/Y/W135 meningococcal polysaccharide vaccine: results from a randomized non-inferiority controlled trial in Uganda. *PLoS Neglected Tropical Diseases*, 2008, 2: e342.

vaccines have typically been used in campaigns in response to outbreaks, for travellers at increased risk of meningococcal disease, including travellers for the Hajj, and for protection of immunodeficient individuals.

#### Conjugate vaccines

Licensed meningococcal conjugate vaccines are currently monovalent (A or C) or quadrivalent (A, C, W135, Y) and also include a combination vaccine based on *Haemophilus influenza* type b and *Neisseria meningitidis* serogroup C vaccines (HibMenC).

The protein conjugate of these vaccines consists of either diphtheria toxoid or a non-toxic mutant of diphtheria toxin (CRM 197), or tetanus toxoid. Serogroup C conjugate vaccines were introduced in the United Kingdom in 1999. Since then, quadrivalent (A, C, W135, Y) and monovalent group A conjugate vaccines have also been licensed. Many countries have introduced conjugate vaccines into their routine vaccination schedules.

All meningococcal conjugate vaccines have an excellent safety record. None has been associated with any serious adverse effects, either during clinical trials or in post-marketing surveillance. Redness, swelling and pain at the site of injection may occur. Such reactions usually start within the first day after immunization and last 1 to 3 days. Less commonly, children may develop a fever or be irritable for a short period.<sup>3, 28</sup>

#### Monovalent serogroup C conjugate vaccines (MenC conjugate vaccines)

These vaccines contain 10 µg of group C oligosaccharide conjugated to 12.5–25.0 µg of the carrier (diphtheria toxoid, CRM-197, or tetanus toxoid); single-dose formulations do not contain preservatives. MenC conjugate vaccines are licensed for children aged >2 months, adolescents and adults. Infants aged 2–11 months are given 2 doses (0.5 ml per dose) with at least 2 months between the doses, followed by a booster dose about one year later.<sup>29</sup> The possible need for boosters is not yet established for individuals >1 year of age, who normally receive one dose only. Immunogenicity studies in healthy adults and adolescents have shown a significant rise in geometric mean titres one month after vaccination with a MenC conjugate vaccine<sup>30</sup> and these vaccines are also highly immunogenic in infants and young children.<sup>31</sup> Similar antibody responses have been obtained when MenC conjugate vaccines are co-administered

vaccins ont habituellement été employés dans des campagnes de vaccination menées en réponse à des flambées, chez des voyageurs exposés à un risque accru de méningococcie, notamment les pèlerins du Hadj, et pour protéger des sujets immunodéficients.

#### Vaccins conjugués

Les vaccins antiméningococciques conjugués homologués sont actuellement monovalents (A ou C) ou quadrivalents (A, C, W135, Y) et comprennent également un vaccin associé renfermant les vaccins anti-*Haemophilus influenza* type b et anti-*Neisseria meningitidis* sérogruppe C (HibMenC).

La protéine conjuguée de ces vaccins est l'anatoxine diphtérique ou un mutant non toxique de l'anatoxine diphtérique (CRM-197), ou encore l'anatoxine tétanique. Les vaccins conjugués contre le sérogruppe C ont été introduits au Royaume-Uni en 1999. Depuis lors, des vaccins conjugués quadrivalents (A, C, W135, Y) et monovalents contre le groupe A ont également été homologués. De nombreux pays ont introduit ces vaccins conjugués dans leurs calendriers de vaccination systématique.

Tous les vaccins antiméningococciques conjugués ont un excellent profil de sécurité. Aucun n'a été associé à des réactions indésirables graves, que ce soit au cours des essais cliniques ou lors de la surveillance après commercialisation. Une rougeur et une tuméfaction douloureuses peuvent apparaître au point d'injection. Ces réactions se manifestent dans les 24 heures suivant la vaccination et durent 1 à 3 jours. Plus rarement, les enfants peuvent présenter de la fièvre ou être irritables pendant une courte période.<sup>3, 28</sup>

#### Vaccins conjugués monovalents contre le sérogruppe C (vaccins conjugués MenC)

Ces vaccins renferment 10 µg d'oligosaccharide du groupe C conjugués à 12,5–25,0 µg de protéine porteuse (anatoxine diphtérique, CRM-197, ou anatoxine tétanique); les formulations monodoses ne contiennent pas de conservateur. Les vaccins conjugués MenC sont homologués pour l'enfant âgé de >2 mois, l'adolescent et l'adulte. Les nourrissons âgés de 2 à 11 mois en reçoivent 2 doses (0,5 ml par dose) espacées d'au moins 2 mois, suivies d'un rappel 1 an plus tard.<sup>29</sup> La nécessité éventuelle des rappels n'est pas encore établie pour les sujets de >1 an qui, normalement, n'en reçoivent qu'une seule dose. Les études d'immunogénicité réalisées chez des adultes et des adolescents en bonne santé ont montré une élévation importante des titres moyens géométriques un mois après la vaccination par le vaccin conjugué MenC,<sup>30</sup> vaccin qui est également hautement immunogène chez le nourrisson et le jeune enfant.<sup>31</sup> On a obtenu des réponses en anticorps comparables lorsque les vaccins conjugués MenC sont administrés simultanément avec

<sup>28</sup> See No 30, 2011, pp 317–324.

<sup>29</sup> Borrow R et al. Immunogenicity of, and immunologic memory to, a reduced primary schedule of meningococcal C-tetanus toxoid conjugate vaccine in infants in the United Kingdom. *Infection and Immunity*, 2003, 71:5549–5555.

<sup>30</sup> Goldblatt D et al. Natural and vaccine-induced immunity and immunologic memory to *Neisseria meningitidis* serogroup C in young adults. *Journal of Infectious Diseases*, 2002, 185: 397–400.

<sup>31</sup> Southern J et al. Immunogenicity of a reduced schedule of meningococcal group C conjugate vaccine given concomitantly with the Prevenar and Pediacel vaccines in healthy infants in the United Kingdom. *Clinical and Vaccine Immunology*, 2009, 16:194–199.

<sup>28</sup> Voir N° 30, 2011, pp 317–324.

<sup>29</sup> Borrow R et al. Immunogenicity of, and immunologic memory to, a reduced primary schedule of meningococcal C-tetanus toxoid conjugate vaccine in infants in the United Kingdom. *Infection and Immunity*, 2003, 71:5549–5555.

<sup>30</sup> Goldblatt D et al. Natural and vaccine-induced immunity and immunologic memory to *Neisseria meningitidis* serogroup C in young adults. *Journal of Infectious Diseases*, 2002, 185: 397–400.

<sup>31</sup> Southern J et al. Immunogenicity of a reduced schedule of meningococcal group C conjugate vaccine given concomitantly with the Prevenar and Pediacel vaccines in healthy infants in the United Kingdom. *Clinical and Vaccine Immunology*, 2009, 16:194–199.

with routine infant vaccines and when they are given alone.<sup>32</sup>

Whereas the short-term efficacy of the MenC conjugate vaccines in England was 97% (95% CI 77–99) for teenagers and 92% (95% CI 65–98) for toddlers,<sup>33</sup> questions remain regarding the long-term effectiveness of these vaccines because only 8–12% of children who had completed a 3-dose series in infancy had rSBA titers  $\geq 1:8$  at 4 years of age.<sup>34</sup> In a clinical trial of 250 children, rSBA titres were tested 6 years after the primary MenC conjugate immunization series; age at priming ranged from 2 months to 6 years. Only 25% (95% CI 20–30) of the children had protective titres  $\geq 1:8$ . However, a booster dose was highly effective in this cohort and resulted in rSBA titres of  $\geq 1:8$  in 99.6% of participants measured 1 year after the booster dose.<sup>35</sup>

Ten years of experience in countries with adequate surveillance systems have shown large reductions in meningococcal serogroup C disease as a result of MenC conjugate vaccine introduction. In England and Wales, mass vaccination campaigns followed by routine infant vaccination have led to sustained control of serogroup C meningococcal disease even though serological protection (rSBA titer  $\geq 1:8$ ) has not been long lasting in those vaccinated as infants or toddlers.<sup>36</sup> This impact on disease reduction despite waning antibody titres has been attributed in part to the development of herd protection as a consequence of reduced nasopharyngeal carriage.<sup>37</sup> Similar results have been seen in Australia, Canada and the Netherlands. However in Spain, where in some regions the catch-up programme was not extended to individuals >5 years of age, there was less evidence of herd protection.<sup>38</sup>

For grading of scientific evidence for the efficacy and safety of MenC conjugate vaccines, see the relevant footnotes.<sup>39, 40</sup>

d'autres vaccins habituels chez les nourrissons ou lorsqu'ils sont administrés seuls.<sup>32</sup>

Alors que l'efficacité à court terme des vaccins conjugués MenC était en Angleterre de 97% (IC à 95%: 77-99) chez les adolescents et de 92% (IC à 95%: 65-98) chez les tout-petits,<sup>33</sup> des questions demeurent concernant leur efficacité à long terme parce que seuls 8 à 12% des enfants ayant reçu les 3 doses au cours de la petite enfance avaient des titres du IABS  $\geq 1:8$  à l'âge de 4 ans.<sup>34</sup> Lors d'un essai clinique portant sur 250 enfants, ces titres ont été recherchés 6 ans après la série de primovaccination par le vaccin conjugué MenC; l'âge auquel cette primovaccination avait été effectuée allait de 2 mois à 6 ans. Seuls 25% (IC à 95%: 20-30) des enfants possédaient des titres protecteurs  $\geq 1:8$ . Cependant, un rappel a été extrêmement efficace dans cette cohorte entraînant l'apparition de titres du IABS  $\geq 1:8$  chez 99,6% des participants un an après l'administration du rappel.<sup>35</sup>

Dix ans d'expérience dans des pays disposant de bons systèmes de surveillance ont montré de fortes réductions du nombre de cas de méningococcie du sérogroupe C suite à l'introduction du vaccin conjugué MenC. En Angleterre et au Pays de Galles, des campagnes de vaccination de masse suivies par la vaccination systématique des nourrissons ont conduit à une lutte soutenue contre la méningococcie due au sérogroupe C, même si la protection sérologique (titre du IABS  $\geq 1:8$ ) n'a pas duré longtemps chez les sujets vaccinés au cours de la petite enfance.<sup>36</sup> Cet effet sur la maladie, malgré des titres d'anticorps déclinants, a été en partie attribué au développement d'une immunité collective découlant de la réduction du portage rhinopharyngé.<sup>37</sup> Des résultats comparables ont été observés en Australie, au Canada et aux Pays-Bas. Cependant, en Espagne, où dans certaines régions le programme de rattrapage n'a pas été étendu aux sujets de >5 ans, l'immunité collective a été moins manifeste.<sup>38</sup>

Pour la classification des données scientifiques relatives à l'efficacité et à l'innocuité des vaccins conjugués MenC, voir les notes.<sup>39, 40</sup>

<sup>32</sup> Halperin S A et al. Simultaneous administration of meningococcal C conjugate vaccine and diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b conjugate vaccine in children: A randomized double-blind study. *Clinical and Investigative Medicine*, 2002, 25:243–251.

<sup>33</sup> Ramsay M E et al. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet*, 2001, 357:195–196.

<sup>34</sup> Borrow R et al. Antibody persistence and immunological memory at age 4 years after meningococcal group C conjugate vaccination in children in the United Kingdom. *Journal of Infectious Diseases*, 2002, 186: 1353–1357.

<sup>35</sup> Perrett K P et al. Antibody persistence after serogroup C meningococcal conjugate immunization of United Kingdom primary-school children in 1999–2000 and response to a booster: A phase 4 clinical trial. *Clinical and Vaccine Immunology*, 2010, 50:1601–1610.

<sup>36</sup> Campbell H et al. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clinical and Vaccine Immunology*, 2010, 17:840–847.

<sup>37</sup> Trotter CL et al. Meningococcal vaccines and herd immunity: Lessons learned from serogroup C conjugate vaccination programs. *Expert Review of Vaccines*, 2009, 8:851–861.

<sup>38</sup> Larrauri A et al. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. *Vaccine*, 2005, 23:4097–4100.

<sup>39</sup> Grading of scientific evidence – Table II a & b (efficacy of MenC conjugate vaccines). Available at [http://www.who.int/entity/immunization/meningococcalC\\_grad\\_efficiency.pdf](http://www.who.int/entity/immunization/meningococcalC_grad_efficiency.pdf).

<sup>40</sup> Grading of scientific evidence – Table III a & b (safety of MenC conjugate vaccines). Available at [http://www.who.int/entity/immunization/meningococcalC\\_grad\\_safety.pdf](http://www.who.int/entity/immunization/meningococcalC_grad_safety.pdf).

<sup>32</sup> Halperin S A et al. Simultaneous administration of meningococcal C conjugate vaccine and diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b conjugate vaccine in children: A randomized double-blind study. *Clinical and Investigative Medicine*, 2002, 25:243–251.

<sup>33</sup> Ramsay M E et al. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet*, 2001, 357:195–196.

<sup>34</sup> Borrow R et al. Antibody persistence and immunological memory at age 4 years after meningococcal group C conjugate vaccination in children in the United Kingdom. *Journal of Infectious Diseases*, 2002, 186: 1353–1357.

<sup>35</sup> Perrett K P et al. Antibody persistence after serogroup C meningococcal conjugate immunization of United Kingdom primary-school children in 1999–2000 and response to a booster: A phase 4 clinical trial. *Clinical and Vaccine Immunology*, 2010, 50:1601–1610.

<sup>36</sup> Campbell H et al. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clinical and Vaccine Immunology*, 2010, 17:840–847.

<sup>37</sup> Trotter CL et al. Meningococcal vaccines and herd immunity: Lessons learned from serogroup C conjugate vaccination programs. *Expert Review of Vaccines*, 2009, 8:851–861.

<sup>38</sup> Larrauri A et al. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. *Vaccine*, 2005, 23:4097–4100.

<sup>39</sup> Cotation des preuves scientifiques – Tableau II a & b (efficacité des vaccins conjugués MenC). Disponible sur [http://www.who.int/entity/immunization/meningococcalC\\_grad\\_efficacy.pdf](http://www.who.int/entity/immunization/meningococcalC_grad_efficacy.pdf).

<sup>40</sup> Cotation des preuves scientifiques – Tableau III a & b (innocuité des vaccins conjugués MenC). Disponible sur [http://www.who.int/entity/immunization/meningococcalC\\_grad\\_safety.pdf](http://www.who.int/entity/immunization/meningococcalC_grad_safety.pdf).



#### Monovalent serogroup A conjugate vaccine (MenA conjugate vaccine)

A MenA conjugate vaccine, intended for use mainly in the African meningitis belt, was licensed in 2010. This lyophilized vaccine contains 10 µg of group A polysaccharide conjugated to 10–33 µg tetanus toxoid, with alum as adjuvant and thiomersal as preservative. MenA conjugate vaccine is licensed for vaccination of individuals 1–29 years of age. The recommended single intramuscular dose induces functional antibody titres against meningococcal serogroup A which are significantly higher and more persistent than those induced by a corresponding polysaccharide vaccine.<sup>41, 42</sup> The possible need for a booster dose has not yet been established. Persons who have previously received a meningococcal A polysaccharide-containing vaccine can be vaccinated with the conjugate vaccine.

The MenA conjugate vaccine has been used in large vaccine campaigns in Burkina Faso, Mali, and Niger and it is being progressively introduced in other countries of the African meningitis belt. For grading of scientific evidence for the efficacy and safety of MenA conjugate vaccine, see the resultant footnotes.<sup>43, 44</sup>

#### Combined Hib plus MenC conjugate (HibMenC) vaccine

A combination vaccine based on *Haemophilus influenzae* type b and *N. meningitidis* serogroup C antigens conjugated to tetanus toxoid was recently licensed. Clinical trials have consistently shown that this vaccine is safe and induces high levels of immunity in the target groups. For sustained protection the manufacturer recommends that the primary series of 3 doses administered at 2, 4, and 6 months of age should be followed by a booster at 12–15 months of age.<sup>45, 46, 47</sup>

#### Quadrivalent meningococcal conjugate vaccines

A quadrivalent (A,C,W135,Y) meningococcal conjugate vaccine using diphtheria toxin as carrier protein (A,C,W135,Y-D) was licensed 2005. This vaccine, initially administered as one dose only, is licensed for individuals 2–55 years of age. A 2-dose series of this vaccine is licensed for use in children aged 9–23 months. The A,C,W135,Y-D vaccine contains 4 µg of each of the se-

#### Vaccins conjugués monovalents contre le sérotype A (vaccin conjugué MenA)

Un vaccin conjugué MenA, principalement destiné à la ceinture africaine de la méningite, a été homologué en 2010. Ce vaccin lyophilisé renferme 10 µg de polysaccharide du groupe A conjugué à 10–33 µg d'anatoxine tétanique, de l'alun comme adjuvant et du thiomersal comme conservateur. Le vaccin conjugué MenA est homologué pour la vaccination des sujets âgés de 1 à 29 ans. La dose intramusculaire unique recommandée entraîne la formation de titres d'anticorps fonctionnels dirigés contre les méningocoques du sérotype A nettement plus élevés et plus persistants que ceux induits par un vaccin polysaccharidique correspondant.<sup>41, 42</sup> La nécessité éventuelle d'un rappel n'a pas encore été établie. Les personnes qui ont précédemment reçu un vaccin renfermant le polysaccharide A peuvent être vaccinées au moyen de ce vaccin conjugué.

Le vaccin conjugué MenA a été employé à l'occasion de grandes campagnes de vaccination au Burkina Faso, au Mali et au Niger, et est progressivement introduit dans d'autres pays dans la ceinture africaine de la méningite. Concernant l'évaluation des données scientifiques relatives à l'efficacité et à l'innocuité du vaccin conjugué MenA, voir les notes.<sup>43, 44</sup>

#### Vaccin associé anti-Hib plus MenC conjugué (HibMenC)

Un vaccin associé préparé à partir d'antigènes d'*Haemophilus influenzae* type b et *N. meningitidis* sérotype C conjugués à de l'anatoxine tétanique a récemment été homologué. Les essais cliniques ont régulièrement montré que ce vaccin est sûr et qu'il induit une forte immunité dans les groupes cibles. Pour une protection prolongée, le fabricant recommande que la série de primovaccination à 3 doses administrées à 2, 4 et 6 mois soit suivie d'un rappel entre 12 et 15 mois.<sup>45, 46, 47</sup>

#### Vaccins antiméningococciques conjugués quadrivalents

Un vaccin antiméningococcique conjugué quadrivalent (A, C, W135, Y), utilisant de l'anatoxine diphtérique comme protéine porteuse (A, C, W135, Y-D) a été homologué en 2005. Ce vaccin, administré au départ en une dose unique, est homologué pour les sujets âgés de 2 à 55 ans. Une administration en 2 doses est homologuée pour l'enfant âgé de 9 à 23 mois. Ce vaccin A, C, W135, Y-D renferme 4 µg de chacun des polysaccharides des séro-

<sup>41</sup> Kshirsagar N et al. Safety, immunogenicity, and antibody persistence of a new meningococcal group A conjugate vaccine in healthy Indian adults. *Vaccine*, 2007, 25 (Suppl. 1):A101–107.

<sup>42</sup> Sow S O et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. *New England Journal of Medicine*, 2011, 364:2293–2304.

<sup>43</sup> Grading of scientific evidence – Table IV a & b (efficacy of MenA conjugate vaccine). Available at [http://www.who.int/entity/immunization/meningococcalA\\_grad\\_efficiency.pdf](http://www.who.int/entity/immunization/meningococcalA_grad_efficiency.pdf).

<sup>44</sup> Grading of scientific evidence – Table V a & b (safety of MenA conjugate vaccine). Available at [http://www.who.int/entity/immunization/meningococcalA\\_grad\\_safety.pdf](http://www.who.int/entity/immunization/meningococcalA_grad_safety.pdf).

<sup>45</sup> Pace P et al. A new combination *Haemophilus influenzae* type B and *Neisseria meningitidis* serogroup C-tetanus toxoid conjugate vaccine for primary immunization of infants. *The Pediatric infectious disease journal*, 2007, 26:1057–1059.

<sup>46</sup> Pace D et al. A novel combined Hib-MenC-TT glycoconjugate vaccine as a booster dose for toddlers: a Phase 3 open randomised controlled trial. *Archives of disease in childhood*, 2008, 93:963–970.

<sup>47</sup> Khatami A et al. Persistence of immunity following a booster dose of *Haemophilus influenzae* type b-meningococcal serogroup C glycoconjugate vaccine: follow-up of a randomized controlled trial. *The Pediatric infectious disease journal*, 2011, 30:197–202.

<sup>41</sup> Kshirsagar N et al. Safety, immunogenicity, and antibody persistence of a new meningococcal group A conjugate vaccine in healthy Indian adults. *Vaccine*, 2007, 25 (Suppl. 1):A101–107.

<sup>42</sup> Sow S O et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. *New England Journal of Medicine*, 2011, 364:2293–2304.

<sup>43</sup> Cotation des preuves scientifiques – Tableau IV a & b (efficacité des vaccins conjugués MenA). Disponible sur [http://www.who.int/entity/immunization/meningococcalA\\_grad\\_efficiency.pdf](http://www.who.int/entity/immunization/meningococcalA_grad_efficiency.pdf).

<sup>44</sup> Cotation des preuves scientifiques – Tableau V a & b (innocuité des vaccins conjugués MenA). Disponible sur [http://www.who.int/entity/immunization/meningococcalA\\_grad\\_safety.pdf](http://www.who.int/entity/immunization/meningococcalA_grad_safety.pdf).

<sup>45</sup> Pace P et al. A new combination *Haemophilus influenzae* type B and *Neisseria meningitidis* serogroup C-tetanus toxoid conjugate vaccine for primary immunization of infants. *The Pediatric infectious disease journal*, 2007, 26:1057–1059.

<sup>46</sup> Pace D et al. A novel combined Hib-MenC-TT glycoconjugate vaccine as a booster dose for toddlers: a Phase 3 open randomised controlled trial. *Archives of disease in childhood*, 2008, 93:963–970.

<sup>47</sup> Khatami A et al. Persistence of immunity following a booster dose of *Haemophilus influenzae* type b-meningococcal serogroup C glycoconjugate vaccine: follow-up of a randomized controlled trial. *The Pediatric infectious disease journal*, 2011, 30:197–202.

rogroup polysaccharides, which are individually conjugated to the carrier. In 2010, a second quadrivalent vaccine, conjugated to CRM-197 (A,C,W135,Y-CRM), became available. In some countries this vaccine is licensed for individuals 2–55 years of age, in others from 11 years with no defined upper age limit. This second vaccine contains 10 µg of polysaccharide A and 5 µg of each of the polysaccharides C, W135 and Y, which are individually conjugated to the carrier. No adjuvants or preservatives are added (single dose formulations).

In Canada and the United States, both of these quadrivalent vaccines are recommended for routine administration to adolescents aged 11–18 years and for selective immunization of individuals aged 2–55 years who belong to certain high risk groups (e.g. persons with asplenia or terminal complement deficiencies, advanced HIV infection, or laboratory personnel working with *N. meningitidis*).

In the United States it is also recommended that all previously vaccinated adolescents receive a booster dose of quadrivalent conjugate vaccine at 16 years of age.

In immunodeficient individuals the need for, and frequency of, repeat doses of quadrivalent conjugate vaccines require further studies. Currently in the United States, 2 doses of MenACW135,Y-D, given 3 months apart, are recommended for children aged 9–23 months who have impaired immunity or are at high risk of exposure to meningococcal infection. For those children, a booster dose of this or an equivalent vaccine is recommended after 3 years and subsequently every 5 years.<sup>48</sup>

A randomized controlled trial comparing the meningococcal A,C,W135,Y-D and quadrivalent meningococcal polysaccharide vaccines, with 423 individuals aged 11–18 years in each group, showed that 28 days after vaccination, rSBA geometric mean titres (GMTs) of  $\geq 128$  were reached in  $\geq 97\%$  of the vaccinees with both vaccines and for all 4 serogroups. Similar results were obtained in a corresponding study that included individuals aged 19–55 years (1280 participants in the A,C,W135,Y-D group and 1098 in the polysaccharide vaccine group).<sup>49</sup>

The safety and immunogenicity of the 2 quadrivalent conjugate vaccines A,C,W135,Y-D and A,C,W135,Y-CRM were compared in children aged 2–10 years.<sup>50</sup> Both vaccines were immunogenic and well tolerated. The response to A,C,W135,Y-CRM was statistically non-

groupes, conjugués individuellement à la protéine porteuse. En 2010, un deuxième vaccin quadrivalent, conjugué à la CRM-197 (A, C, W135, Y-CRM), a été mis sur le marché. Dans certains pays, ce vaccin est homologué pour les sujets âgés de 2 à 55 ans, dans d'autres il l'est à partir de 11 ans sans limite d'âge supérieure. Ce deuxième vaccin renferme 10 µg de polysaccharide A et 5 µg de chacun des autres polysaccharides, tous conjugués individuellement à la protéine porteuse. Aucun adjuvant ni conservateur n'a été ajouté (formulations monodoses).

Au Canada et aux États-Unis, ces 2 vaccins quadrivalents sont recommandés pour la vaccination systématique des adolescents âgés de 11 à 18 ans et pour la vaccination sélective de sujets de 2 à 55 ans appartenant à certains groupes à haut risque (par exemple personnes présentant une asplénie ou des déficits terminaux du complément, une infection à VIH avancée, ou encore le personnel de laboratoire travaillant sur *N. meningitidis*).

Aux États-Unis, il est également recommandé que tous les adolescents précédemment vaccinés reçoivent une dose de rappel du vaccin conjugué quadrivalent à l'âge de 16 ans.

Chez les sujets immunodéficients, la nécessité de doses répétées d'un vaccin conjugué quadrivalent et la fréquence de ces dernières requièrent des études plus approfondies. À l'heure actuelle, aux États-Unis, on administre 2 doses de MenA, C, W135, Y-D à 3 mois d'intervalle aux enfants âgés de 9 à 23 mois présentant une altération de l'immunité ou un risque élevé d'exposition au méningocoque. Pour ces enfants, un rappel de ce vaccin ou d'un vaccin équivalent est recommandé au bout de 3 ans, puis tous les 5 ans par la suite.<sup>48</sup>

Un essai contrôlé randomisé comparant les vaccins antiméningococciques A, C, W135, Y-D et polysaccharidiques quadrivalents, portant sur 423 sujets âgés de 11 à 18 ans dans chaque groupe, a montré que 28 jours après la vaccination, des titres moyens géométriques du IABS  $\geq 128$  ont été atteints chez  $\geq 97\%$  des vaccinés quel que soit le vaccin et pour les 4 sérogroupes. Des résultats analogues ont été obtenus dans une étude correspondante portant sur des sujets âgés de 19 à 55 ans (1280 participants dans le groupe A, C, W135, Y-D et 1098 dans le groupe vaccin polysaccharidique).<sup>49</sup>

L'innocuité et l'immunogénicité des 2 vaccins conjugués quadrivalents (A, C, W135, Y-D et A, C, W135, Y-CRM) ont été comparées chez des enfants âgés de 2 à 10 ans.<sup>50</sup> Ces 2 vaccins ont été immunogènes et bien tolérés. La réponse au second a été statistiquement non inférieure à la réponse au premier pour l'en-

<sup>48</sup> Advisory Committee on Immunization Practices (ACIP). Licensure of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease. *MMWR Morbidity and Mortality Weekly Report*, 2011, 60: 1018–1019.

<sup>49</sup> Bilukha OO et al. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *CDC Surveillance Summaries: MMWR Morbidity and Mortality Weekly Report*, 2005, 54:1–21.

<sup>50</sup> Halperin S et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2–10 years of age. *Vaccine*, 2010, 28:7865–78-72.

<sup>48</sup> Advisory Committee on Immunization Practices (ACIP). Licensure of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease. *MMWR Morbidity and Mortality Weekly Report*, 2011, 60: 1018–1019.

<sup>49</sup> Bilukha OO et al. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *CDC Surveillance Summaries: MMWR Morbidity and Mortality Weekly Report*, 2005, 54:1–21.

<sup>50</sup> Halperin S et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2–10 years of age. *Vaccine*, 2010, 28:7865–78-72.

inferior to A,C,W135,Y-D for all groups, and statistically superior for groups C, W135, and Y.

Concomitant administration of A,C,W135,Y-D and typhoid vaccine or tetanus-diphtheria vaccines did not adversely interfere with the immunogenicity of either of the latter vaccines.<sup>49</sup> Similarly, no serological interference was found when A,C,W135,Y-CRM was administered simultaneously with combined measles, mumps, rubella, and varicella vaccine, combined tetanus, reduced diphtheria and acellular pertussis (Tdap), or with human papillomavirus (HPV) vaccine.<sup>51,52</sup> However, reduced immunogenicity (although not below the assumed protective levels) of 7-valent pneumococcal vaccine has been observed when co-administered with A,C,W135,Y-D.<sup>52</sup>

Recent estimates of the effectiveness of the first licensed quadrivalent vaccine suggest that within 3 to 4 years after vaccination, effectiveness is 80% to 85%.<sup>53, 54</sup>

#### Serogroup B vaccines (MenB vaccines)

The development of vaccines to protect broadly against serogroup B disease has presented challenges because the native B polysaccharide contains epitopes that potentially cross-react with human antigens, and is poorly immunogenic; in addition, other potential antigen targets of group B meningococci are highly diverse. Serogroup B vaccines based on the outer membrane vesicles (OMV) of specific (clonal) outbreak strains were developed to control serogroup B disease in Cuba, New Zealand and Norway. These vaccines have subsequently been used widely in Latin American countries. The Norwegian outbreak strain has also been used to control an outbreak caused by a genetically closely related strain in Normandy, France.<sup>55</sup>

The OMV vaccines are immunogenic, but require multiple doses, especially in infants, and appear to induce protection of relatively short duration. Efforts to find novel vaccine antigens to protect against serogroup B disease have identified several sub-capsular proteins, including factor H binding protein, Neisseria adhesin A, and Neisseria-heparin binding antigen. As the proteins used in these vaccines can also be found across all meningococcal serogroups, such vaccines have the potential to protect against both serogroup B and additional serogroups. Several candidate vaccines that target one or more of these antigens are currently under

seemle des sérogroupes et statistiquement supérieure pour les sérogroupes C, W135 et Y.

L'administration concomitante du vaccin A, C, W135, Y-D et du vaccin antityphoïdique ou du vaccin antitétanique-antidiphtérique n'a pas eu d'effet indésirable sur l'immunogénicité de l'un ou l'autre de ces derniers vaccins.<sup>49</sup> De la même façon, aucune interférence sérologique n'a été observée lorsqu'on a administré le vaccin A, C, W135, Y-CRM simultanément avec le vaccin associé antirougeoleux-antiourlien-antirubéoleux et antivaricelleux, le vaccin associé antitétanique-antidiphtérique-anticoquelucheux acellulaire (Tdca), ou avec le vaccin anti-papillomavirus humain (VPH).<sup>51, 52</sup> Cependant, une immunogénicité réduite (bien que non inférieure aux niveaux protecteurs attendus) du vaccin antipneumococcique heptavalent a été observée lorsqu'il est administré en même temps que le vaccin A, C, W135, Y-D.<sup>52</sup>

Les estimations récentes relatives à l'efficacité du premier vaccin quadrivalent homologué laissent à penser que dans les 3 à 4 ans suivant la vaccination son efficacité est de 80% à 85%.<sup>53, 54</sup>

#### Vaccins contre le séro groupe B (vaccins MenB)

La mise au point de vaccins visant à protéger largement contre le séro groupe B a présenté des difficultés du fait que le polysaccharide B d'origine renferme des épitopes qui présentent potentiellement des réactions croisées avec les antigènes humains et qu'il est peu immunogène; en outre, les autres cibles antigéniques potentielles des méningocoques du groupe B sont extrêmement diverses. Des vaccins contre le séro groupe B préparés à partir des vésicules de la membrane externe de souches particulières (clonales) liées à des flambées ont été mis au point pour venir à bout de la méningococcie du séro groupe B à Cuba, en Norvège et en Nouvelle-Zélande. Ces vaccins ont par la suite été largement employés dans les pays d'Amérique latine. La souche de la flambée norvégienne a également été utilisée pour lutter contre une flambée due à une souche étroitement apparentée sur le plan génétique en Normandie (France).<sup>55</sup>

Les vaccins préparés à partir de la membrane externe sont immunogènes mais exigent l'administration de multiples doses, surtout chez le nourrisson, et semblent induire une protection de durée relativement courte. Les efforts visant à trouver de nouveaux antigènes vaccinaux pour protéger contre le séro groupe B ont permis de repérer plusieurs protéines sous-capsulaires, notamment la protéine de liaison au facteur H, l'adhésine A de *Neisseria*, et l'antigène de liaison à l'héparine de *Neisseria*. Comme les protéines utilisées dans ces vaccins peuvent également être trouvées dans tous les sérogroupes de méningocoques, ces vaccins pourraient protéger contre le séro groupe B et d'autres sérogroupes. Plusieurs vaccins candidats

<sup>51</sup> Arguedas A et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. *Vaccine*, 2010, 28:3171–3179.

<sup>52</sup> Johnson DR. Menactra®. Infant Indication. ACIP Presentation Slides: June 2011 Meeting. <http://www.cdc.gov/vaccines/recs/acip/slides-jun11.htm>

<sup>53</sup> Macneil J R. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. *The Pediatric infectious disease journal*, 2011, 30:451–455.

<sup>54</sup> Grading of scientific evidence – Table VI a & b (efficacy of quadrivalent meningococcal conjugate vaccines). Available at [http://www.who.int/entity/immunization/meningococcal\\_grad\\_efficacy.pdf](http://www.who.int/entity/immunization/meningococcal_grad_efficacy.pdf)

<sup>55</sup> Caron F et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infectious Diseases*, 2011, 11:455–463.

<sup>51</sup> Arguedas A et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. *Vaccine*, 2010, 28:3171–3179.

<sup>52</sup> Johnson DR. Menactra®. Infant Indication. ACIP Presentation Slides: June 2011 Meeting. <http://www.cdc.gov/vaccines/recs/acip/slides-jun11.htm>

<sup>53</sup> Macneil J R. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. *The Pediatric infectious disease journal*, 2011, 30:451–455.

<sup>54</sup> Cotation des preuves scientifiques – Tableau VI a & b (efficacité des vaccins conjugués quadrivalents). Disponible sur [http://www.who.int/entity/immunization/meningococcal\\_grad\\_efficacy.pdf](http://www.who.int/entity/immunization/meningococcal_grad_efficacy.pdf)

<sup>55</sup> Caron F et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infectious Diseases*, 2011, 11:455–463.

investigation in clinical trials. Although preliminary data are promising, the role these vaccines could play in controlling meningococcal disease remains to be determined.<sup>3</sup>

#### Vaccination for travellers

Travellers from low-endemic regions visiting countries which are highly endemic or epidemic for meningococcal disease should consider vaccination. For travellers to the African meningitis belt, the risk of acquiring infection is greatest in the dry season and for those with prolonged contact with the local population. In one study, the incidence rate per month of stay for travellers from industrialized to developing countries was estimated at 0.4 per million, whereas for pilgrims to Mecca the corresponding incidence was estimated at 2000 per million.<sup>56</sup>

Proof of quadrivalent (A,C,W135,Y) vaccination against meningococcal disease is required for persons travelling to Mecca during the annual Hajj and the Umrah pilgrimages.<sup>57</sup>

#### Serogroup replacement

*N. meningitidis* organisms have been shown to switch polysaccharide capsules. For example, the serotype ST11/ET37 has been identified in both serogroup B and serogroup W135 strains. Moreover, meningococci of different serogroups, B and C, but with identical serotype and electrophoretic type were detected in Canada, the Czech Republic and the Pacific Northwest. This raises the possibility that genetic exchange between epidemic and endemic strains may be more common than previously suspected.<sup>3</sup>

Despite these concerns, current evidence does not show significant replacement disease after the introduction of meningococcal vaccines. Extensive carriage studies and surveillance after introduction of MenC vaccine in the United Kingdom in 1999 have found no evidence of capsule replacement from 1988–2005, a time period extending from the pre-vaccination era to 5 years after mass vaccination with MenC vaccines.<sup>58</sup> These results are supported by studies conducted in other countries, including Spain and Italy, which showed that hyper-virulent strains of different serogroups, but with the same electrophoretic subtype, were either insignificant after vaccination, or occurred even without mass vaccination.<sup>59</sup> A study conducted in Spain to assess the possible impact of 2 vaccination campaigns (with A/C polysaccharide vaccine in 1997 and MenC conjugate

ciblant un ou plusieurs de ces antigènes sont actuellement à l'étude dans des essais cliniques. Bien que les données préliminaires soient prometteuses, le rôle que ces vaccins pourraient jouer dans la lutte contre la méningococcie reste à déterminer.<sup>3</sup>

#### Vaccination des voyageurs

Les voyageurs provenant de régions de faible endémie et se rendant dans des pays où la méningococcie est fortement endémique ou épidémique doivent envisager la vaccination. Pour ceux qui se rendent dans la ceinture africaine de la méningite, le risque de contracter l'infection est maximum au cours de la saison sèche et pour ceux qui ont des contacts prolongés avec la population locale. Dans une étude, l'incidence par mois de séjour pour les voyageurs en provenance de pays industrialisés et se rendant dans des pays en développement a été estimée à 0,4 par million tandis que, pour les pèlerins se rendant à La Mecque, l'incidence correspondante est, selon les estimations, de 2000 par million.<sup>56</sup>

Une preuve de vaccination par le vaccin quadrivalent (A, C, W135, Y) est exigée des personnes se rendant à La Mecque au cours des pèlerinages annuels du Hadj et de l'Umrah.<sup>57</sup>

#### Substitution des sérogroupes

On a montré que les *N. meningitidis* changeaient de capsules polysaccharidiques. Par exemple, le sérotype ST11/ET37 a été repéré chez des souches appartenant au séro groupe B et au séro groupe W135. En outre, des méningocoques appartenant à différents sérogroupes, en l'occurrence B et C, mais ayant un sérotype et un type électrophorétique identiques ont été détectés au Canada, dans le nord-ouest du Pacifique et en République tchèque. Cela met en avant la possibilité d'un échange génétique entre des souches épidémiques et endémiques plus fréquent qu'on ne le soupçonnait auparavant.<sup>3</sup>

Malgré ces préoccupations, les données actuelles ne montrent pas de maladie de substitution importante après introduction des vaccins antiméningococciques. Les études étendues sur le portage et la surveillance exercée après l'introduction du vaccin MenC au Royaume-Uni en 1999 n'ont mis en évidence aucun signe de substitution de capsule entre 1988 et 2005, période couvrant une durée allant d'avant la vaccination jusqu'à 5 ans après la vaccination de masse par le MenC.<sup>58</sup> Ces résultats sont confortés par des études menées dans d'autres pays, notamment en Espagne et en Italie, qui ont montré que les souches hyper-virulentes appartenant à différents sérogroupes mais ayant le même sous-type électrophorétique, étaient soit insignifiantes après la vaccination, soit présentes même en l'absence de vaccination de masse.<sup>59</sup> Une étude menée en Espagne afin d'évaluer les effets possibles de 2 campagnes de vaccination (au moyen du vaccin polysaccharidique A/C en 1997 et du vaccin conjugué MenC

<sup>56</sup> Koch S et al. Meningococcal disease in travelers: vaccination recommendations. *Journal of Travel Medicine*, 1994, 1:4–7.

<sup>57</sup> *International travel and health*. Chapter 6: vaccine-preventable diseases and vaccines. Geneva, World Health Organization, 2011 (<http://www.who.int/ith/chapters/ith2011chap6.pdf>, accessed November 2011).

<sup>58</sup> Trotter CL et al No evidence for capsule replacement following mass immunisation with meningococcal serogroup C conjugate vaccines in England and Wales. *Lancet Infectious Diseases*, 2006, 6:616–617.

<sup>59</sup> Stefanelli P et al. First report of capsule replacement among electrophoretic type 37 *Neisseria meningitidis* strains in Italy. *Journal of Clinical Microbiology*, 2003, 41:5783–5786.

<sup>56</sup> Koch S et al. Meningococcal disease in travelers: vaccination recommendations. *Journal of Travel Medicine*, 1994, 1:4–7.

<sup>57</sup> *Voyages internationaux et santé*. Chapitre 6: maladies évitables par la vaccination et vaccins. Genève, Organisation mondiale de la Santé, 2011 (<http://www.who.int/ith/chapters/ithchapter6FR.pdf>, consulté en novembre 2011).

<sup>58</sup> Trotter CL et al No evidence for capsule replacement following mass immunisation with meningococcal serogroup C conjugate vaccines in England and Wales. *Lancet Infectious Diseases*, 2006, 6:616–617.

<sup>59</sup> Stefanelli P et al. First report of capsule replacement among electrophoretic type 37 *Neisseria meningitidis* strains in Italy. *Journal of Clinical Microbiology*, 2003, 41:5783–5786.



vaccine from 2000–2008) showed that the overall diversity of the meningococcal population, measured by the frequency of serotypes and clonal complexes, numbers of alleles, polymorphic sites, and index of association, remained relatively constant throughout the study period.<sup>60</sup>

#### Cost effectiveness of vaccination against meningococcal disease

Six countries undertook economic evaluations before the introduction of meningococcal conjugate vaccines (Australia, Canada (Quebec), the Netherlands, Portugal, Switzerland and United Kingdom). All concluded that one dose in the second year of life was more cost-effective than a 3-dose infant schedule.<sup>61</sup> A dynamic transmission model suggested that the most cost-effective strategy (£569 per life year saved) was routine vaccination of children at 12 months of age combined with a catch-up campaign for all children and adolescents <18 years of age. Taking herd immunity into account improved the cost-effectiveness of the vaccine.<sup>62</sup>

An evaluation of the impact of A,C,W135,Y-D vaccination of US adolescents, toddlers, and infants, utilizing a static model,<sup>63</sup> concluded that routine vaccination would reduce the burden of disease in vaccinated cohorts, but at the relatively high median cost of US\$ 633 000 (US\$ 329 000–US\$ 1 299 000) per case prevented, US\$ 5.0 million (US\$ 2.4–US\$ 10.9 million) per death prevented, and US\$ 121 000 (US\$ 69 000–US\$ 249 000) per life year saved.

A catch-up vaccination programme targeted to counties with a high rate of endemic meningococcal disease would be 3 times more cost-effective than a catch-up and routine vaccination programme for all of the United States.<sup>64</sup> Also, routine vaccination of US first-year students living in dormitories was estimated to be more cost effective than vaccination of all freshmen enrolled in US colleges, regardless of housing status.<sup>65</sup>

No studies on the cost-effectiveness of meningococcal vaccination have yet been reported from developing country settings.

entre 2000 et 2008) a montré que la diversité générale de la population de méningocoques, mesurée par la fréquence des sérotypes et des complexes clonaux, le nombre d'allèles, les sites polymorphiques et l'indice d'association, est restée relativement constante tout au long de la période d'étude.<sup>60</sup>

#### Coût/efficacité de la vaccination contre la méningococcie

Six pays ont entrepris des évaluations économiques avant d'introduire les vaccins antiméningococciques conjugués (l'Australie, le Canada (Québec), les Pays-Bas, le Royaume-Uni, le Portugal et la Suisse). Tous ont conclu qu'une dose de vaccin administrée au cours de la deuxième année de vie était plus rentable qu'un calendrier en 3 doses chez le nourrisson.<sup>61</sup> Un modèle de transmission dynamique laisse à penser que la stratégie ayant le meilleur coût/efficacité (£569 par année de vie sauvée) est la vaccination systématique des enfants à l'âge de 12 mois associée à une campagne de rattrapage visant tous les enfants et les adolescents de <18 ans. Le fait de tenir compte de l'immunité collective améliore le coût/efficacité du vaccin.<sup>62</sup>

Une évaluation des effets de la vaccination A, C, W135, Y-D des adolescents, des tout-petits et des nourrissons aux Etats-Unis, effectuée à l'aide d'un modèle statique,<sup>63</sup> a conclu que la vaccination systématique permettrait de réduire le poids de la maladie dans les cohortes vaccinées, mais au coût médian relativement élevé de US \$633 000 (US\$ 329 000-US\$ 1 299 000) par cas évité, de US\$ 5,0 millions (US\$ 2,4-US\$ 10,9 millions) par décès évité et de US\$ 121 000 (US\$ 69 000-US\$ 249 000) par année de vie épargnée.

Un programme de vaccination de rattrapage axé sur les comtés ayant un taux élevé de méningococcie endémique serait 3 fois plus rentable qu'un programme de vaccination systématique et de rattrapage pour l'ensemble des Etats-Unis.<sup>64</sup> De plus, la vaccination systématique des étudiants américains de première année vivant en résidence universitaire serait, d'après les estimations, plus rentable que la vaccination de l'ensemble des étudiants de première année des collèges américains, quel que soit leur logement.<sup>65</sup>

Il n'a encore été fait état d'aucune étude sur le coût/efficacité de la vaccination antiméningococcique dans les pays en développement.

<sup>60</sup> Vicente D et al. Influence of 2 vaccination campaigns on genetic diversity of invasive *Neisseria meningitidis* isolates in Northern Spain (1997-2008). *PLoS One*, 2009, 4: e8501.

<sup>61</sup> Welte R et al. The role of economic evaluation in vaccine decision making: focus on meningococcal group C conjugate vaccine. *Pharmacoeconomics*, 2005, 23:855–874.

<sup>62</sup> Trotter CL et al. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Medical decision making*, 2006, 26:38–47.

<sup>63</sup> Shepard CW et al. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics*, 2005, 115:1220–1232.

<sup>64</sup> Ortega-Sanchez IR et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clinical Infectious Diseases*, 2008, 46:1–13.

<sup>65</sup> Scott R D et al. Vaccinating first-year college students living in dormitories for meningococcal disease: an economic analysis. *American Journal of Preventive Medicine*, 2005, 23:98–105.

<sup>60</sup> Vicente D et al. Influence of 2 vaccination campaigns on genetic diversity of invasive *Neisseria meningitidis* isolates in Northern Spain (1997-2008). *PLoS One*, 2009, 4: e8501.

<sup>61</sup> Welte R et al. The role of economic evaluation in vaccine decision making: focus on meningococcal group C conjugate vaccine. *Pharmacoeconomics*, 2005, 23:855–874.

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<sup>63</sup> Shepard CW et al. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics*, 2005, 115:1220–1232.

<sup>64</sup> Ortega-Sanchez IR et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clinical Infectious Diseases*, 2008, 46:1–13.

<sup>65</sup> Scott R D et al. Vaccinating first-year college students living in dormitories for meningococcal disease: an economic analysis. *American Journal of Preventive Medicine*, 2005, 23:98–105.

## WHO position / Recommendations

WHO recommends that countries with high (>10 cases/100 000 population/year) or intermediate endemic rates (2–10 cases/100 000 population/year) of invasive meningococcal disease and countries with frequent epidemics should introduce appropriate large-scale meningococcal vaccination programmes. In these countries, the vaccine may be administered through routine immunization programmes, supplementary immunization activities (SIAs), for example during outbreaks, or through private vaccination services. Depending on the national epidemiology and socioeconomic resources, countries should select and implement the most appropriate control policy.

In countries where the disease occurs less frequently (<2 cases per 100 000 population/year), meningococcal vaccination is recommended for defined risk groups, such as children and young adults residing in closed communities, e.g. boarding schools or military camps. Laboratory workers at risk of exposure to meningococci should also be vaccinated. Travellers to high-endemic areas should be vaccinated against the prevalent serogroup(s). In addition, meningococcal vaccination should be offered to all individuals suffering from immunodeficiency, including asplenia, terminal complement deficiencies, or advanced HIV infection.

For each country the choice of vaccine depends on the locally prevalent serogroup(s) of *N. meningitidis* (or serosubtype in case of serogroup B).

Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age. Both conjugate and polysaccharide vaccines are efficacious and safe when used in pregnant women.

When using conjugate vaccines, one recommended approach is initial mass vaccination of all children and adolescents aged from 9 months to 18 years followed by inclusion of the vaccine in the routine childhood immunization programme. Depending on surveillance data, other age groups can be incorporated into the mass vaccination campaign: in the African meningitis belt the broad age group of 1–29 years is the target for MenA conjugate vaccination. An alternative strategy would be to use conjugate vaccines for mass vaccination followed every 3–5 years by SIAs for age groups at particular risk, as dictated by continued surveillance.

Monovalent MenA conjugate vaccine should be given as one single intramuscular dose to individuals 1–29 years of age. The possible need for booster doses is not yet established for this vaccine.

For monovalent MenC conjugate vaccine one single intramuscular dose is recommended for children aged ≥12 months, teenagers and adults. Children 2–11 months

## Position de l'OMS/recommandations

L'OMS recommande que les pays ayant des taux d'endémie élevés (>10 cas/100 000 habitants/an) ou intermédiaires (2–10 cas/100 000 habitants/an) de la méningococcie invasive et que ceux touchés fréquemment par des épidémies introduisent des programmes de vaccination antiméningococcique à grande échelle. Dans ces pays, le vaccin peut être administré par les programmes adéquats de vaccination systématique, à l'occasion d'activités de vaccination supplémentaire, par exemple durant les flambées, ou par les services de vaccination privés. En fonction de l'épidémiologie de la maladie et des ressources socio-économiques dont ils disposent, les pays doivent choisir et mettre en œuvre la politique de lutte la plus appropriée.

Dans les pays où la maladie apparaît moins fréquemment (<2 cas/100 000 habitants/an), la vaccination antiméningococcique est recommandée pour des groupes à risque définis, tels que les enfants et les jeunes adultes résidant dans des communautés fermées, par exemple les internats ou les camps militaires. Les personnels de laboratoire exposés au risque de méningococcie doivent également être vaccinés. Les voyageurs se rendant dans des régions de forte endémie doivent être vaccinés contre le(s) sérogroup(e)s prévalent(s). De plus, la vaccination antiméningococcique doit être offerte à tous les sujets présentant une immunodéficience, notamment une asplénie, des déficits terminaux du complément ou une infection à VIH avancée.

Pour chaque pays, le choix du vaccin va dépendre du(des) sérogroup(e)s de *N. meningitidis* (ou du séro sous type dans le cas du sérogroup B) qui prédomine(nt) localement.

On recommandera les vaccins conjugués de préférence aux vaccins polysaccharidiques en raison de leur potentiel à créer une protection collective et de leur plus forte immunogénicité, en particulier chez l'enfant de moins de 2 ans. Les vaccins conjugués comme les vaccins polysaccharidiques sont sûrs et efficaces lorsqu'ils sont utilisés chez la femme enceinte.

Lorsqu'on fera appel à des vaccins conjugués, une stratégie recommandée consistera à procéder à la vaccination de masse initiale de tous les enfants et adolescents âgés de 9 mois à 18 ans, puis à inclure le vaccin dans le programme de vaccination systématique au cours de l'enfance. En fonction des données de la surveillance recueillies, d'autres classes d'âge pourront être incorporées dans la campagne de vaccination de masse: dans la ceinture africaine de la méningite, la classe d'âge élargie des 1–29 ans est la cible de la vaccination par le vaccin conjugué MenA. Une autre stratégie consisterait à utiliser les vaccins conjugués pour la vaccination de masse, qui serait suivie tous les 3 à 5 ans par des activités de vaccination supplémentaire destinées aux classes d'âge présentant un risque particulier, telles que désignées par la surveillance permanente.

Le vaccin monovalent conjugué MenA doit être administré en une dose intramusculaire unique aux sujets âgés de 1 à 29 ans. La nécessité éventuelle d'un rappel n'est pas encore établie pour ce vaccin.

Pour le vaccin monovalent conjugué MenC, on recommande une dose unique intramusculaire chez les enfants âgés de ≥12 mois, les adolescents et les adultes. Les enfants âgés de 2 à 11 mois

of age require 2 doses administered at an interval of at least 2 months and a booster about 1 year thereafter. If the primary series is interrupted, vaccination should be resumed without repeating the previous dose.

It is not yet known whether booster doses will be needed for long-term protection in healthy individuals who received primary vaccination when aged  $\geq 12$  months.

Quadrivalent conjugate vaccines (A,C,W135,Y-D and A,C,W135,Y-CRM) should be administered as one single intramuscular dose to individuals aged  $\geq 2$  years. A,C,W135,Y-D is also licensed for children 9–23 months of age, and given as a 2-dose series, 3 months apart, beginning at age 9 months. If the primary series is interrupted, vaccination should be resumed without repeating the previous dose.

Polysaccharide vaccines can be used to control outbreaks in countries where limited economic resources or insufficient supply restrict the use of meningococcal conjugate vaccines. In the case of serogroup A or C outbreaks, bivalent A, C polysaccharide vaccine is recommended for mass campaigns. However, due to the limited efficacy of polysaccharide vaccines in children  $< 2$  years of age, in confirmed group C outbreaks MenC conjugate vaccines should be used for protection of those aged 2–24 months. Similarly, during group A outbreaks, MenA conjugate vaccine is the preferred option for protection of children 12–24 months of age.

Meningococcal outbreaks caused by the W135 or Y serogroups require trivalent (A,C,W135) or quadrivalent (A,C,W135,Y) polysaccharide vaccines.

Meningococcal polysaccharide vaccines should be administered to individuals aged  $\geq 2$  years as one single dose; most polysaccharide vaccines are administered cutaneously. One booster 3–5 years after the primary dose may be given to persons considered to be at continued high risk of exposure, including some health workers.

Further studies are needed to determine the frequency of repeat doses of meningococcal vaccines for immunodeficient individuals.

For all countries, knowledge of the meningococcal disease burden is essential for making appropriate use of available vaccines. Countries considering the use of meningococcal vaccines should develop the surveillance systems to characterize meningococcal disease epidemiology, including a standard clinical case definition, field investigation of cases and outbreaks, and laboratory capacity for the confirmation and characterization of *N. meningitidis*. Continued surveillance of invasive meningococcal disease should dictate the need and timing of repeat mass vaccination campaigns.

The ongoing efforts to control invasive group A disease should be completed in all countries in the African meningitis belt. WHO stresses the importance of ensuring high

nécessitent l'administration de 2 doses espacées d'au moins 2 mois et un rappel au bout de 1 an. Si la primovaccination est interrompue, il convient de reprendre la vaccination sans répéter la dose précédente.

On ignore encore si des rappels seront nécessaires pour la protection à long terme des sujets en bonne santé qui reçoivent une primovaccination à partir de l'âge de 12 mois.

Les vaccins conjugués quadrivalents (A, C, W135, Y-D et A, C, W135, Y-CRM) doivent être administrés en une dose intramusculaire unique à partir de l'âge de 2 ans. Le premier est également homologué pour les enfants âgés de 9 à 23 mois et il est alors administré en 2 doses, à 3 mois d'intervalle, à partir de l'âge de 9 mois. Si la primovaccination est interrompue, il convient de reprendre la vaccination sans répéter la dose précédente.

Les vaccins polysaccharidiques peuvent être utilisés pour lutter contre les flambées dans les pays disposant de ressources économiques limitées, ou dans lesquels un approvisionnement insuffisant limite l'utilisation des vaccins antiméningococciques conjugués. Dans le cas des flambées dues au sérotype A ou C, on recommande le vaccin polysaccharidique bivalent A, C pour les campagnes de masse. Cependant, en raison de l'efficacité limitée des vaccins polysaccharidiques chez l'enfant de  $< 2$  ans, dans des flambées confirmées dues au sérotype C, les vaccins conjugués MenC seront utilisés pour protéger ceux âgés de 2 à 24 mois. De la même façon, au cours des flambées dues au sérotype A, on privilégiera le vaccin conjugué MenA pour protéger les enfants âgés de 12 à 24 mois.

Des flambées de méningococcie dues au sérotype W135 ou Y exigent l'administration de vaccins polysaccharidiques trivalents (A, C, W135) ou quadrivalents (A, C, W135, Y).

Les vaccins antiméningococciques polysaccharidiques doivent être administrés en une dose unique à partir de l'âge de 2 ans; la plupart des vaccins polysaccharidiques sont administrés par voie cutanée. Un rappel effectué 3 à 5 ans après la primovaccination peut être administré aux personnes considérées comme exposées à un risque permanent élevé, notamment certains agents de santé.

Des études plus approfondies sont nécessaires afin de déterminer la fréquence des doses à administrer aux sujets immunodéficients.

Pour l'ensemble des pays, il est indispensable de connaître la charge de morbidité de la méningococcie pour utiliser au mieux les vaccins disponibles. Les pays qui envisagent de les employer doivent mettre en place des systèmes de surveillance afin de caractériser l'épidémiologie de la méningococcie, d'établir une définition standard du cas clinique, d'étudier les cas sur le terrain et les flambées, et de mettre en place les moyens de laboratoire permettant de confirmer la présence de *N. meningitidis* et de caractériser cette dernière. La surveillance continue de la méningococcie invasive doit permettre de déterminer s'il est nécessaire d'effectuer des campagnes de vaccination de masse répétées et à quel moment.

Les efforts en cours visant à lutter contre la méningococcie invasive due au sérotype A doivent se poursuivre dans tous les pays de la ceinture africaine de la méningite. L'OMS souligne

quality surveillance in countries introducing the serogroup A meningococcal conjugate vaccine, in order to document its impact on invasive disease and the indirect benefits from reduction in carriage. This effort should also be used to strengthen the routine EPI programme and pharmacovigilance infrastructure in these countries.

Further research into the development and testing of protein-based vaccines against serogroup B is strongly encouraged. The lack of a vaccine against group X meningococci is a cause for concern given the outbreaks caused by meningococci of this serogroup in the past few years.

As the assumed correlation between SBA titres ( $\geq 1:4$  in hSBA or  $\geq 1:8$  in rSBA) and protection against group A, Y or W135 meningococcal disease have not yet been adequately documented, there is a need for rigorous phase IV effectiveness studies to establish the reliability of this correlate beyond group C disease. ■

l'importance d'une surveillance de qualité dans les pays introduisant le vaccin antiméningococcique conjugué contre le sérotype A, pour pouvoir documenter ses effets sur la méningococcie invasive et les avantages indirects tirés de la diminution du portage. Ces efforts doivent également servir à renforcer le PEV et la pharmacovigilance dans ces pays.

Une recherche approfondie en vue de la mise au point et de l'essai de vaccins contre le sérotype B préparés à partir de protéine est vivement encouragée. L'absence d'un vaccin contre les méningocoques du groupe X est une cause de préoccupation étant donné les flambées provoquées par ce sérotype au cours des quelques dernières années.

Comme la corrélation supposée entre les titres d'ABS ( $\geq 1:4$  pour le sérum humain ou  $\geq 1:8$  pour le sérum de lapin) et la protection contre la méningococcie due au groupe A, Y ou W135 n'a pas encore été correctement documentée, il est nécessaire de procéder à des études d'efficacité de phase IV rigoureuses afin d'établir la fiabilité de cet indicateur pour d'autres sérotypes que le sérotype C. ■

#### 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](mailto: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.

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

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## Monthly report on dracunculiasis cases, January–August 2011

In order to monitor the progress accomplished, the number of cases reported to WHO by national programmes is regularly published in the *Weekly Epidemiological Record*. ■

## Rapport mensuel des cas de dracunculose, janvier-août 2011

Afin de suivre les progrès réalisés, le *Relevé épidémiologique hebdomadaire* publiera régulièrement le nombre de cas signalés à l'OMS par les programmes nationaux. ■



30-31 July | 2014

## 9<sup>th</sup> Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



World Health  
Organization

DRAFT AS OF 10/2/14

## Background

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The ninth meeting of the SAGE Polio Working Group (WG) was held on 30-31 July 2014 at the World Health Organization in Geneva, Switzerland.

The meeting was attended by the following WG members: Peter Figueroa (Chair), Elizabeth Miller, Francis Nkrumah, Walter Orenstein, Antoine Kabore, Kimberly Thompson, Nicholas Grassly, Walter Dowdle, Hyam Bashour T Jacob John and Zulfiqar Bhutta.

Participants from WHO included Bruce Aylward, Diana Chang Blanc, Alejandro Costa, Shelley Deeks, Philippe Duclos, Jackie Fournier-Caruana, Andrew Freeman, Tracy Goodman, Hamid Jafari, Hiromasa Okayasu, Elisabeth Pluete, Nicoletta C. Previsani, Alejandro Ramirez Gonzalez, Roland Sutter, Rudi Tagermann, Graham Tallis, and Michel Zaffran

Participants from GPEI partner organizations included Guillaume Chabot-Couture (Institute of Disease Modelling), John Modlin (Bill and Melinda Gates Foundation), Ann Ottosen and Jennifer Rubin (UNICEF).

This note presents a summary of the main findings, conclusions and recommendations from the meeting.

## Objectives of the Meeting

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Since the launch of the Polio Endgame Strategic Plan 2013-2018 in 2013, significant progress has been made towards achievement of withdrawal of oral polio vaccine type 2 (OPV2) and introduction of IPV in routine immunization, as defined in objective 2 of the Plan. In May 2014, the World Health Assembly (WHA) adopted OPV 2 withdrawal readiness criteria and timeline. These criteria include: a) introduction of IPV in OPV-only using countries; b) access to bivalent OPV that is licensed for routine immunization; c) implementation of surveillance and response protocols for type 2 poliovirus (including constitution of a stockpile of monovalent oral polio vaccine type 2); d) completion of phase 1 containment activities under the Global Action Plan (GAP) with appropriate handling of type 2 poliovirus materials and e) verification of global eradication of wild poliovirus type 2. The trigger for setting a definitive date for OPV 2 withdrawal globally will be the absence of all persistent circulating vaccine-derived type 2 polioviruses<sup>1</sup> for at least six months<sup>2</sup>. The current target date is April 2016.

The objective of this WG meeting was to review the status of the preparation towards withdrawal of OPV2, specifically the following:

1. Trigger for OPV2 withdrawal;
2. cVDPV2 risk mitigation strategy at the time of OPV2 withdrawal;
3. Strategic approach to align containment with the new polio endgame;
4. Protocol for the management and use of the mOPV2 stockpile;
5. Plans for environmental surveillance expansion; and
6. Other readiness criteria (e.g. IPV introduction, bOPV licensure )& tOPV Withdrawal Protocol

## Topic 1: Trigger for OPV2 withdrawal

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The WG reviewed progress towards the 'trigger' for OPV2 withdrawal, which is the absence of 'persistent' cVDPV2s for at least 6 months globally, particularly in the context of the timeline of OPV2 withdrawal in April 2016. Despite the significant progress made in reaching more children (e.g. increasing coverage in Nigeria and vaccination of internally displaced populations from previously inaccessible cVDPV2-infected areas in Pakistan), cVDPV2 continues to circulate in Nigeria (since July 2005) and Pakistan (since August 2012).

Since 2005, there have been more than 20 separate emergences of cVDPV2 in Nigeria and some of these strains continue to circulate in the northern states. In 2014 to date there are more cVDPV type 2 cases than

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<sup>1</sup> Persistent cVDPVs refer to cVDPVs known to have circulated for more than six months

<sup>2</sup> World Health Assembly. Poliomyelitis: intensification of the global eradication initiative. Report by the Secretariat. Geneva: World Health Organization, 2014

WPV 1 (18 vs. 5)<sup>3</sup>, and seroprevalence surveys in Sokoto and Kano indicate that the type 2 population immunity is low and has dropped significantly between 2011 and 2013 in Kano (from 75% to 42% among 6-9 months old infants)<sup>4</sup>. Nigeria has implemented very few immunization campaigns with tOPV. Only one large-scale tOPV campaign has been conducted in Northern Nigeria in each of 2012 and 2013, with the most recent campaign implemented 17 months ago. Moreover, vaccination efforts have been compromised due to insecurity and limited access to some areas, particularly in Borno State which has reported 12 of the 18 cVDPV2 cases this year.

Since mid-2012, there have been 5 separate emergences of cVDPV2 in Pakistan. The country has reported 16 cVDPV2 cases so far this year (as of 5 August 2014). Almost all of these cases have occurred in the Federally Administered Tribal Areas (FATA) and Khyber Pakhtunkhwa (KP)<sup>5</sup> where access is compromised due to insecurity. However, recently there has been significant progress in vaccinating children displaced from inaccessible areas through transit vaccination and vaccination of internally displaced persons (IDPs) and their host communities. To date, nearly 0.5 million children have been vaccinated in transit and more than 0.5 million have been vaccinated four times in districts hosting the IDPs. More tOPV rounds are planned in these communities in coming months, as is the targeted use of IPV in campaigns.

During the last meeting in April 2014, SAGE emphasized that the elimination of persistent cVDPV2 should be a high priority for the global eradication effort; it urged countries to optimize the OPV mix in efforts to interrupt transmission of both cVDPV and WPVs in parallel so that OPV2 can be withdrawn during the 'low season' for polio transmission in 2016, as planned<sup>6</sup>. Accordingly, Nigeria is currently planning 3 large scale tOPV campaign between August 2014 and March 2015 in Northern Nigeria (August 2014, November 2014 and March 2015). A modelling analysis by the Institute for Disease Modelling (IDM) indicated that these rounds will increase immunity in children under 5 years of age significantly against type 2 (for example, from 50% to 65% in Sokoto, and from 30% to 50% in Kano). While this increase will drastically reduce cVDPV2 transmission, it is unlikely to stop it entirely (Figure-1). The analysis also indicated that reduction in type 1 immunity which will take place in Northern Nigeria (less than 3-5% in most states) from replacing some bOPV campaigns with tOPV during in second half of 2014 and in early 2015 could be counterbalanced by an increase in campaign quality (Figure-2)<sup>7</sup>.

#### **WG decisions/recommendations**

- To ensure that no new cVDPV2 emergences result in persistent cVDPV2s in advance of the OPV2 withdrawal target date of April 2016, the response to newly emergent cVDPV2s globally must be substantially enhanced, with any new cVDPV2 now recognized and treated as a public health emergency, on par with a wild poliovirus (WPV) outbreak.
- Given the increasing urgency and importance of properly managing cVDPV2s to facilitate timely withdrawal of OPV2 globally, the GPEI should by September 2014 develop a new, standard data format for tracking and communicating new and persistent cVDPVs and carry out the work to ensure their rapid interruption (including timing, epidemiology, location of emergence, interventions).
- The current vaccination strategy in Nigeria of 3 large scale tOPV rounds between August 2014 and March 2015, is not likely to stop the widespread, multiple persistent cVDPV2s in the country. This represents a major threat to the global timeline for OPV2 withdrawal in the 1<sup>st</sup> quarter of 2016, and a major risk to the children of Nigeria and surrounding countries. The Nigeria Expert Review Committee (ERC) is urged to review the new analyses on type 2 immunity in the country and the relative impact of tOPV vs bOPV campaigns on population immunity to poliovirus types 1 and 2 through March 2015. Based on these analyses, the increasing burden of type 2 disease in 2014, and the escalating risk of another major cVDPV type 2 epidemic, Nigeria must consider using tOPV in at least 4 large-scale SIAs across the northern states between August 2014 and March 2015, and possibly more in the

<sup>3</sup> Global Polio Eradication Initiative (2014).

<http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx> (Accessed on 12 August 2014)

<sup>4</sup> Unpublished data

<sup>5</sup> Global Polio Eradication Initiative (2014).

<http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx> (Accessed on 12 August 2014)

<sup>6</sup> World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 – conclusions and recommendations. Weekly epidemiological record. 2014: 89, 221-236

<sup>7</sup> IDM (2014). Unpublished analysis

northwest where neither WPV1 nor WPV 3 has been isolated in the past 2 years. Population immunity analyses suggest that this approach can address the goals for cessation of both WPV1 and cVDPV2. Nigeria should also consider the use of IPV (simultaneously with OPV) in SIAs in areas with low type 2 immunity, to the extent possible.

- Pakistan must use the current opportunity and population access in the north-west of the country to stop the persistent cVDPV2 by end-2014 by ensuring that tOPV is used in a sufficient number of the upcoming SIAs targeting children from conflict-affected areas and considering the judicious use of IPV (simultaneously with tOPV) to the extent possible. Sustaining Pakistan's usual approach in which tOPV is used in up to 50% of SIAs will be essential in this cVDPV2-infected population through end-2014.

## Topic 2: cVDPV risk mitigation strategy at time of OPV2 withdrawal

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The WG reviewed modeling data related to risks and risk mitigation strategies associated with the OPV2 withdrawal, presented by three modeling groups; Kim Thompson (Kid Risk; SAGE WG member), Guillaume Chabot-Couture (IDM) and Nick Grassly (Imperial College; SAGE WG member).

The modeling by Kid Risk included characterization of the risk of cVDPV emergence in different situations (e.g. different levels of population immunity, routine immunization coverage, frequency of SIAs and impact of SIAs). The results suggest the risk of cVDPV emergence is real (less than 10%), and cVDPV2 outbreaks will most likely happen within 12 months after OPV2 withdrawal. To achieve sufficient population immunity to transmission (defined as a function of the entire population and considering the potential for reinfection and waning) before the OPV2 withdrawal to prevent the creation of cVDPV2, tOPV campaigns may be needed in some countries shortly before OPV2 withdrawal<sup>8</sup>. In those places that fails to prevent cVDPV2 outbreaks, the same analysis also suggested that the outbreak response with mOPV2 that successfully stops the outbreak is unlikely to cause the reemergence of cVDPV in the outbreak population, although more modelling is needed to explore the neighboring areas. Further modelling demonstrated that although IPV introduction in routine immunization offers protection from paralysis to vaccinated recipients who seroconvert to that dose, giving a dose of IPV to already OPV-vaccinated children as a simultaneous extra dose does not significantly improve the population immunity, because most of the children receiving the dose will already be recently immune and IPV doses not spread secondarily to infect and increase immunity in contacts (as occurs with OPV)<sup>9</sup>. The model indicated that tOPV SIAs prior to OPV2 cessation would help to increase population immunity high enough to cause any circulating OPV2-related viruses to die out after OPV2 cessation. Specific analyses for India and Nigeria demonstrated the impacts of different potential immunization strategies on population immunity and cVDPV risks<sup>10</sup>.

The model by IDM suggested that if there are no tOPV campaigns before OPV2 withdrawal, there is a significant risk of type 2 cVDPV emergence (around 3 emergences in total; 2 expected within 12 months after OPV 2 cessation, with the risk of emergence subsequently decreasing). These risks are concentrated in a few high-risk countries (e.g. Angola, DRC, Nigeria, Somalia, Chad, Madagascar and Ethiopia) and are not homogenous in large countries (e.g. Nigeria). It also showed that tOPV campaigns in these high-risk areas before OPV 2 withdrawal are likely to mitigate the risk of cVDPV2 emergence significantly (1.07 emergences with one SIA, 0.41 with two SIAs, and 0.16 with three SIAs, assuming 50% SIA coverage)<sup>11</sup>.

The analysis presented by Nick Grassly (Imperial College; WG member) indicated that tOPV SIAs carried out before OPV2 withdrawal could paradoxically increase the risk of cVDPV emergence depending on baseline routine immunization coverage, tOPV efficacy and SIA coverage<sup>12</sup>. The risk diminished with increases in the number and coverage of tOPV SIAs, suggesting that where additional tOPV SIAs are planned there should be several (minimum 2-4) rounds with high coverage. The analysis also suggested that in areas with poor routine immunization coverage, no recent tOPV SIA or circulation of VDPV2, the risks of introducing tOPV SIAs may

<sup>8</sup> Thompson KM, Duintjer Tebbens RJ. Modeling the dynamics of oral poliovirus vaccine cessation. *J Infect Dis* 2014; In press.

<sup>9</sup> Duintjer Tebbens RJ, Thompson KM. Modeling the potential role of inactivated poliovirus vaccine to manage the risks of oral poliovirus vaccine cessation. *J Infect Dis* 2014; In press.

<sup>10</sup> Kalkowska DA, Duintjer Tebbens RJ, Thompson KM. Modeling strategies to increase population immunity and prevent poliovirus transmission in the high-risk area of northwest Nigeria. *Journal of Infectious Diseases* 2014; In Press.

<sup>11</sup> IDM (2014). Unpublished analysis

<sup>12</sup> Grassly N and Pons-Salort M (2014). Unpublished data

outweigh the benefits, unless the number of campaigns and coverage is high (e.g. at least 5 SIAs depending on expected vaccine efficacy).

The WHO secretariat summarized the risks of cVDPV2 emergence and outlined the risk mitigation strategies, which are to: 1) stop persistent cVDPV2; 2) achieve and maintain high population immunity against type 2; 3) ensure that high coverage is achieved in SIAs; 4) enhance surveillance sensitivity, and 5) ensure adequate response capability. The presentation also pointed out the significant heterogeneity in risks for emergence of cVDPV, surveillance quality, and immunization schedules even amongst Tier 1 countries. Therefore, appropriately targeted tOPV campaigns in high risk areas will help to reduce the risk of cVDPV2 emergence.

#### **WG decisions/recommendations**

- Modelling reaffirms that the risk of cVDPV emergence after OPV2 withdrawal, while low, is real, and not homogenous across countries or within large countries (e.g. Nigeria) and can be reduced with targeted tOPV campaigns in the period immediately prior to OPV2 withdrawal (i.e. within four months of withdrawal). The strategies for reducing this risk, particularly the use of tOPV campaigns, should be tailored appropriately, based on a risk assessment that includes location, historical VDPV emergence, population size, and population susceptibility.
- Polio-free countries that are planning to conduct SIAs in the coming 18 months, should ensure an appropriate mix of tOPV and bOPV (i.e. for planning purposes, at least 50% of SIAs should be with tOPV). In the four months immediately before OPV2 withdrawal, all SIAs should be conducted with tOPV. The possible exception to the sole use of tOPV in campaigns may be areas that have been newly infected with wild poliovirus, and their contiguous areas, as this constitutes a public health emergency.
- To facilitate OPV demand forecasting, by end-September 2014, a specific plan for the conduct of tOPV SIAs immediately before OPV2 withdrawal should be developed based on an appropriate risk assessment and addressing:
  - which Tier 1 countries should conduct 2-4 nationwide campaigns;
  - which Tier 1 countries should conduct 2-4 sub-national campaigns targeting high risk areas;
  - which, if any, Tier 2 countries should consider 1 or more sub-national campaigns targeting at-risk areas.

Pre OPV2-withdrawal tOPV campaigns must have exceptional planning to ensure sufficient coverage to reach previously unvaccinated children and foci of low coverage, thereby minimizing the risk of cVDPV emergence.

- In areas and countries with high routine polio vaccination coverage (in Tier 3 or 4 countries for example), the WG does not anticipate the need for additional pre-OPV2 withdrawal campaigns.
- As modelling reaffirms that the first 12 months following OPV2 withdrawal represent the period of highest risk for cVDPV emergence, the Global Polio Eradication Initiative must anticipate such emergencies and optimize capacity to detect and respond by:
  - strengthening VDPV2 surveillance, especially in high risk areas, and
  - preparing adequate mOPV2 stockpile and effective outbreak response capacity.

### **Topic 3: Containment of polioviruses**

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The Global Action Plan (GAPIII) on containment of poliovirus was first drafted in 2009, outlining primary (i.e., facility containment), secondary and tertiary safeguards (i.e. sewage systems, vaccination coverage, and environmental conditions for efficient poliovirus transmission). The draft GAPIII is now being revised to align with the new polio Endgame Plan, which now includes a phased removal of Sabin viruses, and universal IPV introduction. In the “Poliovirus Type 2 Containment Period” (between OPV2 withdrawal and OPV cessation), type 2 poliovirus is contained with fewer primary safeguards (e.g. no effluent and, air/exhaust treatment required) because of existing population immunity sustained by the introduction of IPV and backed-up by the existence of the mOPV2 stockpile. It is also envisaged that in the long term, Sabin viruses may be contained with fewer safeguards than wild polioviruses (i.e. the same requirements as those in “Poliovirus Type 2 Containment Period”), due to the lower risk of Sabin virus transmission. The updated plan aims at reducing biosafety risks associated with the use of poliovirus while allowing necessary activities such as Sabin IPV production in developing countries, existing wild IPV production in industrialized countries, laboratory testing for poliovirus, and poliovirus research. These revisions of GAPIII will also be presented to the Expert

Committee on Biological Standardization (ECBS) later in 2014. Once endorsed by ECBS, the revised GAPIII will be submitted for endorsement by the World Health Assembly (WHA) in May 2015.

#### **WG decisions/recommendations**

- The new strategic approach to align GAPIII with the Polio Endgame strategy and timelines, is endorsed, particularly the provisions to:
  - phase the containment of polioviruses in line with the planned withdrawal of OPV serotypes (i.e. beginning with type 2), and
  - establish specific containment requirements for the 'Poliovirus Type 2 Containment Period' (i.e. 2016-2018).
- Containment requirements for the 'Poliovirus Type 2 Containment Period' must include the following:
  - primary safeguards that prevent operator infection and ensure the decontamination of materials and equipment, and
  - secondary safeguards that ensure population immunity with at least 1 dose of IPV at coverage levels in line with that achieved for DPT3.
- In the context of the overall containment strategy, WHO should maintain a registry of every chronic excretor of a vaccine-derived poliovirus (iVPDV) and all countries with such excretors should ensure very high population immunity with an appropriate IPV schedule in relevant areas.
- For the 'Longterm Containment Period', requirements for wild poliovirus must include the full safeguards (full primary, secondary, tertiary) currently described in GAPIII; further work should be done to determine whether the proposed 'Poliovirus Type 2 Containment Period' requirements would be appropriate for all Sabin viruses in the long-term.
- Revised GAPIII should include clear guidelines for non-poliovirus facilities holding faecal collections, which are potentially contaminated with poliovirus.
- The current working draft of GAPIII makes substantial progress in reflecting the new strategic approach to containment in the context of the 'Polio Endgame'. However, it requires substantial revisions to adequately address the management of potentially infectious materials (for both wild and Sabin viruses) during the 'Type 2 Containment Period', the specific details and implications of the primary safeguards for both laboratory and vaccine manufacturer environments in the 'Type 2 Containment Period', and the process and timelines for finalizing the primary safeguards for Sabin virus during the 'Long term Containment Period'.
- Phase 1 inventory activities (including for Sabin 2 viruses) must be completed as a matter of urgency in all countries and WHO Regions to ensure completion by end-2015 as required to achieve global readiness for OPV2 withdrawal. The provisions for 'appropriate handling of residual type 2 materials' during the 'Type 2 Containment Period' must be defined and communicated as a matter of urgency to facilitate the completion of Phase 1 inventory activities.
- GPEI should establish a process to review the merits and risk-benefit of, and to oversee conduct of, any proposed research – including for vaccine development – that is deemed critical or of substantial value to long term security from polio and requires use of live attenuated type 2 viruses during the Type 2 Containment Period of GAPIII; if such research or development is required during this period, the provisions for use of any such attenuated type 2 virus during the Type 2 Containment Period should be aligned with the safety profile of any such strains, particularly with respect to lack of virulence and limited transmissibility.

#### **Topic 4: mOPV2 stockpile governance, management and use**

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The WG reviewed the stockpile release protocol drafted by WHO secretariat. The protocol aims at ensuring: 1) rapid deployment of vaccines for countries with a type 2 outbreak, and 2) outbreak response capacity for emergency vaccination against any type 2 poliovirus. The proposed criteria for release include: 1) detection of a case of AFP associated with type 2 poliovirus (through lab-confirmation or a cluster of cases compatible with polio in a susceptible population exposed to accidental release of poliovirus), or detection of circulating type 2 virus through environmental surveillance and 2) the decision by the the Director-General of the World Health Organization based on advice by a standing expert advisory group. Based on the experience with response to WPV outbreaks, the plan proposes to maintain a minimum stock of 100 million doses of OPV in filled and finished form (assuming 5 million doses/campaign, 3 rounds of campaign/outbreak, maximum of 3 outbreaks,

and 50% buffer) and 500 million doses of bulk. The stock of mOPV will be replenished if 25 – 50 million doses of final products have been used.

#### WG decisions/recommendations

- The proposed protocol for the governance, management and use of the mOPV2 stockpile requires further specificity in the areas of the release criteria, the responsibilities and processes for decision-making and authorization for release of mOPV2, and the speed of mOPV2 dispatch and bulk replenishment.
- Specific criteria for the release of the stockpile must be defined and, given the risks associated with mOPV2 use following OPV2 withdrawal, must be linked to strength of the evidence of confirmed type 2 transmission (as opposed to simply type 2 virus detection). The protocol should include definitions for:
  - i. **Confirmed** type 2 transmission (e.g. detection of an infected individual without documented physical exposure to a virus in a laboratory or a vaccine production facility),
  - ii. **Probable** type 2 transmission (e.g. detection of genetically related viruses from 2 or more environmental samples over time and space consistent with circulation in the population), and
  - iii. **Possible** type 2 transmission (e.g. isolation of a type 2 virus in a single environmental sample or in an individual with documented exposure<sup>13</sup>).

The protocol must define the specific implications/actions for stockpile management and release for each of these scenarios.

- Recognizing the need for very rapid decision-making regarding the release of the stockpile, and the associated risks with mOPV2 use following OPV2 withdrawal, the ultimate decision on use of the stockpile should rest with the Director-General of the World Health Organization; the protocol should include provision for a standing expert advisory group on stockpile release that can be convened (e.g. by teleconference) and provide an expert opinion and risk assessment to the Director-General within 24 hours of notification of a confirmed, probable, or possible type 2 transmission event (as defined above).
- A minimum stock of 100 million doses of finished mOPV2 products should be available as part of the global stockpile in advance of OPV2 withdrawal; decisions on the size of the stock of finished product should be adjusted as needed based on further work to determine the time needed to convert further bulks to finished product and to replenish bulk mOPV2 if required.
- National stockpiles are to be discouraged to minimize the risk of uncontrolled re-introduction of Sabin type 2 viruses, into an increasingly type 2 susceptible population globally, following OPV2 withdrawal.
- GPEI should explore options for ensuring sufficient IPV is available if needed in an outbreak response (e.g. through stock management by IPV manufacturers).
- GPEI should by September 2014 develop a specific protocol for post-cessation type 2 response; this protocol will need to be aligned with and facilitate finalization of the stockpile protocol.

#### Topic 5: Plans for the expansion of environmental surveillance

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Environmental surveillance (ES) is currently used to supplement AFP surveillance as it increases the sensitivity of the surveillance system, especially in areas where AFP surveillance is under-performing. Following OPV2 withdrawal, there will be a need for early detection of any new emergence of cVDPV or failure of containment of Sabin 2 viruses. Therefore in the Endgame Strategy it is proposed that environmental sampling sites be established in at least 15-20 additional cities and locations globally, prior to the switch in 2016, as a primary tool to detect cVDPV2.

The objectives of the expansion of the plan include:

- Improve surveillance to detect early the emergence of cVDPV2 and to support rapid detection and eradication of wild type viruses; and
- Monitor effectiveness of poliovirus containment, particularly type 2, including Sabin 2 viruses, following OPV2 withdrawal

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<sup>13</sup> When an individual is known to be significantly exposed to the contaminated material (e.g. exposed to highly concentrated vaccine bulk in the vaccine production facility)

ES is established in all three endemic countries, and some currently infected or recently infected countries (Kenya, Israel) and many polio free countries such as Egypt, China, India, and many European Region countries. The strategy for expansion is proposed according to the following criteria:

- Establish in priority areas for cVDPV2 emergence (i.e. Tier 1 countries) (e.g. Kenya, Somalia)
- Sustain in endemic areas and expand to capture “silent” areas within endemic countries (e.g. southern Afghanistan)
- Establish in priority countries along overland WPV exportation routes (e.g. Cameroon, Chad, southern Niger, eastern Mali)

ES is also an essential tool in monitoring poliovirus facility-associated risk from essential facilities including laboratories and vaccine manufacturing sites.

Reporting of cVDPV2 and Sabin 2 will also need to be enhanced in preparation for the switch. While the global polio laboratory network is already capable to detect cVPDV and Sabin viruses in a timely fashion, prior to the switch there is a need to accelerate the timeliness of detection and reporting of cVDPV2 and Sabin 2 viruses (the latter currently not being reportable). Endorsement of Governing Bodies will be sought on requirements for immediate notification of type 2 polioviruses.

#### **WG decisions/recommendations**

- Environmental surveillance must be recognized as a fundamental part of the surveillance strategy for OPV2 withdrawal (i.e. early detection of and interruption of cVDPV2s), and not simply a complement to AFP surveillance, which was designed for a different purpose (to guide the eradication of wild virus).
- The overall GPEI strategy for expanding environmental surveillance sites in the short to medium term should be driven primarily by and aligned with the Tiering of countries and areas based on the risk of cVDPV2 emergence and circulation. This must be the primary and immediate driver of expansion and these sites must be established and functioning by no later than Q3 2015 to be able to generate meaningful information on virus disappearance following OPV2 cessation. AFP Surveillance continues to be the mainstay of surveillance for WPV. Expansion of environmental surveillance in endemic, Tier 1 and other countries at high risk of WPV transmission will serve to enhance surveillance for WPV, in addition to the immediate need to identify cVDPV in these countries.
- The planning of environmental surveillance expansion should encompass a longer-term horizon that captures and is aligned with the sites retaining type 2 viruses in the long term and the risks associated with residual type 2 virus stocks and their handling (e.g. IPV production sites).
- The fundamental importance of environmental surveillance to OPV2 withdrawal should be reflected in, and in fact driving, an operational research agenda on the new and emerging technologies to facilitate environmental sampling and analysis; particular priority should be given to technologies that would be rapidly scalable – especially in difficult field environments – in the setting of new type 2 events in the post-OPV2 era to help determine whether the event reflects actual type 2 virus transmission and, if yes, the extent of that transmission.
- The protocols for the mOPV2 stockpile and type 2 poliovirus outbreak response in a post-OPV2 era must reflect the central role of environmental surveillance in the management of the risks associated with OPV2 withdrawal.

#### **Topic 6: Other readiness criteria (e.g. IPV introduction, bOPV licensure )& tOPV withdrawal protocol**

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Significant progress has been made in facilitating introduction of IPV in in OPV-using countries. To date, out of 194 WHO Member States, 72 countries (37%) have introduced IPV and 84 countries (43%) have either decided or declared their intent to introduce IPV by end-2015. As a prerequisite to OPV2 cessation, bOPV must be licensed for use in routine immunization in 144 countries that use tOPV in their immunization program (124 tOPV-only and 20 IPV-tOPV in a sequential schedule). GPEI proposed that it will work with bOPV suppliers and regulatory authorities to develop a global framework to license bOPV (e.g. universal approval to use) which reduces the burden on bOPV suppliers to prepare and file for individual licensure in each of 144 countries and which will address other individual country demands (e.g. need to conduct local clinical trials).



The WG also reviewed the operational guideline for the tOPV-bOPV switch. It outlines the steps required to implement a globally synchronized “switch” (i.e. withdrawal of tOPV, and its replacement by stocks of bOPV) in all countries currently using tOPV. The guideline proposes that countries should plan for a period of two weeks during which stocks of tOPV should be withdrawn from all sites. The National tOPV-bOPV Switch Date should be scheduled within two weeks of the Global tOPV-bOPV Switch Date. Only bOPV should be used in both routine and supplementary immunization campaigns after the National tOPV-bOPV Switch Date, and countries should continue to use tOPV in routine immunization and an appropriate mix of vaccines in supplementary immunization campaigns up until the switch date.

At global level, a small emergency stock of tOPV will be maintained to respond to any short-term shortages at country level to avoid stock outs during the period immediately preceding the tOPV-bOPV switch. The guidelines classify countries into “high risk” and “low risk” and propose different governance structures and mechanisms. In all countries, a National Switch Committee will be responsible for overseeing and managing the switch process. These committees will be assisted by a Switch Support Team to develop and track inventories of existing stocks of tOPV and to operationalize the movement of tOPV stocks within the country to minimize wastage and if needed to recall any unused tOPV stocks at the time of the Switch.

The UNICEF Supply division presented the global supply planning and implementation plan to support IPV introduction and OPV2 withdrawal. The presentation stressed the importance of closely coordinating different stakeholders (GPEI partners, countries, OPV/IPV suppliers) and forecasting vaccine demand to ensure the timely and sufficient production and procurement of IPV and OPV.

#### **WG decisions/recommendations**

- Significant progress has been made toward introducing IPV in all OPV-using countries. All countries should introduce IPV by end-2015, and plan carefully the best way to manage the number of injections that may need to be given simultaneously. Evidence suggests that a country can give infants three or more injections during a single visit without compromising vaccine safety or efficacy<sup>14 15 16</sup>.
- The SAGE recommendation that countries using wP-based DTP should retain wP-DTP in their schedule is reiterated.
- GPEI should develop a global framework to license bOPV for use in routine immunization (e.g. through “universal approval to use”, endorsed by WHA) thereby reducing the burden on bOPV suppliers to prepare and file for individual licensure in each of the 144 tOPV-using countries and address individual country requests (e.g. for local clinical trials).
- The tOPV withdrawal protocol is well thought out and the principles are endorsed. GPEI should develop a more detailed work plan for the switch, which would address recent IPAC recommendations as needed (e.g. separating scientific and operational aspects, communicating to target audience)<sup>17</sup>.
- The tOPV-bOPV switch must be globally synchronized, including with countries that use an IPV/OPV sequential schedule, to reduce the risk of emergence and circulation of cVDPVs. In addition to the current planning, the GPEI should develop contingencies with partners to ensure the coordination in the context of a possible delay associated with failure to meet one of the prerequisites despite continued aggressive efforts to meet all of the prerequisites.

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<sup>14</sup> Offit PA, Quarles J, Gerber MA et al. Addressing Parents’ Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant’s Immune System? *Pediatrics* 2002; 109; 124

<sup>15</sup> Institute of Medicine. Immunization Safety Review: Multiple immunizations and immune dysfunction. Stratton K, Wilson CB, McCormick M (editors). Washington, DC: National Academies Press; 2002.

<sup>16</sup> Wallacea AS, Mantel C, Mayers G et al. Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: Lessons for vaccine introduction. *Vaccine* (in press)

<sup>17</sup> World Health Organization (2014). Immunization practices advisory Committee (IPAC) 11-12 June 2014: Final meeting report and recommendations.

## Summary and next steps for the SAGE Working Group

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The 9<sup>th</sup> meeting of the SAGE WG reviewed the progress of the preparation for the OPV2 withdrawal. The WG reviewed and endorsed the risk mitigation strategy before OPV2 cessation, a revised containment policy, stockpile protocol and environmental surveillance plans.

Overall, the WG concluded that the OPV2 withdrawal during the 'low season' for polio transmission in 2016 is feasible if the persistent cVDPV2s in Nigeria and Pakistan are eliminated by Q3 2015.

The WG requested a follow-up conference call in September 2014, before the next SAGE meeting to finalize the July decisions and discuss several remaining items, including:

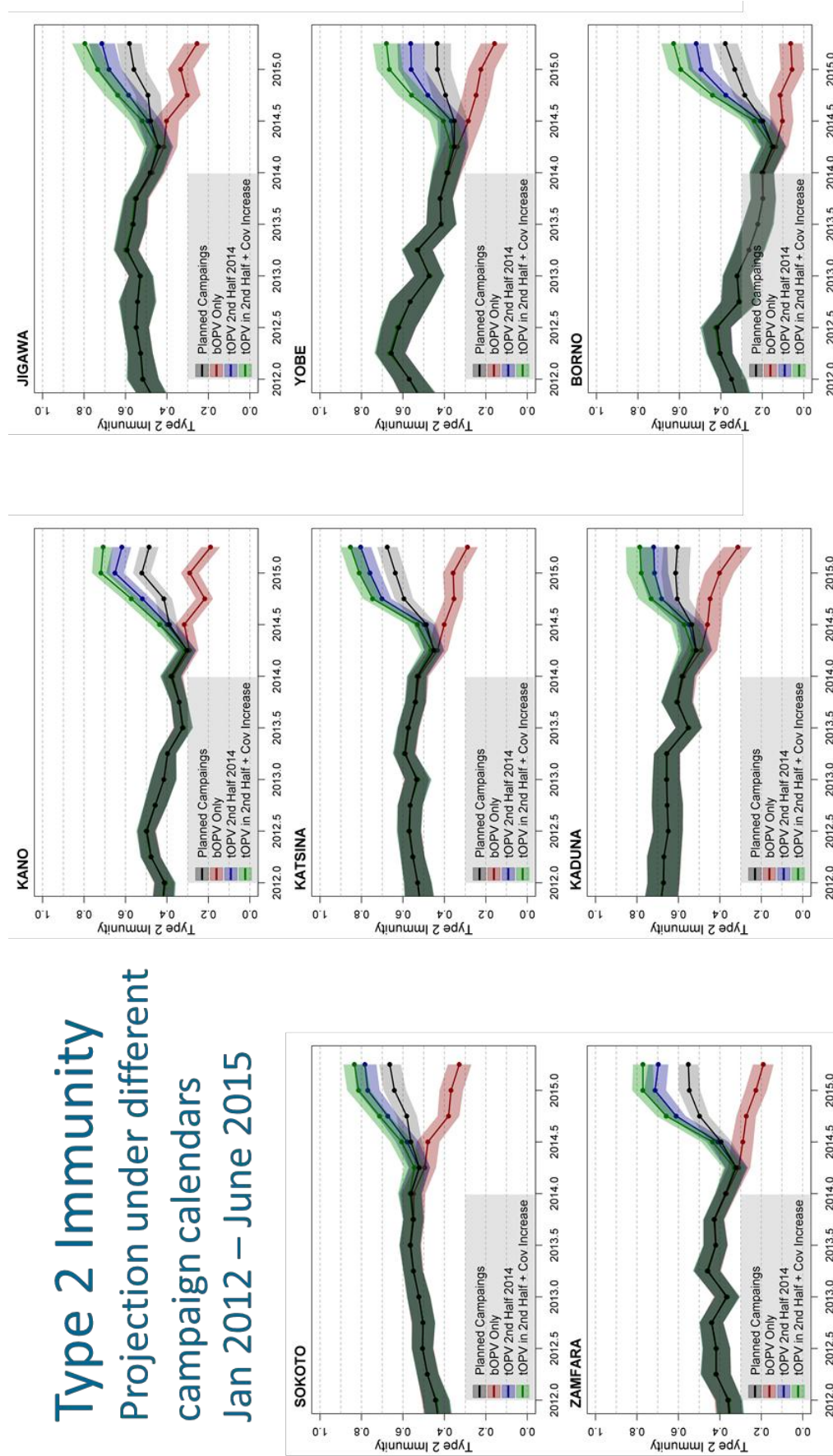
- New standard data format for tracking and communicating newly emerged and persistent cVDPVs, to ensure the timely interruption of persistent cVDPVs before March 2015
- Plan for conducting tOPV SIAs immediately before OPV2 withdrawal based on risk assessment
- Specific protocol for post-cessation type 2 outbreak notification and response
- Updated GAPIII draft, addressing the comments by WG
- Updated protocol for mOPV2 stockpile governance, management and use, including specific criteria for release (i.e. confirmed type 2 transmission) and mechanism of release (i.e. WHO DG's decision based on the recommendation by a standing expert advisory group)
- Updated tOPV-bOPV switch protocol, including a detailed work plan incorporating IPAC recommendations

# Type 2 Immunity

## Projection under different campaign calendars

### Jan 2012 – June 2015

Figure-1: Projection of type 2 immunity in children under 5 years old in 8 regions of Nigeria (IDM polio team)

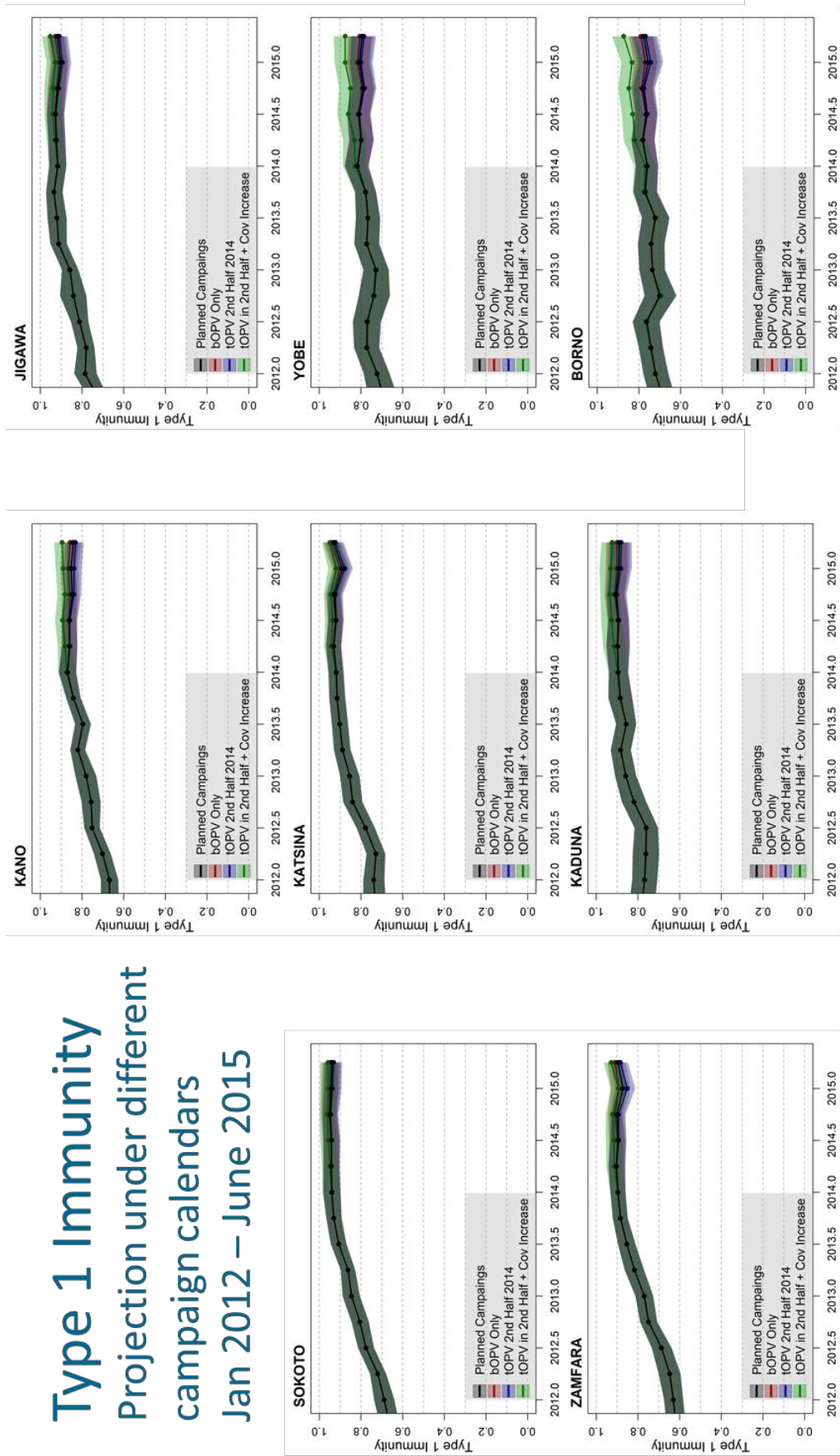


# Type 1 Immunity

## Projection under different campaign calendars

### Jan 2012 – June 2015

Figure-2: Projection of type 1 immunity in children under 5 years old in 8 regions of Nigeria (IDM polio team)



# **Hepatitis E: epidemiology and disease burden**

A document prepared for

Strategic Advisory Group of Experts on Immunization (SAGE)

by the

Hepatitis E Vaccine Working Group

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## Introduction

Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in the developing world. The epidemiology and clinical presentation of HEV infection vary greatly by geographic location, based primarily on differences in HEV genotypes (Teshale, 2011; Kamar 2012, Aggarwal 2012). The overall burden of disease is the highest in parts of the world where clean drinking water is scarce, as fecal contamination of drinking water is a major route of transmission (Rein 2012). In these areas, the predominant HEV genotypes are genotypes 1 and 2. By contrast, in the developed world, where disease burden is lower, zoonotic transmission, mainly through consumption of uncooked or undercooked meat, is a well-recognized mode of transmission (Kamar, 2012), and HEV genotype 3 is the predominant genotype. HEV genotype 4 causes disease mainly in China and Taiwan and mode of transmission is mainly zoonotic. A few sporadic cases of hepatitis E caused by HEV genotype 4 have been reported in Europe. Other modes of transmission of HEV infection include transmission from pregnant mothers to their fetuses, and rarely through blood transfusion (Arankalle, 1999; Robson, 1992; Boxall, 2006; Mansuy, 2009; Hewitt, 2014). Two recombinant subunit vaccines have undergone human trials, and a few others are under development (Shrestha, 2007; Zhang 2010). One of the recombinant vaccines (Hecolin®) was licensed for use in China in 2012. This has led to an interest in the use of HEV vaccines as a public health tool to reduce the burden of hepatitis E. Strategies for vaccine use would need to take into account the varying epidemiologic patterns across different regions of the world and populations vulnerable to severe disease. This paper summarizes the current knowledge of burden of disease, disease outcome, and vulnerable groups, to inform policy for vaccination.

## Hepatitis E

Hepatitis E is a disease caused by infection with hepatitis E virus (HEV), an RNA virus that exists in both enveloped and non-enveloped forms and was first recognized in the early 1980s (Balayan, 1983). The virus is member of the *Hepeviridae* family. It has at least 4 known mammalian genotypes (named 1 to 4), which belong to a single serotype. The viral genome contains three non-overlapping open reading frames (ORF 1-3). Of these, ORF2 codes for the viral capsid protein which is the target of neutralizing antibodies against HEV (Bradley DW, 1995). To date, genotypes 1 and 2 have been found only in humans, whereas genotypes 3 and 4 have also been found in several mammalian species. The virus is relatively stable in the environment (Clemente-Cesares P, 2003), and is sensitive to heat, chlorination and ultraviolet light (Albinana-Gimenez, 2006; Girones, 2014).

Clinical features of hepatitis E are indistinguishable from acute hepatitis caused by other hepatotropic viruses. The incubation period ranges from 15–60 days, with a mean of 40 days (Viswanthan R, 1957). HEV-infected persons exhibit a wide clinical spectrum, ranging from asymptomatic infection through acute icteric hepatitis to fulminant hepatitis. The ratio of symptomatic to asymptomatic infection has not been reliably determined, and may vary with viral genotype and epidemiologic setting. Acute hepatitis E usually manifests with icterus, malaise, anorexia, fever, hepatomegaly, and occasionally pruritus. Studies in non-human primates have shown a relationship between the host's immunological response and degree of liver injury with the dose of viral inoculum (Tsarev SA, 1994). Immunosuppressed persons, in particular solid organ transplant recipients on immunosuppressive drugs, fail to clear the virus leading to chronic HEV infection (lasting >6 months); such cases have mostly had HEV genotype 3 infection, except for one child who had infection with genotype 4 HEV (Kamar, 2008; Kamar 2008; Dalton, 2009; Fujiwara, 2014; Geng, 2014). The laboratory abnormalities in acute hepatitis E are similar to those in acute viral hepatitis caused by other viruses. Laboratory



diagnosis of recent HEV infection is based on detection of HEV-specific IgM (IgA in some countries) antibodies or detection of HEV RNA in clinical samples (Khudyakov, 2013). Past HEV infection is characterized by specific IgG antibodies against ORF2, which may confer protection against reinfection; however, the protective titer and the duration of their persistence are uncertain. (Table 1 and table 2 summarize select virologic and epidemiologic characteristics of HEV infection.)

Certain population sub-groups are at a higher risk for severe disease following HEV infection. These include pregnant women, persons with pre-existing liver disease and persons with immunosuppression (Kamar, 2008; Teshale, 2010; Kumar 2007, Khuroo, 1981). During HEV epidemics, fulminant hepatitis occurs with a disproportionately high rate among pregnant women (Khuroo, Ramalingaswami, 1988; Tsega, 1993). During a recent outbreak in northern Uganda, a high mortality rate was recorded among children younger than 2 years (Teshale, 2010); however, the cause of death in these children was not verified. Overall case-fatality rates from hepatitis E have ranged from 0.1% to 4%; however, case-fatality rates among pregnant women are much higher, being 10%-25%.

Treatment for acute hepatitis E is generally supportive. Chronic hepatitis E in solid organ transplant (SOT) recipients on immunosuppressive treatment has been successfully treated by withdrawal or reduction of immunosuppressive drugs, administration of ribavirin, administration of interferon or a combination of these measures (Pischke, 2013; Kamar, 2012).

## Methods

General information on the agent, disease, and disease outcome was obtained from existing literature. Data on incidence and prevalence of HEV infection and disease in the general population were obtained from a systematic review on hepatitis E and seroprevalence published by the WHO in 2010 (Aggarwal, 2010), which included data published during the period 1980 to 2007, and through a search of the literature published subsequently using methods similar to those used for that previous review to identify articles published during the period 2009-2013 (Myrian Saboui, personal communication).

Articles were first screened at a title and abstract level to determine if they were eligible for inclusion. Eligible articles included original articles, studies reporting on outcomes of interest including HEV prevalence, incidence, mortality or HEV related outbreaks, studies representative of the general population, and case reports, case-series, cohorts, cross-sectional and case-control studies. Studies focusing on high-risk populations, reviews, animal studies, environmental studies, studies not reporting any HEV outcomes of interests listed above, and articles reporting data solely on travellers were excluded. Additionally, studies not reporting numerators and denominators for HEV outcomes were excluded. Data was extracted from studies that met the inclusion criteria. For HEV seroprevalence, we grouped countries based on geographic proximity, economic development, and known HEV genotypes associated with locally acquired disease, all of which are important determinants of the epidemiology of hepatitis E.

## Hepatitis E disease burden and epidemiologic patterns

HEV is the leading cause of enterically-transmitted viral hepatitis. Hepatitis E as sporadic disease or outbreaks have occurred in at least sixty three countries; about half of these countries have reported large outbreaks (Aggarwal, 2010). There are also countries where no sporadic disease or outbreak is reported but have reported seroprevalence of HEV which suggests that

HEV infection may be endemic. A global burden of disease study estimated that HEV genotypes 1 and 2 account for approximately 20.1 million incident HEV infections, 3.4 million cases of symptomatic disease, 70,000 deaths, and 3,000 stillbirths (Rein, 2012).

In developing countries, where HEV genotype 1 and 2 are the cause of hepatitis E, the disease mainly affects young adults (15-39 years of age); conversely, in developed countries where HEV genotype 3 is the main cause of disease, median age of hepatitis E cases is 50 years. There is significant male gender preponderance among cases in developed countries; in the developing countries, this is less marked. HEV infection in persons with pre-existing chronic liver disease causes decompensation and death more often than in previously healthy persons. Table 2 summarizes the epidemiologic and clinical characteristics of hepatitis E by HEV genotype.

In developed countries, HEV infection in persons who receive immunosuppressive treatment following solid organ transplant is associated with risk of progression to chronic hepatitis E (Kamar, 2008). However, this phenomenon has not been observed in developing countries where infections are mainly caused by HEV genotypes 1 and 2. While hepatitis E causes high mortality among pregnant women in developing countries, there have been no reports of this phenomenon from developed countries. Hepatitis E is rare among children in developed countries; however, in developing countries, hepatitis E occurs in children and, according to a single report, mortality in very young children may be high (Sharapov, 2009). A study in India found that a prolonged HEV viremia (longer than 100 days) occurs among icteric and non-icteric adolescents (Arora, 1999). During waterborne outbreaks children may develop severe hepatitis E as a result of co-infection with hepatitis A virus (Tian, 2009).

Large waterborne outbreaks of hepatitis E occur in developing countries where contamination of drinking water occurs (Labrique 1999; Gurley, 2014); large outbreaks have not been reported from developed countries. However, a few small clusters of hepatitis E associated with foodborne transmission have occurred in Europe and Japan (Matsuda, 2004).

Whereas HEV genotype 1 and 2 exclusively infect humans, genotype 3 and 4 mainly infect animals with cross-species transmission to humans. The distribution of HEV genotype 2 has been focal with the majority of cases reported from Mexico, Nigeria, Namibia and a few other West African countries (Kim 2014). Despite the ubiquity of HEV genotype 3 in the swine population, to date clinically apparent human infections with genotype 3 had occurred almost exclusively in developed countries. There is one report of hepatitis E caused by genotype 3 from South Africa (Andersson, 2013). In recent years, HEV genotype 4 has been noted to widely circulate in animals in India and China, and has recently been found in several European countries; most human cases of genotype 4 occur in China and Taiwan. Despite high prevalence of HEV genotype 4 in pigs, hepatitis E caused by HEV genotype 4 in humans has not been reported from India (Aarankalle, 2002). However, a case of hepatitis E genotype 4 has been reported in a traveller returning from India (Rolfe, 2010). Figure 1 shows the global distribution of human HEV genotypes.

Epidemiologic and clinical characteristics of hepatitis E in different parts of the world depend in a large measure on the human HEV genotype circulating in a particular region and the water, sanitation and hygiene conditions, which in turn depend on socioeconomic circumstances. The population vulnerable to severe disease also depends on the geographic location where infection is acquired, which in turn depends on HEV genotype. For this reason, this paper presents the epidemiology and burden of disease caused by human genotypes associated with waterborne transmission (genotypes 1 and 2) and zoonotic transmission (genotypes 3 and 4) separately.



## Hepatitis E caused by genotype 1 and 2

HEV genotypes 1 and 2 are the most commonly identified causative agents of hepatitis E in developing countries. HEV genotype 1 and 2 cause large waterborne outbreaks in countries where water and sanitary conditions are below acceptable standards. HEV genotype 1 mainly affects young adults including women of reproductive age, with slight male preponderance. However, once infection occurs, the outcome significantly varies by pregnancy status, stage of pregnancy, and pre-existing liver disease. Among healthy persons HEV infection results in a spectrum of illness ranging from asymptomatic infection, to anicteric illness, to icteric hepatitis. There are estimates that the symptomatic to asymptomatic ratio ranges from 1:2 to 1:10 or even more and may be dependent on age at infection. Hepatitis E occurs among children and symptomatic disease increases with increasing age. The risk of symptomatic disease in children is lower compared to persons older than 15 years of age (Verghese 2014). Although waterborne HEV outbreaks result in large number of cases over a short period of time, the majority of hepatitis E cases in developing countries are a result of sporadic transmission. The risk factor for sporadic hepatitis E is less well understood, although water contamination may play a role. There is no evidence for sexual transmission of HEV (Mirazo, 2014). HEV is transmitted from mother to her unborn fetus and results in poor fetal outcomes (Khuroo, 2003). Transfusion transmission of HEV occurs and is well documented, however, the contribution of transfusion transmitted HEV to the overall disease burden is negligible (Khurro, 2004)

Waterborne hepatitis E outbreaks have been reported from at least thirty countries from three continents; all were caused by either HEV genotype 1 or 2. Large waterborne hepatitis E outbreaks frequently occur in the Indian subcontinent (Labrique, 1999). In recent years, outbreaks have been regularly identified in camps for displaced persons (refugees) in Africa, resulting in substantial morbidity and mortality. These outbreaks are caused by HEV genotype 1. Persons living in such camps may not have adequate access to clean water and sanitary conditions, leading to a risk of exposure to a higher infectious dose. There is evidence that other modes, including person-to-person transmission, contribute to the prolonged course of outbreaks particularly in displaced populations (Teshale, 2010). There is anecdotal evidence that hepatitis E occurs in health care workers from developed countries who respond to outbreaks in such situations.

The unique characteristic of hepatitis E caused by HEV genotypes 1 and 2 is high mortality among pregnant women. While in the general population the mortality from hepatitis E ranges from 0.1 to 4%, among women in the third trimester of pregnancy, mortality can reach up to 25%. A population-based verbal autopsy study in Bangladesh found that approximately 20% of maternal deaths were associated acute jaundice illness, many of which could be hepatitis E (Gurley 2012). Another group prone to develop severe morbidity following HEV infection are those with pre-existing chronic liver disease. Persons with advanced liver disease, including cirrhosis, can develop acute hepatic failure when super-infected with HEV (Monga, 2004). Chronic infections due to HEV genotypes 1 or 2 have not been described; there are no reports in solid organ transplant recipients or in HIV-infected persons (Naik, 2013; Feldt, 2013). Data on HEV genotype 1 infection and HIV is also scarce.

## Hepatitis E caused by genotypes 3 and 4

The clinical feature of hepatitis E caused by genotypes 3 and 4 is similar to that of acute viral hepatitis caused by other hepatotropic viruses including genotype 1 and 2 HEV. However, in immunocompetent persons, acute illness is often mild and infrequent. Hepatitis E caused by genotype 3 commonly affects older persons (median age 50 years) and predominantly male

(about two-third of cases) (Nelson, 2011). HEV genotype 4 disease is prevalent in China and Taiwan, however, isolated cases have occurred in some European countries. In recent years a notable epidemiologic shift has occurred in China from genotype 1 to genotype 4; the reason remains to be explained. Hepatitis E associated with HEV genotype 3 occurs in locations where genotype 1 or 2 are not endemic. In this area genotype 1 infections occur only as a result of importation by travellers to countries where this genotype is prevalent.

While the majority of hepatitis E caused by genotype 3 is mild and self-limited illness, in immunocompromised persons it can result in chronic hepatitis E (persistence of HEV infection for at least 6 months). The clinical manifestation and progression of chronic hepatitis E is variable with some cases progressing to significant fibrosis in a relatively short period of time. There is no data to show that infection with genotype 3 in pregnant women carries the same risk of high mortality as hepatitis E caused by genotype 1 or 2. Hepatitis E in persons with pre-existing liver disease is not common in developed countries, however, there is a report of severe liver failure as a result of HEV infection of an undiagnosed case of cirrhosis (Crossan, 2014).

There is limited data on the clinical presentation of disease caused by HEV genotype 4. It is believed that hepatitis E caused by genotype 4 closely resembles, but is milder than disease caused by HEV genotypes 1 or 2. Hepatitis E with genotype 4 has occurred in Germany (Wichmann O, 2008), northern France (Tesse S, 2012) and southern France (Colson, 2012) as well as Italy (Garbuglia et al., 2013). Chronic hepatitis E following HEV genotype 4 infection is uncommon, however, there is a recent report of chronic infection in a child with acute lymphoblastic leukaemia (Geng 2014).

In the 1980s hepatitis E in developed countries was associated with travel to countries where HEV genotype 1 infections are endemic. Autochthonous hepatitis E, caused by genotype 3 HEV, has been increasingly reported in developed countries over the last decade (Kamar, 2005; Dalton, 2007; Amon 2007; Tohme 2010). Hepatitis E genotype 3 disease occurs as sporadic cases except for a few small clusters reported as a result of consumption of undercooked game meat and in one instance consumption of shellfish on a cruise ship (Said, 2009). Transfusion transmitted hepatitis E is documented in a recent retrospective study which also found that one in 2848 blood units collected in southeast England had HEV RNA (Hewitt, 2014). The demographic characteristics of acute cases remains striking with the majority of infections occurring in older males. Disease often occurs among solid organ transplant (SOT) recipients (Dalton, 2008; Kamar, 2008). One study found that the incidence of hepatitis E among immunosuppressed SOT recipients in southern France is 3.2 per 100 person-years of follow-up (Abravnel, 2011).

The unique characteristic of HEV genotype 3 infection is chronicity in persons who receive immunosuppressive therapy following SOT and persons with severe immunodeficiency from other causes. In one small study, about two thirds of SOT patients with acute hepatitis E progressed to chronic hepatitis E. The course of chronic hepatitis E is variable and the differential diagnosis can be complex including: subacute rejection of transplanted organ, autoimmune hepatitis, and CLD of unknown etiology. The diagnosis of acute and chronic hepatitis E in immunosuppressed persons may be challenging due to the inability of such persons to mount an immune response. The mortality from chronic hepatitis E can be high. Small case series have shown that treatment, with reduction of the dose of immunosuppression therapy and/or ribavirin, can result in a high rate of sustained virologic response. Although HIV infected patients are at high risk for HEV infection, the number of acute infections is low and very few chronic cases have been reported (Robbins, 2014; Fujiwara, 2014). There is scarcity of data

regarding hepatitis E genotype 3 infections and disease in children, pregnant women, persons with pre-existing liver disease, and otherwise healthy persons.

## **Sero-epidemiology of HEV infection**

Surveillance for hepatitis E disease is very limited and information on disease occurrence and distribution are available only from a few European countries, and most of the data from other parts of the world are limited to reports of outbreaks and case series. By contrast, much more information is available on the seroprevalence of antibodies to HEV, a marker of previous exposure to HEV. However, the interpretation of seroprevalence data is immensely challenging for several reasons. These challenges include the lack of comparability of results from the different assays, high seroprevalence in populations where disease is rare or never reported, the presence of multiple genotypes with different disease patterns and inability of serological tests to distinguish between genotypes, and lack of data for reliable mathematical modelling to determine disease burden from seroprevalence. Furthermore, the majority of seroprevalence studies do not involve a representative sample of any population making it difficult to infer prevalence and trends to the population.

Poor laboratory assay performance is the major challenge in interpreting seroprevalence study results. Many studies have shown poor concordance between commercial IgG HEV assays; some reports showed significant batch to batch variability of IgG anti HEV assays (Abravanel, 2013; Drobeniuc, 2010). The lack of a gold standard test to determine the performance of IgG assays is another challenge. Recent studies comparing the diagnostic accuracy of assays commonly used in Europe and the US for the detection of antibodies against HEV have yielded a significant discrepancy in performance (Drobeniuc, 2010; Abravanel, 2013).

The protective efficacy and the long-term persistence of IgG antibodies against HEV following natural infection has not been clearly determined. In Kashmir, researchers conducted serological follow up of 320 persons who were known to have hepatitis E during the 1978 HEV outbreak. In 50% of the cases there was detectable IgG anti-HEV 14 years after infection (Khuroo, 2010). In another short term follow-up study, researchers found that 100% of persons maintained evidence of past infection 3 years later (Chadha, 1999). However, the implication of the persistence of antibodies is not clear. The fact that the prevalence of anti-HEV in the population does not reach the very high levels observed with hepatitis A and that attack rates are higher among young to middle aged adults suggests that infections may not confer lifetime protection or infections usually occur later in life. This intriguing finding is complicated by the recurrence of outbreaks in countries where past epidemics in the population would have resulted in immunity to prevent future outbreaks. The duration of anti-HEV IgG and the protective efficacy of naturally acquired antibodies are important because of the implications for long term vaccine efficacy. In spite of all these challenges, seroprevalence data provides a general picture as to whether HEV infection is endemic in a country, if population has a disproportionately high rate of infection (e.g., persons with animal contact), and for estimation of population level susceptibility to HEV infection.

## **Seroprevalence in developing countries**

There are several studies that have examined the prevalence of antibodies against HEV in different population groups. However, the sero-epidemiology of hepatitis E in developing countries is not uniform and often does not follow the pattern of clinical disease. Many studies have consistently observed that the prevalence of antibodies against HEV is much lower than the

prevalence of anti-HAV. In a study in Pune, India, researchers found that the prevalence of anti-HAV increased rapidly and reached a peak of around 90% by age 10 years. However, the prevalence of anti-HEV remained low until age 15 years at which point it slightly increased and peaked at around only 50% (Arankalle, 1995). There is no clear explanation for the relatively low prevalence of anti-HEV but it may be due to loss of serological evidence following natural infection (Mathur, 2001). On the contrary, serological data from Egypt have shown that anti-HEV could reach 100% with a very high prevalence even at a very young age (Fix, 2000). Table 1 summarizes salient features of HEV infections and recent seroprevalence estimates.

### **Seroprevalence in developed countries**

The discordance between seroprevalence and incidence of hepatitis E is even more dramatic in developed countries. Despite the high seroprevalence in many European countries and the US, the occurrence of disease is generally low. As demonstrated by many studies, the anti-HEV prevalence in the general population is high and a number of studies have shown that the anti-HEV prevalence among persons with close work contacts with pigs is even higher. The HEV seroprevalence in most study populations is higher among older persons, generally increasing with age, but not different by gender (Drobeniuc, Wenzel, 2014; Faber, 2012; Christensen, 2008; Mast, 2000; Meng, 2002; Kuniholm, 2009; Teshale 2014). In the US, in a nationally representative sample tested using the same assay, the HEV seroprevalence declined significantly during the period 1988-94 to 2009-10 from 21% to 10% (Teshale 2014). There is no clear explanation for this observed decline but a similar trend had been documented in Germany and Denmark (Teshale, 2014, Christensen, 2008, Wenzel 2014). Table 1 summarizes salient features of HEV infection and recent seroprevalence estimates.

### **Special populations**

Hepatitis E manifests with variable severity both in areas where the prevalent cause of disease is genotype 1, 2, and 4 or genotype 3. Infection with HEV genotype 1 is associated with fulminant hepatitis and death in pregnant women and persons with pre-existing CLD. The extent to which such severe disease occurs with genotype 2 and 4 is not very well known. Due to the nature of the living conditions including over crowding and poor hygiene, displaced persons and refugees experience the highest attack rate whenever outbreaks occur. However, such outbreaks are not observed in regions where disease is mainly caused by genotype 3 virus; in this region HEV causes severe disease including chronic hepatitis E in immunocompromised persons. Travellers from developed countries to developing countries also belong to this special population group because of the increased risk of exposure to the virus due to environmental factors.

### **Pregnant women**

HEV infection in pregnant women is typically severe during the third trimester of pregnancy (Kumar, 2004; Khuroo, 2003). Mortality rates among pregnant women in the third trimester range from 10%-25%. To date, the exact mechanism for the disproportionately high mortality among pregnant women is unknown (Naveenethan, 2008). The causes of death include fulminant liver failure and obstetric complications including excessive bleeding (Hussaini, 1997; Tsega, 1993). This HEV-associated high mortality occurs in countries where disease is commonly caused by HEV genotype 1. Similar high mortality in pregnant women has not been reported from western countries. A case of genotype 3 hepatitis E was reported in a 26 weeks pregnant woman from Germany who did not develop fulminant hepatitis and had a normal foetal outcome (Tabatabai, 2014). HEV genotype 1 infection during pregnancy is associated with poor foetal outcomes including abortion, premature delivery, and stillbirths.

## Persons with chronic liver disease

Persons with pre-existing chronic liver disease represent another group in developing countries prone to develop severe morbidity following HEV infection. Persons with advanced liver disease, including cirrhosis, can develop acute hepatic failure when super-infected with HEV (Monga, 2004). The same phenomenon has been observed with hepatitis A super-infection of persons with chronic liver disease and was the basis for administration of hepatitis A vaccination to persons with chronic liver disease (MMWR, 1999). The data from developed countries is limited; there is a report of severe liver failure as a result of HEV infection of an undiagnosed case of cirrhosis (Crossan, 2014). Hepatitis E was found to be the culprit in a number of studies where drug induced liver injury was erroneously diagnosed (Dalton, 2007; Davern, 2011). The burden of HEV-induced acute liver failure in patients with pre-existing chronic liver disease is unknown.

## Persons with immunosuppression

The unique characteristics of HEV genotype 3 infection is chronicity (persistence of HEV infection for at least 6 months) in persons who receive immunosuppressive therapy following SOT or persons with severe immunodeficiency from other causes. In solid organ transplant recipients, acute hepatitis E can progress to chronicity in up to 60% of infected patients. (Kamar, 2011). Risk factors independently associated with chronic infection include heavy immunosuppression, reflected by a shorter time from transplantation to infection, lower CD2, CD3, CD4 and total lymphocyte counts as well as being on a tacrolimus versus a cyclosporine regimen (Halleux, 2012). In one small study, about two third of SOT patients with acute hepatitis E progressed to chronic hepatitis E (Krain, 2013). Solid organ transplant recipients are advised to avoid raw or undercooked pork and seafood to prevent HEV infection. A few small case series have shown that treatment with reduction of dose of immunosuppression therapy and/or ribavirin can result in a high rate of sustained virologic response. Although HIV infected patients are at risk for HEV infection, the number of acute infections is low and very few chronic cases were found thus far (Robbins, 2014; Fujiwara, 2014). A study of kidney transplant recipients that looked for chronic hepatitis E in India did not reveal chronic infection (Naik, 2013).

## International travelers

Prior to the documentation of autochthonous cases of hepatitis E in developed countries, hepatitis E was mainly a disease imported back by international travelers. The first serologically confirmed travel-associated cases of hepatitis E in the US were reported as early as 1985 (DeCock, 1985). Surveillance data from England and Wales showed that travel related hepatitis E contributes to 28% of reported cases. In most countries there is no reporting of hepatitis E whether it is autochthonous or travel associated. It is therefore difficult to determine the magnitude of imported hepatitis E in western countries and the risk of infection among international travelers. As the number of autochthonous hepatitis E increased, the attention shifted from travel associated genotype 1 or 2 disease to genotype 3 disease which is believed to be zoonotically transmitted in such countries. The epidemiologic and clinical characteristic of travel associated hepatitis E cases in developed countries is different from autochthonous cases. Hepatitis E has occurred among international health workers providing assistance during hepatitis E outbreaks.

## Internally-displaced populations

Recent large outbreaks have occurred among displaced persons in Sudan, Chad, and Uganda (Kim, 2014; Teshale, 2010; MMWR, 2013; CID, 2004). The first such outbreak documented in Africa occurred among Angolan refugees in Namibia in 1983. A recent outbreak in South Sudan shares similar epidemiologic characteristics with other HEV outbreaks in such settings. Similar to a 2007 outbreak in northern Uganda, the Sudanese outbreak started during the rainy season with high attack rates (7.4%) among camp residents and high mortality among pregnant women (10.4%) (MMWR, 2013). A serosurvey conducted during this outbreak showed that more than half of residents had no evidence of recent or past HEV infection, suggesting that these persons remained uninfected and were still susceptible to HEV infection 3 months after the implementation of control measures. Like the Ugandan outbreak, the South Sudanese outbreak took a protracted course of well over a year, demonstrating that prevention and control efforts in such outbreaks is challenging.

Table 1: Salient features of HEV infection prevalence and hepatitis E by geographic region.

<i>Region</i>	<i>Country or sub-region</i>	<i>Salient features</i>
North America, Europe, Japan, Australia	USA, Canada	Mainly genotype 3 disease Seroprevalence ~ 15-25% No outbreaks Chronic infection among immunosuppressed
	Europe	Mainly genotype 3 disease Seroprevalence 4-52% Sporadic disease more common Frequent progression to chronic hepatitis E in organ transplant (OT) recipients Mortality in OT recipients 4-9% Overall disease burden is low
	Japan	Mainly genotype 3 disease Seroprevalence 2-20% Few food-borne outbreaks
Latin America and the Caribbean	Mexico, Brazil, Venezuela, Uruguay, Cuba	All genotypes except genotype 4 cause disease Seroprevalence 1%-16% First recorded HEV genotype 2 outbreak in Mexico
Northern Africa and Middle East	Egypt, Libya, Morocco, Iraq, Iran	Mainly genotype 1 disease Seroprevalence 1%-58% Infrequent disease among pregnant women Outbreaks reported in Egypt, Libya, Iraq, Morocco
Sub-Saharan Africa	Uganda, South Sudan, Kenya	Predominantly genotype 1 Waterborne outbreaks common Outbreaks among displaced persons High mortality among pregnant women
South Asia	India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka,	Genotype 1 disease Seroprevalence 10-40% High mortality among pregnant women and



	Afghanistan	persons with liver disease High stillbirth in hepatitis E (35-90%) Waterborne outbreaks common No chronic infection reported
Central and Eastern Asia and Caucasus		Predominantly genotype 1 disease Seroprevalence 0.6-40% Occasional outbreaks
South-eastern Asia and Oceania	Southeast Asia, New Caledonia	Genotype 1, 3, and 4 disease Seroprevalence 0-12% Waterborne outbreak reported from Indonesia, Myanmar and Vietnam Genotype 3 disease

**Figure 1. The global distribution of HEV genotypes.** (The figure is reproduced with the permission of the Deutsches Ärzteblatt International (Pischke et al., 2014))

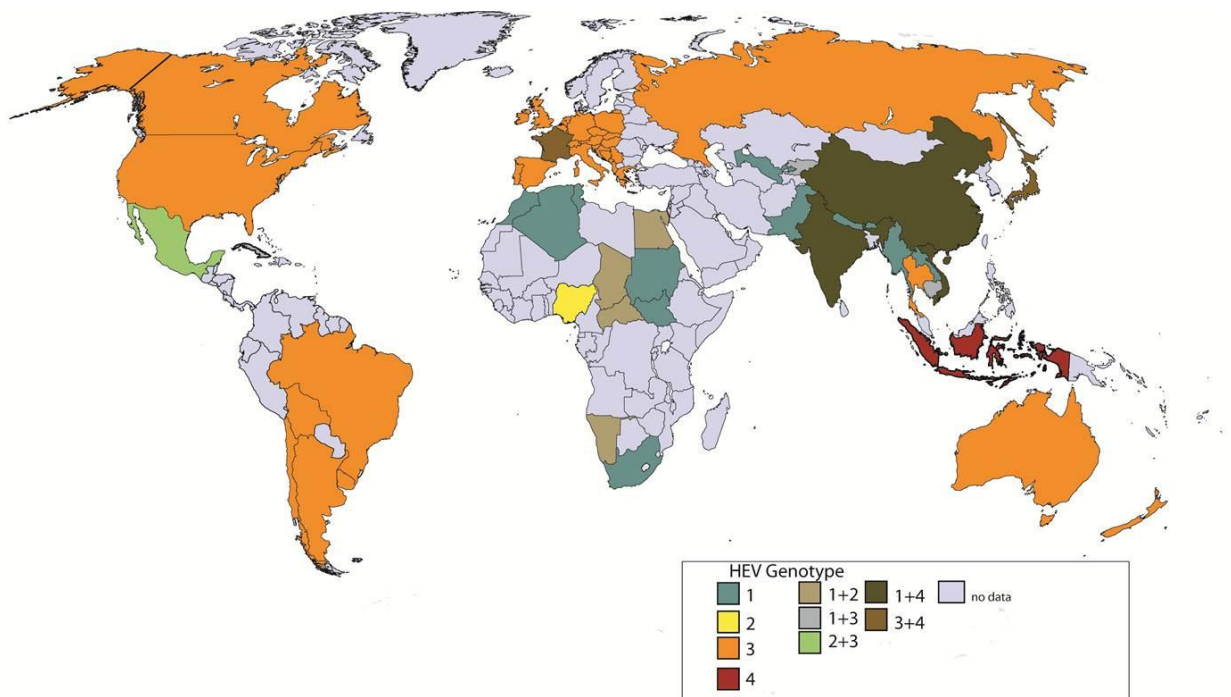




Table 2: Select characteristics of human (genotype 1 and 2) and zoonotic (genotype 3 and 4) HEV

Characteristics	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Distribution of virus: humans	Asia, Africa and the Middle East	Mexico, West Africa	North America, Europe, Latin America, Japan	China, Taiwan, South-East Asia
Distribution of virus: animals	Not identified	Not identified	Widespread, reported in all continents	China, Taiwan, India, with a few recent reports from Europe and North America
Inter-species transmission	Only human-to-human; no inter-species transmission	Only human-to-human; no inter-species transmission	Animal-to-human (pigs, wild boar and deer)	Animal to human (pigs, wild boar)
Water-borne transmission	Yes, frequent (from human feces)	Yes, frequent (from human feces)	No	No
Food-borne transmission	Not recognized	Not recognized	Yes (from contaminated animal meat)	Yes (from contaminated animal meat)
Zoonotic transmission	No	No	Yes	Yes
Occurrence of epidemics	Yes	Yes, but fewer, focal and small-scale	No, except for a few small food-borne (pig meat) outbreaks	Not reported
Relation of attack rate with age	Most common in young adults (15-44 years)	Most common in young adults (15-44 years)	Mostly middle age and older (>50 years)	Limited data
Mortality among pregnant women	High	Not reported	Not reported	Not reported
Chronicity in immune-compromised persons	No	No	Yes	Yes

## Conclusion

Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths (Rein, 2012). Most cases occur in developing countries where occasional large scale outbreaks also occur. Hepatitis E case fatality is highest among pregnant women, which can be as high as 20% when disease occurs in the third trimester of pregnancy (WHO). Hepatitis E is also known to disproportionately affect certain population groups (persons with pre-existing chronic liver disease, immunosuppressed persons, and refugees) for which targeted prevention may be required. International travellers and healthcare workers in outbreak settings may be at a higher risk of exposure to infection if they do not follow the appropriate precautions to prevent foodborne or waterborne transmission. There is anecdotal evidence of the occurrences of hepatitis E among international health care workers during HEV outbreaks, however, there is no evidence that health care workers are at increased risk of HEV infection as long as they adhere to standard waterborne infection prevention measures.

Data regarding burden of hepatitis E is limited owing to lack of hepatitis E surveillance in most countries; estimates of annual infections and cases are based on a modelling study (Rein, 2012). Most studies of burden are based on seroprevalence surveys of populations or specific groups without information about disease. The lack of knowledge of the protective immunity of natural infection undermines the findings of the seroprevalence study. There is no acceptable estimate of the symptomatic to asymptomatic ratio of hepatitis E in a population. Therefore, the seroprevalence estimates can barely shed light on the possible incidence of disease in that community. The diagnosis of acute hepatitis E or past infection with HEV is challenging due to the lack of well validated sensitive and specific assays (Drobeniuc, 2010). The lack of valid laboratory assays also affects interpretation of seroprevalence studies and head to head comparison of such results. The lack of surveillance data remains an important obstacle to prevention of hepatitis E worldwide. Efforts toward collection of data in particular in the area of HEV transmission and propagation in in outbreak setting, disease incidence and burden, understanding characteristics of vulnerable populations, and in the area of vaccine safety, immunogenicity and efficacy in vulnerable populations should be a priority. However, even with these limitations, some conclusions can be made about groups at highest risk for disease or death.

Hepatitis E (a vaccine preventable disease) is also emerging as a leading cause of acute viral hepatitis, maternal death and wastage of pregnancy. The burden of the infrequent, but serious autochthonous hepatitis E in Europe, is substantial with disease affecting persons on immunosuppressive treatment for organ transplant and resulting in chronic infection with death in up to 10% of affected patients (Kamar, 2012). Hepatitis E outbreaks are frequent in Asia and Africa and result in high morbidity and mortality particularly when occurring in displaced persons camps (Teshale, 2010; MMWR, 2013). Current understanding of HEV transmission indicates that effective prevention and control depend on ensuring a safe drinking water supply, adequate sanitation, and proper personal and environmental hygiene. However, in settings where hepatitis E outbreaks occur, it is difficult to mount adequate prevention measures in a timely manner mainly due to rapid transmission of HEV and the long incubation period.

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**Hepatitis E Vaccine: Composition, Safety, Immunogenicity and Efficacy**  
A document prepared for Strategic Advisory Group of Experts on Immunization  
(SAGE) by the Hepatitis E Vaccine Working Group

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## **Executive Summary**

Hecolin®, a recombinant vaccine used for prevention of hepatitis E, contains hepatitis E virus (HEV)-like particles prepared using a recombinant *Escherichia coli* expression system. The vaccine is approved for use in China in people aged 16 and above, and is recommended for individuals at high risk of HEV infection. Hecolin® is well tolerated and has been demonstrated to be safe for use in adults. The main adverse events associated with its use have been local reactions at the injection site.

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

The vaccine protects against symptomatic HEV infection, with a very high efficacy rate. Data on this protection are primarily applicable to genotype 4 disease; data on disease caused by other genotypes are either too limited (genotype 1) or are not available (genotype 2 and 3). The vaccine can effectively lower, but not eliminate, the risk of asymptomatic infection. The duration of follow-up in the available published reports has been for a period of up to nearly 2 years; in addition, some unpublished data for up to 4 years after completing immunization are available. Long-term efficacy beyond this time point, duration of protection, and the need and timing for booster dose remain to be determined. Also, there are no data on protection against severe forms of disease, namely acute liver failure, which is particularly frequent in pregnant women.

Data on safety and efficacy in children or persons aged above 65 years are lacking. Some limited available data suggest that the vaccine is safe in pregnant women; data on immunogenicity and protection specifically in this group are lacking. The vaccine also appears to be safe and immunogenic in hepatitis B carriers; whether these extend to persons with chronic liver disease needs further study. Also, data on protective efficacy in this group are not available. There are currently no data on the use of Hecolin® in children <16 years old, immunosuppressed persons, or its efficacy in protecting against genotype 2 or 3 HEV infection. Further, the efficacy of the vaccine when administered in a post-exposure setting or in controlling disease outbreaks has not yet been studied. Data on these aspects should help better determine the clinical and public health applications of this vaccine.

## Background - Hecolin®

Hecolin®, a recombinant vaccine used for prevention of hepatitis E, has been developed and is manufactured by Xiamen Innovax Biotech Co., Ltd. in Xiamen, China. Hecolin® (generic name: Recombinant Hepatitis E Vaccine [*Escherichia coli*]) is prepared using a genetically engineered strain of *E. coli*. It was granted a marketing authorization in China by the then State Food and Drug Administration (SFDA; now China Food and Drug Administration) in December 2011. It has been on the Chinese market since October 2012, where it is approved for use in people aged 16 years and above, and is recommended for individuals at high risk of hepatitis E virus (HEV) infection, including those involved in animal husbandry, food handlers, students, members of the armed forces, women of childbearing age, as well as travellers to endemic areas (<http://www.innovax.cn/en/pro1.aspx?CateID=52#103>).

This document reviews the data on composition, safety, immunogenicity and clinical efficacy of this vaccine. The data included in this review were derived from articles identified in a search of several databases [MedLine OvidSP (1946-present), EMBASE, Cochrane CENTRAL, PubMed (1946-present) and ICTRP], using the following search terms: ‘Hepatitis E Vaccin\*’, ‘Hecolin’, ‘Virus-like particle’, ‘Hepatitis E/immunology’, ‘Hepatitis E/prevention and control’ and ‘Hepatitis E virus/immunolog\*’. The search was limited to human studies. No language restrictions were used. Titles and abstracts of articles identified during the literature search till June 21, 2014 were screened as per the inclusion and exclusion criteria highlighted in Box 1. In addition, the manufacturer of the licensed vaccine was contacted to obtain all the published and unpublished information about studies done with their vaccine.

### Box 1: Inclusion and exclusion criteria applied

#### Inclusion criteria

- Articles that include research on Hepatitis E Vaccine, specifically Hecolin® or *Escherichia coli* expressed HEV 239 VLP recombinant protein vaccine
- Clinical Trials and Post Licensure Studies
- Populations: All
- Languages: No language restriction

#### Exclusion criteria

- Not Hepatitis E Vaccine or Hecolin® Vaccine
- Non-Human studies
- Pre-clinical studies, systematic review, non-peer reviewed papers, and grey literature

The search strategy identified a total of 3617 records. After initial screening using article titles, 85 articles were included for abstract and full-text assessment. Of these, six articles met the inclusion criteria and were included for analysis.

## Composition

Hecolin® is based on a 239 amino acid long recombinant HEV peptide, termed HEV 239, corresponding to amino acids 368-606 of open reading frame 2 (ORF2) which encodes the capsid protein of HEV. The amino acid sequence is derived from a genotype 1 Chinese HEV strain (Li et al., 2005a). HEV 239 is expressed in *Escherichia coli*, where it forms inclusion bodies. The recombinant antigen is then purified using Triton X-100 and urea, and dialyzed against phosphate buffered saline, to enable renaturation of the antigen, followed by further purification by gel filtration high performance liquid chromatography (Li et al., 2005b). The

peptide forms a homodimer and assembles into ~23 nm particles. These dimeric particles have surface protrusions that correspond to a protruding domain on the surface of the HEV capsid that is believed to be responsible for eliciting neutralizing antibodies. Monoclonal antibodies 8C11 and 8H3, previously shown to neutralize HEV infectivity in rhesus macaques (*Macaca mulatta*), have been shown to bind to the dimeric form of HEV 239 as do convalescent sera from patients with hepatitis E. HEV 239 is immunogenic in mice as well as in Rhesus macaques (Li et al., 2005a). Furthermore, HEV 239 has been shown to induce a vigorous T cell response in mice (Wu et al., 2007).

In challenge studies in rhesus macaques, aluminium hydroxide-adjuvanted HEV 239 provided protection against infection by both homologous (genotype 1) and heterologous (genotype 4) strains of HEV with an intravenous challenge of  $10^4$  genome equivalents (Li et al., 2005a). In the vaccinated animals challenged with a larger HEV inoculum of  $10^7$  genome equivalents, viral infection occurred in some animals but hepatitis (elevation of liver enzymes) was completely prevented.

Following human clinical trials and licensing, HEV 239 was given the trade name Hecolin®. Each 0.5 ml dose of Hecolin® contains 30 µg of purified recombinant HEV antigen, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, 0.8 mg aluminium hydroxide, 25 µg thiomersal, and water for injection. The product is a white suspension with each dose of vaccine supplied in a pre-filled syringe (one per package, which measures 13.2 cm X 3.7 cm X 2.15 cm = 100 cm<sup>3</sup>); the syringe does not get disabled after use. As per the manufacturer's recommendations, the vaccine should be stored at 2°C to 8°C, out of direct sunlight, and has an approved shelf life of 36 months under appropriate storage conditions. The vaccine is stable for at least 45 months. The product is not yet approved for packaging as multi-dose vials (unpublished data; Innovax).

Analysis of Hecolin® bulks as well as the final product revealed that the vaccine was stable for when stored at 30 to 37°C for two weeks. Higher temperatures and longer incubation periods have not been investigated (unpublished data, Innovax).

Consistency of the Hecolin® manufacturing process has been evaluated by determination of vaccine antigenicity in mice using the final aqueous product. A sandwich ELISA, utilizing capture monoclonal antibodies 8C11 and 1B7, demonstrated very similar relative potencies of 5 commercial scale manufacturing lots of Hecolin® (Wei et al., 2014). Virus-like particles, determined by a variety of methods, remained a consistent size (20-30 nm) during scale-up of the fermentation and for over 30 lots prepared on the commercial manufacturing scale; other parameters such as thermal stability and antigenicity were comparable between vaccine lots (Zhang et al., 2014).

The company has a bulk production capacity of 20 million doses annually; however, currently they have ability to fill/package 5 million doses annually (unpublished data, Innovax). The lead time for production of a new batch (with 2 million doses) is about 6 months (unpublished data, Innovax).

## **Safety**

The safety of Hecolin® has been evaluated during the preclinical as well as the clinical stages of its development. Preclinical toxicity of HEV 239 was evaluated according to Chinese regulatory requirements. This included evaluation of intramuscular irritation of HEV 239 in rabbits; of acute and developmental toxicity in mice and of immunotoxicity in rats (Zhang et al., 2013).

The safety of HEV 239 in humans was evaluated throughout the pre-licensing clinical trials (phase I-III) and in retrospective cohort post-marketing studies (Table 1).

### *Phase I study*

In the phase I safety study, HEV 239 was well tolerated with no vaccine-related serious adverse events (SAEs) in any of the 44 adult subjects each of whom received two 20- $\mu$ g doses, by intramuscular administration, separated by one month. There was no evidence of clinically significant changes in liver or kidney function 30 days following the second dose of HEV 239 (Zhang et al., 2013).

### *Phase IIa/b trial*

The phase II study had two parts, namely IIa and IIb (Zhang et al., 2009). The phase IIa study investigated safety and dose scheduling of HEV 239 vaccine in 457 anti-HEV negative adults, aged 16-55 years, from a rural area in southern China. The subjects were randomized (ratio of 1:1:1) into three groups; the first received two 20- $\mu$ g doses of vaccine at 0 and 6 months; the second received three 20  $\mu$ g doses at 0, 1 and 6 months; the third group received as placebo a licensed hepatitis B virus (HBV) vaccine containing 5  $\mu$ g of hepatitis B virus surface antigen (HBsAg) at 0, 1 and 6 months. The subjects received 0.5 ml volumes of the HEV vaccine, and an equivalent volume of the HBV vaccine control i.e. a standard dose. The phase IIb part of the study investigated dose escalation and included 155 high school students, aged 16 years and above, randomized into four groups (in ratio of 2:2:2:1), that received three 10, 20, 30 or 40- $\mu$ g doses administered at 0, 1 and 6 months (Zhang et al., 2009).

After receiving each dose of the vaccine, subjects were observed on site for at least 30 minutes with daily visits thereafter for 3 days. Adverse events (AEs), local and systemic, were recorded by physicians who were not aware of the type of vaccine received. AEs occurring within 30 days of vaccination were documented and subjects with symptoms lasting more than 3 days were visited daily until resolution. Severity of AEs was graded using guidelines issued by the SFDA with grade 3 defined as follows: pain, headache and fever defined as preventing normal activities; redness/swelling at the injection sites exceeding a diameter of 50 mm; and fever  $\geq 39^{\circ}\text{C}$  (Zhang et al., 2009).

The vaccine was well tolerated with only mild local AEs, i.e. itching/swelling at the injection site, and occasional fever; no subject had local or systemic AEs of greater than grade 3 in severity. The rate of local reactions was similar between the vaccine dosages, but was higher in individuals who received HEV 239 compared to the control group (Table 2); it was proposed that this was due to the higher protein content of HEV 239 compared to the hepatitis B vaccine control (Zhang et al., 2009).

### *Phase III trial*

The phase III, double-blinded, placebo controlled trial evaluated the efficacy and safety of HEV 239 in 112,604 subjects from 11 townships in the Jiangsu Province, China (Zhu et al., 2010). Healthy adults, aged 16-65 and of either gender, were randomized to receive three doses of HEV 239 or three doses of a placebo – a licensed HBV vaccine, at 0, 1 and 6 months. Of the 56,302 subjects in each group, 48,693 received all three 30- $\mu$ g doses of HEV 239 whereas 48,663 subjects received all three doses of the placebo.

After each vaccine dose, subjects were observed for at least 30 minutes. They were also requested to report any AEs within 1 month of vaccination. Hospital records and deaths of any

trial subjects were also reviewed. The classification of adverse events followed the definitions set out in the ICH endorsed Medical Dictionary for Regulatory Activities.

Active surveillance of AEs was performed by following a reactogenicity subset of subjects from one township; this subset comprised 1,316 and 1,329 subjects in the HEV 239 group and the placebo group, respectively. Subjects in this subset were visited at home at 6 h, 24 h, 48 h, 72 h, 7 days, 14 days and 28 days after every dose, and any AEs were recorded. There were more local AEs in the HEV 239 vaccinated group than the placebo group i.e. 13.5% vs. 7.1% ( $p < 0.0001$ ), respectively. AEs were mainly pain and swelling with itching at the injection site. The rate of systemic AEs was similar in the HEV 239-vaccinated and the placebo groups (20.3% vs. 19.8%, respectively). AEs of grade 3 or more were reported only very rarely, and included injection site swelling in 2 subjects in the HEV 239 vaccine group compared to 1 in the placebo group, fever in 6 individuals in the HEV 239 group compared to 3 receiving placebo, and headache or fever in 2 subjects in the HEV 239 vaccine group compared to none who received placebo (Zhu et al., 2010).

In the total cohort (excluding the reactogenicity subset), the rate of solicited local adverse events occurring within 72 hours of each dose was 2.8% and 1.9% for the vaccine and placebo groups, respectively. Both groups had the same rate of solicited systemic adverse events occurring within 72 hours of each dose (i.e. 1.9%).

For the total vaccinated cohort, there was no significant difference in the rates of unsolicited or serious adverse events for the two groups within 30 days of vaccination with each dose (Table 3). Similar rates of adverse events were observed for the two vaccinated groups up to 19 months (Table 3).

The rates of hospitalization and death among the study subjects in the two groups during the study period were similar (Table 3); none of these events was determined by the Data Safety Monitoring Board to be related to vaccine administration. The study was adequately powered for detection of rare AEs, i.e. a power of 85% to detect an event whose rate in the vaccine group was 0.03% and rate ratio was 5.0 (Zhu et al., 2010).

Data collected during an extended follow up period of between 19 to 55 months from the first vaccine dose (i.e. between 1 year to 4 years after completion of vaccination), showed the number of reported SAEs (4792 vs 4667;  $p = 0.179$ ) and the number of subjects with one or more SAE (4602 vs 4490;  $p = 0.221$ ) to be comparable between the vaccine and placebo groups (unpublished data, Inovax). The number of deaths over this extended period was nearly 10% higher in the vaccine recipients (408 of 56302) when compared to the placebo recipients (370/56032); however, the difference was not statistically significant ( $p = 0.172$ ) (unpublished data, Inovax).

### *Phase III retrospective cohort study - pregnant women*

Following completion of the phase III clinical trial (Zhu et al., 2010), it was found that 37 women in the HEV 239 vaccine group (out of 31,791) and 31 women in the placebo group (out of 31,735) were either pregnant upon commencement of the study or became pregnant during the trial, even though pregnancy was an exclusion criterion for this study. Data for this group of subjects were reviewed carefully (Wu et al., 2012a).

The 37 women in the HEV 239 vaccine group had received 53 vaccine doses (22 single doses, 14 double doses and one triple dose). The vaccine was well tolerated in the pregnant women with only one woman reporting grade 1 inoculation site pain. The rate of AEs was similar in the pregnant women who had inadvertently received HEV 239 vaccine and the

vaccinated non-pregnant women. Half (19; 51.3%) of the pregnant women in the HEV 239 group underwent elective abortion; the rate was 45.2% in the placebo group. No spontaneous abortions occurred in the vaccine group and the remaining 18 babies, delivered either by normal vaginal delivery (n=7) or caesarean section (n=11), were as healthy as those in the control group (vaginal delivery n=7; caesarean delivery n=10); none of the babies had any congenital abnormality. Birth weights ( $3573.5 \pm 356.7$  g vs.  $3565.6 \pm 531.6$  g), lengths ( $50.7 \pm 1.3$  cm vs.  $50.8 \pm 1.5$  cm) and gestational ages ( $276.2 \pm 7.6$  d vs.  $276.6 \pm 7.1$  d) of the babies born to the mothers in the vaccine group and the placebo group were comparable.

#### *Phase III retrospective cohort study: HBsAg-positive individuals*

Superinfection with HEV is a risk in chronic liver disease patients, and given the high rates of hepatitis B in China, a look back was performed to review the safety and immunogenicity of HEV 239 in HBsAg-positive subjects from the phase III study (Zhu et al., 2010, Wu et al., 2013). Blood was available from subjects from two townships before and after vaccination with either HEV 239 or the placebo. Of the 14,065 subjects from the two townships, 830 (5.9%) were positive for HBsAg at the onset of the trial; none had evidence of chronic liver disease.

Rates of AEs were similar in HBsAg-positive and HBsAg-negative individuals that received HEV 239. The rate of AEs was higher in the HEV 239 group than in the placebo group, irrespective of HBsAg status (Wu et al., 2013).

#### *Data from post-marketing surveillance*

Nearly 200,000 doses of the vaccine have been distributed in the private market in China since the vaccine was licensed; the actual number used and indications are not known. There has been only one report of local adverse event during such use (unpublished data, Inovax), though the completeness of reporting is unclear.

#### *Forthcoming data*

A phase 4 trial on nearly 400 elderly (>65 years) persons is currently underway. In that study, a group of elderly subjects have been divided into two groups i.e. anti-HEV seronegative or seropositive, with the former group receiving the usual 3-dose course of Hecolin® at 0, 1 and 6 months whilst the latter group receiving no intervention. All 400 elderly subjects have been requested to report any AEs that occur during the first, second and sixth months post entry. As an immunogenicity control, a further 200 subjects (aged from 16-65) have received 3 doses of Hecolin® according to the normal schedule. This study should provide additional safety data as well as information on immunogenicity of Hecolin® in older persons. Hecolin® is also being used as a placebo in an ongoing phase 3 trial of HPV16/18 vaccine among about 7,300 healthy women aged 18-35 years (randomization ratio = 1:1).

#### *Safety: overall summary*

Based on evidence from the phase I, II and III trials conducted by the manufacturer, Hecolin® was well tolerated and demonstrated to be safe for use in healthy adults, with main AEs being local reactions at the injection site. There are limited data on safety of Hecolin® on maternal and fetal outcomes following use during pregnancy, and none for its use among organ transplant recipients, other immunosuppressed persons or persons with chronic liver disease.

Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety of Hecolin® in its meeting held in June 2014 (World Health Organization, 2014), and concluded as follows:

In summary, available safety data on Hecolin® derived from Phase 1, 2 and 3 clinical trials in healthy subjects are reassuring. However, GACVS noted that there are no safety data in paediatric subjects (<16 years of age), the elderly (>65 years of age), persons with underlying diseases or conditions such as those who are immunosuppressed persons or have liver disease and thus recommended that studies be conducted to assess the safety of Hecolin® in these subpopulations. Any follow-up of those inadvertently vaccinated in pregnancy during the HPV trial should be useful to assess safety in this group. The committee also noted that there are as yet no studies to evaluate the safety and immunogenicity of Hecolin® when given concomitantly with other vaccines. In addition, GACVS recommended that a Phase 4 post-marketing study be conducted once the vaccine is in more widespread use to further assess the safety profile of Hecolin®, in particular with regard to serious and rare adverse events.

### **Immunogenicity**

The immunogenicity of the HEV 239 vaccine in humans has been studied in a phase II and a phase III study.

#### *Phase II study*

In this immunogenicity study, HEV 239 was studied in healthy persons aged 16-65 years (Zhang et al., 2009). It had two parts: a dose-scheduling component to determine the optimum number of vaccine doses and a dose-escalation component to determine the optimum dose of the vaccine.

The phase IIa (dose-scheduling) study included 457 seronegative subjects who were randomly assigned to receive intramuscular injection of either two 20-µg doses at months 0 and 6, or three 20-µg doses at months 0, 1 and 6. The subjects assigned to the control group received intramuscular injections of three 5-µg doses of hepatitis B vaccine at months 0, 1 and 6. Immunogenicity was assessed using seroconversion rates and geometric mean concentrations (GMC) of anti-HEV, using the Wantai anti-HEV assay (Wantai Biologic Pharmacy Enterprise, Beijing, People's Republic of China), which uses the dimeric E2 antigen which retains the conformational epitopes present in HEV virions and in the HEV 239 used for HEV vaccine (Zhang et al., 2012). Subjects in both the intervention arms and the control arm of the trial were followed-up at months 0, 2, 6, 7 (one month after the third vaccine dose) and month 13. Serum samples were obtained at these times for the determination of concentration of IgG antibody against HEV (Zhang et al., 2009). The HEV 239 vaccine recipients achieved 98% and 100% seroconversion rates after two and three doses, respectively, compared to only 8% seroconversion rate in the control group. The geometric mean antibody titer levels induced by the three dose regimen were two-fold higher than those induced by the two-dose regimen (geometric mean titer = 15.9 World Health Organization units (Wu)/ml [95% confidence interval (CI) 13.8-18.2] versus 8.6 (95% CI: 6.5-11.3) Wu/ml.

In the phase IIb (dose-escalation) component, subjects received three doses each of 10, 20, 30, or 40-µg (at 0, 1, and 6 months). In this study, the antibody titers induced in previously seronegative young adults (aged 16-19 years) by the three-dose vaccine regimen progressively increased from 10.1 to 23.4 Wu/ml as the amount in each vaccine dose increased from 10-µg to 40-µg, but the differences among the three highest dosages did not reach statistical significance. The GMC of anti-HEV in the vaccinated groups (15.9 Wu/ml) were lower than that in serum



samples of patients with history of hepatitis E (43 Wu/ml), but higher than that in healthy persons who were HEV seropositive, but lacked prior history of hepatitis (0.76 Wu/ml).

### *Phase III study*

In a large phase III study using this vaccine (Zhu et al., 2010), serum samples were taken from a subset of 11,165 subjects (the immunogenicity subset) before vaccination and 1 month after receipt of the third dose. Of the 5567 subjects in this subset in the HEV 239 vaccine group (nearly half of them were anti-HEV seropositive at enrollment), 5494 (98.7%) had a four-fold or greater increase in antibody concentration following vaccination. GMC of anti-HEV in these subjects rose from 0.14 Wu/ml to 19.0 Wu/ml (95% CI: 18.6–19.4). By contrast, 119 (2.1%) of 5598 subjects in the placebo group showed an antibody response; all these subjects were believed to have had subclinical HEV infection. Subsequently, in the phase III clinical trial discussed above, the immunogenicity of the vaccine in persons with pre-existing chronic hepatitis B infection included in this trial was analyzed (Wu et al., 2013). At month 7, the subjects who were HBsAg-positive or HBsAg-negative at baseline showed similar anti-HEV seroconversion rates (98.38% and 98.69%, respectively), and post-vaccination anti-HEV IgG titers (19.32 Wu/ml [95%CI, 17.68–21.12] and 19.00 Wu/ml [95%CI 18.59–19.42], respectively). Antibody dynamics after vaccination were similar for HBsAg-positive and HBsAg-negative subjects, regardless of their baseline anti-HEV status.

The immunogenicity of the vaccine has not yet been evaluated in persons younger than 16 years and older than 65 years of age, or in populations at risk for severe hepatitis E disease, such as persons with chronic liver disease, pregnant women, persons with immunodeficiency states (e.g. HIV/AIDS), and transplant patients receiving immunosuppressive therapy (Crum-Cianflone et al., 2012; Davern et al., 2011; Kamar et al., 2012). The immunogenicity of the vaccine when administered by subcutaneous or intradermal routes, or in an accelerated regimen, e.g., 0, 1 and 2 months has not been studied. There are no data on immunogenicity of this vaccine when co-administered with another vaccine.

The anti-HEV antibodies induced by the vaccine decline with time, but remain detectable up to 4.5 years after the first dose. Persons who were anti-HEV antibody positive at entry into the trial achieved higher antibody titers post-vaccination, and had a slower antibody titer decline over time; in these individuals, an increase in antibody titer and a slow decline of titer post-vaccination was seen even if they had received only one or two of the recommended three doses (unpublished data, Inovax).

The interpretation of data on immunogenicity and persistence of anti-HEV antibody are made difficult by lack of information on protective antibody titer against HEV infection.

### **Efficacy**

Vaccine efficacy is defined as proportional reduction in the incidence of disease among people who have received a vaccine compared to that in a similar group of people who have not been vaccinated, under optimal conditions, such as in a randomized controlled trial. It refers to the clinical benefit provided by a vaccine in the ‘best case scenario’, and differs somewhat from ‘effectiveness’ which relates to ability of vaccine to prevent outcomes of interest in the ‘real world’ situation.

Efficacy of Hecolin® has been assessed to a limited extent in a randomized phase II study (Zhang et al., 2009) and in more detail in a phase III randomized clinical trial (Zhu et al., 2010).

### *Phase II study*

In a phase II dose-scheduling study mainly directed at studying safety, immunogenicity and optimum dose-schedule of the HEV 239 vaccine, occurrence of new HEV infections was studied as one of the secondary outcomes (Zhang et al., 2009). This was done by following up the study subjects, who received three 20- $\mu$ g doses of HEV vaccine (at 0, 1 and 6 months; group A, n=155), two 20- $\mu$ g doses of HEV vaccine (at 0 and 6 months; group B, n=151) or three doses of a hepatitis B vaccine (at 0, 1 and 6 months; group C, n=151), for evidence of HEV infection, by looking for spontaneous seroconversion or a >3-fold rise in the level of IgG anti-HEV antibody in paired sera.

Among 151 control subjects in group C (who received hepatitis B vaccine), 20 had evidence of new HEV infection, including 17 with seroconversion to anti-HEV antibody and three others who showed a >3-fold rise in IgG anti-HEV level (6, 19 and 78-fold, respectively). Among the 306 subjects who received HEV vaccine (groups A and B), 13 had new HEV infections, including three with spontaneous seroconversion and 10 with >3 fold rise in anti-HEV antibody levels between vaccine doses that could not be related to vaccine administration. The detailed results are shown in the Table 4 (adapted from: Zhang, 2009). The frequency of new HEV infections in group A after the second dose, and in groups A and B after the completion of vaccination, was significantly lower than that in the control group, suggesting that administration of two or more doses of the vaccine may have prevented new HEV infections. However, none of the 20 persons in the control group and 13 vaccine recipients who had seroconversion reported any hepatitis-like illness.

### *Phase III randomized field trial*

This study included a total of 112,604 healthy adults aged 16-65 years residing in Jiangsu Province of China, who were randomly assigned to receive three 30- $\mu$ g doses of HEV 239 vaccine (adsorbed to aluminium hydroxide) or a placebo (hepatitis B vaccine) administered intramuscularly at 0, 1 and 6 months (Zhu et al., 2010). Randomization was stratified by age and sex, and the study subjects, care providers and investigators were unaware of the group assignment. Both groups were followed up for 19 months, using an active hepatitis surveillance system comprising 205 sentinels, including 162 community clinics, 30 private clinics, 11 central hospitals located in townships and two central hospitals in one large city, to identify cases with hepatitis. Hepatitis was defined as persons (i) presenting with constitutional symptoms (fatigue, loss of appetite or both) for longer than 3 days and (ii) serum alanine aminotransferase (ALT) exceeding 2.5 times the upper limit of normal. Paired sera were obtained from such subjects at the time of presentation and 2-6 weeks later. The initial serum was tested for markers of infection with various hepatitis viruses, and the paired sera were tested for anti-HEV IgM and IgG, and HEV RNA. For a person with hepatitis to be diagnosed as acute hepatitis E, an additional condition had to be fulfilled, i.e. positive IgM anti-HEV and RNA, or  $\geq 4$ -times increase in IgG anti-HEV, or both.

Primary efficacy analysis included eligible subjects who had received all three doses of either vaccine (per protocol analysis). The primary endpoint was prevention of hepatitis E (as defined by fulfillment of three conditions, i.e. constitutional symptoms [fatigue, loss of appetite or both] for at least 3 days, serum ALT elevation [of 2.5-fold upper limit of normal range or more], and evidence of HEV infection [positive anti-HEV IgM and HEV RNA,  $\geq 4$ -times increase in anti-HEV IgG, or both]) in the per-protocol population during the 12 months from the 31<sup>st</sup> day after the third dose. Efficacy analysis was based on accrued person-time in the

vaccine and control groups, and used an exact conditional procedure under the assumption that the numbers of patients with hepatitis E in the two groups were independent Poisson random variables. In addition, efficacy was also assessed using a Cox proportional hazard model and log-rank test.

In the primary (per protocol) analysis, 15 of the 48,663 placebo recipients (with 48,555.1 person-years at risk) and none of the 48,693 vaccine recipients (with 48,594.6 person-years at risk) developed hepatitis E during the 12 months from the 31<sup>st</sup> day after the third dose, with a vaccine efficacy of 100% (95% CI = 72.1% to 100%;  $p < 0.0001$ ).

An intention-to-treat analysis was also done. It included all eligible subjects who had received at least one dose of either vaccine followed up for 19 months. In this analysis, 22 of the 56,302 placebo recipients and one (with only one vaccine dose) of the 56,302 vaccine recipients had hepatitis E, with vaccine efficacy of 95.5% (95% CI = 66.3% to 99.4%;  $p < 0.0001$ ). Another analysis in the same groups for 12 months from the 31<sup>st</sup> day after the receipt of the final dose (which was the first, second or third dose in those who received one, two or three doses, respectively) revealed 16 cases among placebo recipients and one among vaccine recipients, with protective efficacy of 93.8% (95% CI = 59.8% to 99.9%).

Assessment of efficacy using a Cox proportional hazard model and log-rank test, showed a significant difference between the vaccine and the placebo groups in cumulative incidence of hepatitis E ( $p < 0.0001$ ).

An additional analysis evaluated vaccine efficacy after two doses of the vaccine, i.e. in the period between 14 days after the second dose and before the third dose. This revealed five cases among 54,973 placebo recipients (20,196.8 person years) and none among the 54,986 vaccine recipients (20,202.1 person years of follow-up) with efficacy of 100.0% (95% CI = 9.1% to 100.0%) (Zhu et al., 2010).

#### *Longer-term efficacy*

A subset of subjects in the above phase III randomized trial (residing in two of the 11 rural townships included in the original trial) has been followed up till 25 months after full vaccination course (or 31 months after start of vaccination), to obtain data on longer-term efficacy of hepatitis E vaccine (Zhang et al., 2013). In this report, rates of infection with HEV occurring over the 24 months after vaccination were assessed by comparing the antibody levels in paired serum samples obtained in months 7 and 19 after starting vaccination (i.e. first year after vaccination) and in months 19 and 31 (i.e. second year after vaccination). HEV infection was indicated by a positive anti-HEV seroconversion (when previously seronegative) or by a 4-fold or greater rise in anti-HEV antibody level (when previously seropositive).

Of the 14,094 subjects initially randomly assigned, 14,069 had pre-vaccination antibody testing and were eligible for intention-to-treat analysis. The per-protocol cohort included 12,409 subjects who received all three doses of the HEV vaccine ( $n = 6,176$ ) or placebo ( $n = 6,233$ ); of these, 8,670 subjects (4,322 vaccine and 4,348 placebo recipients) had paired sera taken at months 7 and 19 and 7,478 (3,758 vaccine and 3,720 placebo recipients) had paired sera taken at months 19 and 31. Mean age, gender ratio, baseline anti-HEV IgG seroprevalence and level were comparable between the vaccine and placebo groups.

In the placebo group, 115 subjects had HEV infection, including 98 with positive seroconversion (probable primary infection) and 17 with  $\geq 4$ -fold rise in antibody level (possible re-infection). In the vaccine group, 24 subjects had HEV infection, including 6 with positive seroconversion and 18 with  $\geq 4$ -fold rise in antibody level. Of the total 139 HEV infection

events (115 + 24), only three episodes (all primary infections in control subjects) were associated with clinical illness (hepatitis like symptoms for  $\geq 3$  days and ALT elevation  $\geq 2.5$  times the upper limit of normal) and the remaining 136 were entirely asymptomatic.

The overall per-protocol efficacy was 79.2%, being similar in the first and second year post-vaccination. Overall efficacy in subjects who had received at least one dose of vaccine (intention-to-treat analysis) was 77.0%.

Data from continued follow-up of the original cohorts of vaccinated and unvaccinated persons during the phase III study for 55 months since enrollment (i.e. for 4 years beginning one month after the third dose of vaccine or placebo), showed persistence of protection against hepatitis E with overall protective efficacy of 87% (unpublished data; Innovax).

#### *Efficacy in specific high-risk or other subgroups*

No data are available on efficacy of hepatitis E vaccine in high-risk or other special subgroups, such as children (<16 years), elderly persons (>65 years), pregnant women, persons with chronic liver disease, immunosuppressed persons, or persons with other co-existing diseases.

#### *Efficacy against various HEV genotypes*

The HEV 239 vaccine is a recombinant protein based on amino acid sequence corresponding to HEV belonging to a genotype 1 Chinese strain. In the large phase 3 trial, of the 23 persons who had HEV infection (22 in placebo group and 1 in vaccine group), viral genotype could be studied in 13 patients (Zhu et al., 2010). Of these 13 isolates (all in placebo group), 12 belonged to genotype 4 and one to genotype 1. This indicates that protection offered by the HEV 239 vaccine was primarily against infection with genotype 4 HEV, a heterologous strain than the one use for developing the vaccine.

There are no data on specific protection offered by the HEV 239 vaccine against genotype 1, 2 or 3 HEV infection, though it is quite likely that it protects against symptomatic infection with these HEV genotypes too. Studies in rhesus macaques have demonstrated protection by HEV 239 vaccine against infection with HEV genotype 1 and 4 (Li et al., 2005a). A cross-genotype conserved neutralizing monoclonal antibody (8G12) binds recombinant E2 peptides from all four HEV genotypes with equivalent affinity, providing indirect evidence of expected cross protection by HEV 239 against HEV genotypes 1-4. In vitro neutralization of HEV infectivity (genotypes 1 and 4) in cell culture has also been shown for 8G12. Further studies have shown that in rhesus macaques, 8G12, prevents disease in animals infected HEV genotypes 1, 3 and 4 (unpublished data, Innovax).

#### *Efficacy in post-exposure setting*

No data are available on efficacy of hepatitis E vaccine in the post-exposure setting.

#### *Efficacy in preventing disease transmission*

No data are yet available on the effect of HEV vaccination on fecal viral excretion or transmission of HEV infection.

### *Effectiveness*

No real-life effectiveness data on the use of hepatitis E vaccine are available.

### *GRADE Tables*

Following the systematic review of Hecolin®, five key questions concerning the efficacy, safety and immunogenicity of Hecolin® were assessed using evidence summaries and the GRADE approach ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)). The questions were as follows:

- 1a. Efficacy of hepatitis E vaccination in immunocompetent individuals
- 1b. Efficacy of hepatitis E vaccination in immunocompetent individuals against hepatitis E disease
- 02. Vaccine safety of Hepatitis E vaccine in immunocompetent individuals
- 03a. Duration of protection following primary immunization with hepatitis E vaccination in immunocompetent individuals
- 03b. Duration of protection against disease following primary immunization with hepatitis E vaccination in immunocompetent individuals

GRADE tables (and a listing of data sources on which these are based) for each of these questions are appended at the end of this document.

## Tables

**Table 1: Summary of safety studies with Hecolin®**

<i>Phase</i>	<i>Aim</i>	<i>Number of subjects</i>	<i>Adverse events</i>	<i>Reference</i>
I	Safety	44	Well tolerated	(Wu et al., 2012b; Zhang et al., 2013)
IIa	Safety; dose scheduling	457	Well tolerated	(Zhang et al., 2009)
IIb	Safety; dose escalation	155	Well tolerated	(Zhang et al., 2009)
III	Safety; immunogenicity; efficacy	112,604	Well tolerated; no evidence of SAEs in pregnant women or congenital abnormalities in babies born to vaccinated mothers*	(Zhu et al., 2010; Wu et al., 2012a; Wu et al., 2013)

\*Inadvertent vaccination of 37 pregnant women who received one or more dose

**Table 2: Reactogenicity of HEV 239 vaccine in phase II study**

<i>Vaccination</i>		<i>Subjects</i>			<i>Number of doses</i>	<i>% Total (grade 3) AE/dose</i>	
<i>Group</i>	<i>Dose</i>	<i>Number</i>	<i>Age Mean <math>\pm</math> SD (range)</i>	<i>M/F</i>		<i>Local</i>	<i>Systemic</i>
Dose schedule	3 x 20 $\mu$ g HEV 239	155	30.1 $\pm$ 12.3 (17-55)	0.67	447	8.5 (1.6)	7.6 (0)
	2 x 20 $\mu$ g HEV 239	151	32.8 $\pm$ 12.5 (17-55)	0.66	286	5.2 (0)	4.9 (0)
	3 x 5 $\mu$ g placebo*	151	33.6 $\pm$ 12.5 (16-55)	0.74	446	2.0 (0)	5.6 (0)
Dose escalation	3 x 10 $\mu$ g HEV 239	45	18.0 $\pm$ 0.62 (17-19)	0.36	132	8.3 (0)	15.2 (0.8)
	3 x 20 $\mu$ g HEV 239	49	18.0 $\pm$ 0.56 (17-19)	0.58	147	6.8 (0)	12.9 (0)
	3 x 30 $\mu$ g HEV 239	41	17.9 $\pm$ 0.66 (17-19)	0.58	121	8.3 (0)	9.9 (0)
	3 x 40 $\mu$ g HEV 239	20	17.9 $\pm$ 0.45 (16-19)	0.67	60	8.3 (1.7)	11.7 (1.7)

AE = adverse event

\*Licensed HBV vaccine

Adapted from Zhang et al., 2009

**Table 3: Reactogenicity of HEV 239 vaccine in phase III study in the entire vaccinated cohort**

<i>Characteristic</i>	<i>Vaccine group</i>	<i>Placebo group</i>	<i>p value</i>
Number of subjects receiving one or more dose	56,302	56,302	
<i>Unsolicited events within 30 days after each dose</i>			
All	6,771 (12.0%, 11.76-12.30)	6,724 (11.9%, 11.68-12.21)	0.666
≥Grade 3	839 (1.5%, 1.39-1.59)	792 (1.4%, 1.31-1.51)	0.241
<i>SAEs within 30 days after each dose*</i>			
All	284 (0.4%, 0.39-0.50)	245 (0.4%, 0.38-0.49)	0.892
Hospital admission	238 (0.4%, 0.37-0.48)	233 (0.4%, 0.36-0.47)	0.817
Disability	0 (0.0%, 0.00-0.01)	0 (0.0%, 0.00-0.01)	-
Death	10 (0.0%, 0.01-0.03)	12 (0.0%, 0.01-0.04)	0.607
<i>SAEs during period from month 2 to month 6 and from month 7 to month 19*</i>			
All	1,423 (2.5%, 2.40-2.66)	1,430 (2.5%, 2.41-2.67)	0.894
Hospital admission	1,328 (2.4%, 2.23-2.49)	1,336 (2.4%, 2.25-2.50)	0.875
Disability	0 (0.0%, 0.00-0.01)	0 (0.0%, 0.00-0.01)	-
Death	95 (0.2%, 0.14-0.21)	94 (0.2%, 0.13-0.20)	0.952

Adapted from Zhu et al., 2010.

Data in parenthesis represent (%; 95%CI)

\*Data and Safety Monitoring Board did not deem any of the SAEs to be related to vaccination.



**Table 4: Efficacy of HEV 239 vaccine in preventing episodes of new HEV infection, as detected by serological testing, in a phase II trial**

Subjects		Observation periods		New infection		
Group	Number	Months of study	Person-months	Episodes of HEV infection	Episodes per 100 person-month	Percent efficacy (95% CI)
<i>During vaccination</i>						
A	128	2-6	512	1	0.20*	86.0 (18.3–99.4)
B	109	1-6	545	10	1.83	--
C	131	0-6	786	11	1.40	--
<i>After vaccination</i>						
A	102	7-12	412	1	0.16*	88.7 (31.0–99.5)
B	78	7-12	468	1	0.21*	85.2 (9.8–99.3)
C	104	7-12	624	9	1.44	--

Adapted from Zhang et al, 2009.

Group A received three 20-μg doses of HEV vaccine (at 0, 1 and 6 months), group B received two 20-μg doses of HEV vaccine (at 0 and 6 months) and group C received three doses of a hepatitis B vaccine (at 0, 1 and 6 months). Episodes of new infection were identified by the spontaneous HEV serological changes observed in consecutive pairs of serum samples taken from group A on months 2 and 6 and on months 7 and 13; from group B on months 1 and 6 and on months 7 and 13, or, in successive pairs of samples taken from group C on months 0,2,6,7 and 13 of the study. (\* Significantly lower than control group).

**Table 5: Efficacy of HEV 239 vaccine in preventing HEV infection in the phase III trial**

<i>Cohorts</i>	<i>Months post-vaccination</i>	<i>Infection rate (episodes/person-year)</i>		<i>Efficacy % (95% CI)</i>
		Vaccine group*	Placebo group*	
Per-protocol	1-24 (overall)	0.30 (24/8080)	1.43 (115/8068)	79.2 (67.7-86.6)
	1-12	0.26 (11/4322)	1.49 (65/4348)	83.0 (67.8-91.0)
	13-24	0.35 (13/3758)	1.34 (50/3720)	74.3 (52.6-86.0)
Intention-to-treat	1-24	0.33 (28/8610)	1.41 (121/8564)	77.0 (65.3-84.7)

Adapted from Zhu et al, 2010.

\* In the parenthesis, numerators indicate the number of subjects with infection and the denominators indicate the total number of subjects studied.

## GRADE Table 01a. Efficacy of hepatitis E vaccination in immunocompetent individuals

**Population :** Immunocompetent individuals(>16 years)

**Intervention:** Hepatitis E vaccination (Hecolin®)

**Comparison:** Non- Hepatitis E vaccination

**Outcome :** Infection with Hepatitis E

<i>What is the scientific evidence of the efficacy of primary immunization with Hepatitis E vaccination (versus control) to prevent infection with Hepatitis E in immunocompetent individuals?</i>				
		Rating	Adjustment to rating	
Quality Assessment	No. of studies/starting rating		3/ RCT 1/ observational <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>2</sup>	-1
		Inconsistency	None serious	0
		Indirectness	Serious <sup>3,4</sup>	-1
		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
	<b>Final numerical rating of quality of evidence</b>			<b>2</b>
Summary of Findings	<b>Statement on quality of evidence</b>			Our confidence in the estimate of the effect on the health outcome is limited.
	<b>Conclusion</b>			Our confidence in the estimate of the effect is limited that primary immunization with hepatitis E vaccine (HEV) decreases the incidence of hepatitis E infection significantly compared to a control. A phase II trial estimated that after receipt of the 3 HEV doses, the vaccinated groups had a significantly lower percentage of episodes of subclinical Hepatitis E per person month (0.21% and 0.16% vs 1.44%).

<sup>1</sup> A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009(2) reported on the occurrence of new Hepatitis E infection among 457 study subjects by assessing IgG anti-Hepatitis E vaccine (HEV) levels in successive pairs of consecutive serum samples. Within the control group, 20 episodes (17 individuals) of seroconversion and 13 episodes (13 individuals) within the vaccinated group were reported during the study period of 12 months. After receipt of 3 HEV doses, the vaccinated groups had a significantly lower percentage of episodes per person month (0.21% and 0.16% vs 1.44%). Vaccine efficacy was 85.2%(95% CI: 9.8-99.3% using a 2 dose schedule) and 88.7%(95%CI: 31.0-99.5% using a 3 dose schedule). All 33 episodes were subclinical as no study subject revealed a history of Hepatitis E during the trial. Zhu et al. 2010 (3) reported only on clinical 23 hepatitis E cases (22 cases in placebo vs 1 case in the vaccine group) within a large phase III RCT including 122,179 subjects corresponding with an estimated vaccine efficacy within the follow-up period of 19 months of 95.5% (95% CI 66.3-99.4%) within an intention to treat analysis that included everybody having received at least one dose (though most received 3 doses) and assessed a significant difference in incidence ( $p < 0.0001$ ) of hepatitis E between placebo and vaccine group. No data on protection against subclinical infection is available. The significant difference for a reduced risk of infection after vaccination ( $RR = 0.15$ , 95% CI 0.3-0.83) was confirmed within a 24-month post-vaccination follow-up RCT of 12,409 subjects from Zhang et al 2013 (4). The estimated vaccine efficacy was 79.2% (95%CI 67.7-86.6) over the 2 year study period. An observational subset of hepatitis B surface antigen positive subjects (Wu et al. 2013 (1)) showed no significant difference (98.38% vs. 98.69%,  $p = .06063$ ) in seroconversion rates to anti-HEV IgG after 3 doses of HEV.

<sup>2</sup> Allocation concealment not clearly stated (Zhang et al. 2009 (2) and Zhu et al. 2010 (3)). The vaccine proved to be efficacious against genotype 1 and 4. The phase III trial was conducted in a region where both genotype 1 and 4 co-circulate. No proved protection against genotype 2 and 3.

<sup>3</sup> Only healthy individuals aged 16- 65 were included, no data available on immunization of children and the immunocompromised. No downgrading for indirectness, as the determined age group in which the vaccine should be used may vary among settings.

<sup>4</sup> The phase III trial provided no data on efficacy against subclinical infection with Hepatitis E.

### Reference List<sup>1-4</sup>

1. Wu T, Huang SJ, Zhu FC et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. *Hum Vaccin Immunother* 2013;9:2474-2479.
2. Zhang J, Liu CB, Li RC et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. *Vaccine* 2009;27:1869-1874.
3. Zhu FC, Zhang J, Zhang XF et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010;376:895-902.
4. Zhang J, Zhang XF, Zhou C et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. *Clin Microbiol Infect* 2014;20:O397-405.

**GRADE Table 01b. Efficacy of hepatitis E vaccination in immunocompetent individuals against hepatitis E disease**

**Population** : Immunocompetent individuals(>16 years)

**Intervention** : Hepatitis E vaccination (Hecolin®)

**Comparison** : Non-hepatitis E vaccination

**Outcome** : Hepatitis E disease

<i>What is the scientific evidence of the efficacy of primary immunization with Hepatitis E vaccination (versus control) to prevent Hepatitis E disease in immunocompetent individuals?</i>				
		Rating	Adjustment to rating	
<b>Quality Assessment</b>	No. of studies/starting rating		2/ RCT 1/observational <sup>5</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>6</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious <sup>7</sup>	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
	<b>Final numerical rating of quality of evidence</b>			<b>3</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.	
	<b>Conclusion</b>		Our confidence in the estimate of the effect is moderate that primary immunization with hepatitis E vaccine (HEV) decreases the incidence of hepatitis E disease significantly compared to placebo. A large phase III trial estimated a vaccine efficacy of 95.5% (95% CI 66.3-99.4%) after at least one dose of HEV.	

<sup>5</sup> A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009 (2) reported on the occurrence of new Hepatitis E infection among 457 study subjects by assessing IgG anti-Hepatitis E vaccine (HEV) levels in successive pairs of consecutive serum samples. Within the control group, 20 episodes (17 individuals) of seroconversion and 13 episodes (13 individuals) within the vaccinated group were reported during the study period of 12 months per person years. After receipt of the 3 HEV doses, the vaccinated groups had a significantly lower percentage of episodes per person month (0.21% and 0.16% vs 1.44%). Vaccine efficacy was 85.2% (95% CI: 9.8-99.3% using a 2 dose schedule) and 88.7% (95%CI: 31.0-99.5% using a 3 dose schedule). All 33 episodes were subclinical as no study subject revealed a history of Hepatitis E during the trial. Zhu et al. 2010 (3) reported 23 hepatitis E cases (22 cases in placebo vs 1 case in the vaccine group) within a large phase III RCT (122,179 subjects) and estimated vaccine efficacy within the follow-up period of 19 months to be 95.5% (95% CI 66.3-99.4%) within an intention to treat analysis that included everybody having received at least one dose (though most received 3 doses) and assessed a significant difference in incidence ( $p < 0.0001$ ) of hepatitis E between placebo and vaccine group. An observational trial subset of hepatitis b surface antigen positive (Wu et al. 2013(1)) showed no significant difference (98.38% vs. 98.69%,  $p = 0.06063$ ) in seroconversion rates to anti-HEV IgG after 3 doses of HEV.

<sup>6</sup> Allocation concealment not clearly stated (Zhang et al. 2009 (2) and Zhu et al. 2010(3)). The vaccine proved to be efficacious against genotype 1 and 4. The phase III trial was conducted in a region where both genotype 1 and 4 co-circulate. No proved protection against genotype 2 and 3.

<sup>7</sup> Only healthy individuals aged 16- 65 were included, no data available on immunization of children and immunocompromised. No downgrading for indirectness, as the determined age group in which the vaccine should be used may vary among settings.

### Reference List<sup>1-3</sup>

1. Wu T, Huang SJ, Zhu FC et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. *Hum Vaccin Immunother* 2013;9:2474-2479.
2. Zhang J, Liu CB, Li RC et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. *Vaccine* 2009;27:1869-1874.
3. Zhu FC, Zhang J, Zhang XF et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010;376:895-902.

## GRADE Table 02. Vaccine safety of hepatitis E vaccine in immunocompetent individuals

**Population** : Immunocompetent individuals (>16 years)

**Intervention** : Hepatitis E vaccination (Hecolin®)

**Comparison** : Non-Hepatitis E vaccination

**Outcome** : Serious adverse events following immunization

<i>In immunocompetent individuals, what is the incidence of serious adverse events following immunization (versus control) with any dose of Hepatitis E vaccine?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT 3/ observational <sup>8</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>9</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious <sup>10</sup>	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		We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.	
	Conclusion		Our confidence in the estimate of the effect is moderate that incidence of serious adverse events following Hepatitis E vaccination is low. Judged on the Phase I, II and III trials and the reactogenicity subset of the latter study, the rates of solicited adverse events were not concerning. Nevertheless the safety follow-up surveillance was largely passive, only healthy individuals aged 16-65 years were included and the pregnancy safety data was limited.	

<sup>8</sup> Based on encouraging safety assessments in the observational phase I trial (Wu et al. 2012(2)), a phase IIa/IIb randomized controlled trial (Zhang et al. 2009 (4)) with a total of 457 (16-55years) (20 µg at 0,1,6 months or at 0,6 months, Hepatitis B vaccine as control) and 155 subjects (16-19years) (10, 20, 30, 40 µg at 0,1,6 months) indicated no serious adverse events (SAE) following immunization above grade 3 (SFDA Guideline). No significant difference in grade 3 local or systemic reactions between the vaccine group and the control. One large phase III trial (Zhu et al. 2010 (5)) with 112 604 healthy individuals (30 µg at 0,1,6 months) showed no significant difference of adverse events between vaccine and control group within the total cohort. Within a reactogenicity subset including 1645 subjects, solicited local adverse events within 72h after each dose were higher (<0.0001) in the vaccine group (13.5%) than in the placebo group (7.1%). Systemic adverse events were similar for both groups (20.3%vs.19.8%). These findings are reflected within the entire cohort. Safety was confirmed in two observational study subsets: A pregnancy subset- retrospective analysis of the phase III trial (Wu et al. 2012(1)) found no significant difference of SAE in women or their infants when receiving vaccine or placebo. Same applies to an analysis of a subset within the phase III trial of individuals with pre-existing chronic hepatitis B (Wu et al. 2013 (3)).

<sup>9</sup> Allocation concealment not clearly stated (Zhang et al. 2009 and Zhu et al. 2010)

<sup>10</sup> Only healthy individuals aged 16- 55 were included, no data available on immunization of children and immunocompromised. No downgrading as the determined age group in which the vaccine should be used may vary among settings. Limited data on 12 cases of ALT increase excluded from analysis on safety by the DSMB, no downgrading regarding this issue (5).

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**GRADE Table 03a. Duration of protection following primary immunization with hepatitis E vaccination in immunocompetent individuals**

**Population** : Immunocompetent individuals (>16 years)

**Intervention** : Hepatitis E vaccination (Hecolin®)

**Comparison** : Non-hepatitis E vaccination

**Outcome** : Infection with hepatitis E virus

<i>What is the scientific evidence of the continuous duration of protection against infection with Hepatitis E following primary immunization with Hepatitis E vaccination (versus control) to prevent infection with Hepatitis E in immunocompetent individuals?</i>				
			Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		3/ RCT <sup>11</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>12</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious <sup>13</sup>	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
	<b>Final numerical rating of quality of evidence</b>			<b>3</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.	
	<b>Conclusion</b>		Our confidence in the estimate of the effect is moderate that primary immunization with hepatitis E vaccine (HEV) decreases the incidence of hepatitis E infection significantly compared to placebo within a period of ≤24 months following immunization though no data is available on the long-term protection following primary immunization with HEV.	

<sup>11</sup> A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009 (1) with 457 study subjects reported a significant difference in hepatitis E episodes after receipt of 3 doses of Hepatitis E vaccine (HEV) within the 12 months study period. A phase III RCT (Zhu et al. 2010 (3)) including 122,179 subjects reported a significant difference in incidence ( $p < 0.0001$ ) of hepatitis E between placebo and vaccine group within the follow-up period of 19 months. The significant difference for a reduced risk of infection after vaccination ( $RR = 0.15$ , 95% CI 0.3-0.83) was confirmed within a 24-month post-vaccination follow-up of 12,409 subjects from the Zhang et al 2013 (2) RCT. The estimated vaccine efficacy was 79.2% (95%CI 67.7-86.6) over the 2 year study period.

<sup>12</sup> Allocation concealment not clearly stated (Zhang et al. 2009 (1) and Zhu et al. 2010 (3))

<sup>13</sup> Only healthy individuals aged 16- 65 were included, no data available on immunization of children and immunocompromised. No downgrading as the determined age group in which the vaccine should be used may vary among settings.

### Reference List<sup>1-3</sup>

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**GRADE Table 03b. Duration of protection following primary immunization with hepatitis E vaccination in immunocompetent individuals**

**Population** : Immunocompetent individuals (>16 years)

**Intervention** : Hepatitis E vaccination (Hecolin®)

**Comparison** : Non-hepatitis E vaccination

**Outcome** : Hepatitis E disease

<i>What is the scientific evidence of the continuous duration of protection against Hepatitis E disease following primary immunization with Hepatitis E vaccination (versus control) to prevent infection with Hepatitis E in immunocompetent individuals?</i>				
		Rating	Adjustment to rating	
<b>Quality Assessment</b>	No. of studies/starting rating		2/ RCT <sup>14,15</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>16</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious <sup>17</sup>	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
	<b>Final numerical rating of quality of evidence</b>			<b>3</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		<b>We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.</b>	
	<b>Conclusion</b>		<b>Our confidence in the estimate of the effect is moderate that primary immunization with hepatitis E vaccine (HEV) decreases the incidence of hepatitis E cases significantly compared to placebo within a period of ≤19 months following immunization. No data is available on the long-term protection following primary immunization with HEV.</b>	

<sup>14</sup> A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009 (1) with 457 study subjects reported a significant difference in hepatitis E episodes after receipt of 3 doses of Hepatitis E vaccine (HEV) within the 12 months study period. A phase III RCT (Zhu et al. 2010(2)) including 122.179 subjects reported a significant difference in incidence ( $p < 0.0001$ ) of hepatitis E between placebo and vaccine group (22 cases in placebo vs 1 case in the vaccine group) within the follow-up period of 19 months.

<sup>15</sup> Unpublished data reports that within a follow-up period of 55 months of Zhu et al. 2010 (2), vaccine efficacy after 3 doses of HEV was estimated to be 93% (95%CI:79-98%), though these data could not be graded due to lack of publication.

<sup>16</sup> Allocation concealment not clearly stated (Zhang et al. 2009 (1) and Zhu et al. 2010 (2))

<sup>17</sup> Only healthy individuals aged 16- 65 were included, no data available on immunization of children and immunocompromised. No downgrading as the determined age group in which the vaccine should be used may vary among settings.

### **Reference List<sup>1-3</sup>**

1. Zhang J, Liu CB, Li RC et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. *Vaccine* 2009;27:1869-1874.
2. Zhu FC, Zhang J, Zhang XF et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010;376:895-902.

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safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet*, 376, 895-902.

# **Recommendations of HEV Working Group on the use of hepatitis E vaccine**

A document prepared for

Strategic Advisory Group of Experts on Immunization (SAGE)

by the

Hepatitis E Vaccine Working Group

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### **1. Executive summary**

The Hepatitis E Vaccine Working Group recognizes that its recommendations are limited by several information gaps in the available data. These information gaps mainly relate to:

1. Information on safety and efficacy of the vaccine in specific subgroups (pregnant women, persons with chronic liver disease, immunosuppressed persons).
2. Information on safety and efficacy of the vaccine in specific age groups (children <16 years and elderly persons >65 years).
3. Epidemiology of hepatitis E, in particular the incidence and mortality of disease in the general population as well as in special population groups.
4. Efficacy of hepatitis E vaccine against disease caused by HEV belonging to genotypes 1, 2 and 3.
5. Efficacy of schedules of hepatitis E vaccine with fewer than three doses or shorter duration.
6. The duration of protection following hepatitis E vaccine and the possible need for boosters.

Thus, as and when data on some of the current information gaps become available, the recommendations for one or more of the situations discussed above will need reconsideration.

Further, the Working Group's recommendations are meant for general use of vaccine. The Group recognizes that there could be special situations where the risk of disease or that of serious disease or mortality could be particularly high, and that these may override other considerations. The Group's recommendations should not preclude the use of this vaccine in these special situations. However, in all such situations, experience with the use of vaccine, including the occurrence of any adverse events, should be documented.

The Hepatitis E Vaccine Working Group of SAGE makes the following recommendations. Details of the evidence base and justification for the recommendations can be found in the pages to follow.

#### **Recommendations on the use of hepatitis E vaccine:**

1. Routine vaccination for populations where epidemic and sporadic hepatitis E disease is common is not recommended at this time.
2. Routine vaccination in pregnant women or in women of child-bearing age living in areas where hepatitis E disease is common is not recommended at this time.
3. Routine vaccination of chronic liver disease patients is not recommended at this time.
4. Routine vaccination of persons on organ transplant wait-list is not recommended at this time.
5. Routine vaccination of travellers from low-endemicity areas to high-endemicity areas is not recommended at this time.
6. Use of the vaccine during outbreaks of hepatitis E could be considered.



## 2. Introduction

Hepatitis E virus (HEV) infection is associated with an acute hepatitis, which can sometimes be severe leading to acute liver failure. This virus is most often transmitted by the fecal-oral route. The disease manifests as waterborne outbreaks and as frequent sporadic cases in areas where water supplies are prone to contamination with human feces. In these areas, infection is mostly due to genotype 1, and less frequently to genotype 2 virus. Serious illness is particularly common in pregnant women and persons with pre-existing chronic liver disease. Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in the developing world. Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths.

In areas where water supplies are safe, the disease occurs as occasional cases which are believed to be related to zoonotic transmission of genotype 3 or 4 virus, possibly through ingestion of undercooked infected meat (livers from pig, wild boar or deer). In immunosuppressed persons, such infection has the potential to become persistent (lasting longer than 6 months), leading to chronic hepatitis. In these areas, hepatitis E also occurs among travellers to areas where waterborne hepatitis E is common.

A recombinant subunit-protein vaccine has been developed against hepatitis E virus infection, which has been tested in a phase III field trial in China, and was found to be safe and effective against hepatitis E disease. The vaccine has been approved and is currently commercially available (as Hecolin®) in China.

Hepatitis E Vaccine Working Group set up by the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization prepared four background papers and then met to discuss the role of hepatitis E vaccine in various population groups. This current document is a synthesis of the information contained in the four background papers and the discussions during the Working Group meeting. This document should therefore be read in conjunction with the following four background documents:

- (i) Hepatitis E: Epidemiology, surveillance and disease burden,
- (ii) Hepatitis E vaccine pipeline (posted on website only),
- (iii) Hepatitis E vaccine: Composition, safety, immunogenicity and efficacy, and
- (iv) Cost-effectiveness of Hepatitis E vaccine (work still in progress, posted on website only).

The Working Group considered the use of hepatitis E vaccine for the general populations residing in areas with high disease burden and also for some specific population groups which are considered at higher risk of infection (e.g. travellers to disease-endemic areas, persons living in camps for displaced persons with limited access to clean water, or persons at risk for waterborne transmission due to disruption of supplies of clean water e.g. flooding, pregnant women in disease-endemic areas) or more often have serious outcomes of disease (pregnant women, persons with chronic liver disease, and immunosuppressed persons such as solid organ transplant recipients). Evidence and recommendations for each of these groups is discussed below.

### 3. Use of hepatitis E vaccine in general population in area with high endemicity

Epidemic hepatitis E occurs in geographical areas where water contamination is common; in addition, in these areas, HEV infection is responsible for a proportion of sporadic acute viral hepatitis. In areas where water supplies are safe, hepatitis E does occur; however, the number of cases in these areas is small.

Based on a mathematical modelling study, HEV is estimated to cause nearly 3.4 million clinical cases of acute hepatitis and nearly 70,000 deaths and 3,000 stillbirths annually in Asia and Africa, which are areas with high disease burden. This disease burden may be comparable to that of several other vaccine-preventable-diseases for which universal vaccination is currently recommended.

**Table: Global disease burden of various vaccine-preventable diseases in comparison to that of hepatitis E.**

<i>Disease</i>	<i>Number of annual deaths worldwide</i>	<i>Estimated global vaccination coverage (2013)<sup>3</sup></i>
Hepatitis E (modelling data)	70,000	*
Pertussis (2012) <sup>1</sup>	67,059	84% (3 doses of DTP)
Diphtheria (2012) <sup>1</sup>	2,615	84% (3 doses of DTP)
Tetanus(2012) <sup>1</sup>	66,129	84% (3 doses of DTP)
Measles (2012) <sup>1,4</sup>	130,461	84% (at least one dose of measles-containing vaccine)
Rotaviral enteritis (2010) <sup>2</sup>	250,900	14% (2 doses of rotavirus vaccine)
Influenza (2010) <sup>2</sup>	507,900	No global estimate available
Hepatitis B (2010) <sup>2</sup>	786,000	81% (3 doses of Hep B vaccine), 38% (birth dose)

<sup>1</sup>WHO Global Health Estimates (GHE) 2014: [http://www.who.int/healthinfo/global\\_burden\\_disease/estimates/en/index1.html](http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html)

<sup>2</sup>Lozano et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010: Lancet 2012; 380: 2095–128 ([http://ac.els-cdn.com/S0140673612617280/1-s2.0-S0140673612617280-main.pdf?\\_tid=4e74d82e-1c9d-11e4-a264-00000aabb0f01&acdnat=1407242448\\_c4e9609829c3624b87afa57e8c785e70](http://ac.els-cdn.com/S0140673612617280/1-s2.0-S0140673612617280-main.pdf?_tid=4e74d82e-1c9d-11e4-a264-00000aabb0f01&acdnat=1407242448_c4e9609829c3624b87afa57e8c785e70) )

<sup>3</sup>WHO Global Immunization Data; [http://www.who.int/immunization/monitoring\\_surveillance/data/gs\\_gloprofile.pdf?ua=1](http://www.who.int/immunization/monitoring_surveillance/data/gs_gloprofile.pdf?ua=1)

\*HEV vaccine is currently not included in vaccination schedules in any part of the world.

<sup>4</sup>In 2000, measles was estimated to have killed 562,400 children. Between 2000 and 2012, 13.8 million deaths were prevented by the measles vaccine (compared to a scenario of no vaccination).

WHO. Global control and regional elimination of measles, 2000-2012. Weekly Epidemiological Record. 2014;89:45-52.

The available hepatitis E vaccine (Hecolin®) has been studied in a large field trial in China, in which nearly 112,000 healthy adults (16 – 65 years old) of either gender were randomized to receive either Hecolin® or a hepatitis B vaccine in a three dose, 0, 1 and 6 month schedule. Near half the study subjects had pre-existing anti-HEV antibodies. In this phase III trial, the vaccine was shown to be safe and had a protective efficacy of 95.5% [95% confidence interval = 66.3% to 99.4%] in an intention-to-treat analysis and of 100% [95% CI = 72.1% to 100%] in a per-protocol analysis against hepatitis E disease following the completion of immunization. In addition, unpublished follow-up data from this trial indicate an 87% protective efficacy on

intention-to-treat basis, and 93% in those who had completed the full 3-dose schedule, over a period extending up to 4 years after completion of immunization.

The existence of substantial disease burden due to hepatitis E and availability of an efficacious vaccine for its prevention have led to the idea of using the vaccine to interrupt the transmission of this virus, particularly in regions/populations in which outbreaks and sporadic cases of hepatitis E occur frequently.

The Working Group discussed the issue of hepatitis E vaccination for general populations in areas where hepatitis E is highly endemic, in view of the following:

1. The burden of hepatitis E disease is high among populations without consistent access to clean drinking water, sanitation and hygiene. These populations have frequent hepatitis E outbreaks (with genotype 1 and 2 virus), and these outbreaks are associated with significant mortality particularly in vulnerable groups like pregnant women. The disease burden is the highest among young adults.
2. The data on safety and efficacy of this vaccine are strong for healthy adults aged 16-65 years, which overlaps with the age group most affected by the disease.

**Recommendation:** The Working Group agreed that, based on the available data, routine vaccination for populations where epidemic and sporadic hepatitis E disease is common is not recommended at this time.

The reasons for the above recommendation of the Working Group are as follows:

1. Generalizability of the results of the only one available vaccine trial to other geographic regions and populations may be limited:
  - a. The only available trial was conducted in an area with very low disease incidence. In such situations, the viral inoculum may be low. By contrast, in areas with or during periods of high rate of transmission of HEV infection (e.g. during water-borne outbreaks of hepatitis E), the exposure to HEV may be very high. The efficacy of the vaccine in such situations is not known.
  - b. The phase III trial with the vaccine primarily assessed its efficacy only against genotype 4 (since >90% of infections in the placebo group were caused by genotype 4 virus), and to only a limited extent against genotype 1 disease (occasional cases in the placebo group had infection with genotype 1 HEV). Even though *in vitro* data suggest that the vaccine may be effective against genotype 1, 2 and 3 HEV infection, direct data on this aspect are lacking. By contrast, most of the cases of hepatitis E in areas with high disease endemicity are caused by genotype 1 or 2 viruses.
2. There is lack of data on protection against severe disease and death (such as is seen in pregnant women infected with HEV). The pathogenesis of such disease may be different from the usual hepatitis E.

3. It is unclear whether the use of vaccine would control fecal excretion of the virus or transmission of infection.
4. The anti-HEV antibody titers after vaccination decline with time. Thus far, the protective efficacy of the vaccine is known to last for at least 4 years. Data on long-term protection are not yet available. Lack of information on antibody level threshold for protection against HEV infection or disease means that antibody titer modelling studies cannot be used to predict the likely duration of protection following hepatitis E vaccination. Continuing follow up of participants in the phase III clinical trial should in future provide such data on the duration of protection by the vaccine.
5. Data on efficacy and safety are limited to persons in the age group of 16-65 years, and no data are available in children below 16 years of age and in adults older than 65 years of age. The vaccine is therefore difficult to incorporate into existing immunization schedules which are targeted primarily at children.
6. Data on the incidence of hepatitis E and on the number of deaths due to this disease in the general population, even in areas where hepatitis E disease is common, are quite limited. Moreover, the available data on prevalence of anti-HEV antibodies, a key input into the mathematical modelling for burden of hepatitis E disease, and on incidence and mortality of this disease have limitations related to suboptimal performance characteristics of anti-HEV assays and various types of selection biases in sample studies. These factors imply that there is an inherent uncertainty in the estimates of hepatitis E disease burden.

In addition, the group noted that (i) the existing vaccine production capacity is limited, (ii) the cost of vaccine is high, (iii) there are logistic issues related to large additional cold-chain space requirements with single-dose packaging.

#### **4. Use of hepatitis E vaccine in special population groups or situations**

##### **a. Pregnancy / Women of child-bearing age**

In areas of the world where water-borne hepatitis E is frequent, pregnant women are at a higher risk of developing clinical disease than men and non-pregnant women. This subgroup is also at a higher risk of developing severe disease, i.e. fulminant hepatic failure and death. In an outbreak in Kashmir valley in India, of the 208 pregnant women, 36 (17.3%) developed acute hepatitis and 8 (4% of all pregnant women) developed fulminant liver failure. By contrast, of the 7172 non-pregnant women and men, 178 (2.5%) developed acute hepatitis and 3 developed fulminant hepatic failure. These data translate to risk ratios of 7.0 (95% confidence intervals = 5.0 to 9.7) and 92.0 (95% confidence intervals = 24.6 to 344.1), for acute viral hepatitis and fulminant hepatic failure, respectively, among pregnant women as compared to men and non-pregnant women. In addition, hepatitis E in pregnancy is also associated with adverse fetal outcomes such as stillbirth, premature delivery, increased risk of neonatal complications such as hypoglycemia, and mother-to-infant transmission of HEV infection. However, to-date there are no population-based data on the incidence of or mortality related to hepatitis E among pregnant women or neonates in any region of the world.

The only currently licensed hepatitis E vaccine is not approved for use during pregnancy. There are no data on vaccine immunogenicity specifically in pregnant women. Though the phase III trial of this vaccine had pregnancy as an exclusion criterion, 37 pregnant women inadvertently received the vaccine, and 18 of them opted to continue the pregnancy to term (the other 19 underwent elective termination of pregnancy). None of these 18 women had a serious adverse event or poor fetal outcome. These data are too limited to infer vaccine safety during pregnancy and further data on vaccine safety during pregnancy are needed. However, since the vaccine is a recombinant subunit vaccine, its safety profile can be reasonably expected to be similar to other recombinant vaccines which have been quite safe. There are no data yet on whether hepatitis E vaccine prevents the particularly severe hepatitis E seen during pregnancy.

Use of vaccine to prevent hepatitis E in pregnancy also poses some logistic issues pertinent to vaccine schedule and when to vaccinate. There are two possible approaches to reach this group, i.e. immunizing (i) women in child-bearing age group before they become pregnant, and/or (ii) women in early pregnancy or those in mid-pregnancy with the use of an accelerated schedule. Large variations in age of child-bearing between populations and within each population make it difficult to target the hepatitis E vaccine, whose long-term efficacy is uncertain, to a particular age group. The approach of immunization in early pregnancy poses difficulties of identifying and reaching women in early phase of pregnancy, the time taken to achieve protective efficacy, and safety of vaccine when administered during pregnancy. There are no data yet on the use of accelerated schedules for hepatitis E vaccine.

**Recommendation:** In view of limited data on safety and efficacy during pregnancy, the Working Group does not currently recommend at this time the routine use of vaccine in pregnant women or in women of child-bearing age living in areas where hepatitis E disease is common.

The Working Group felt that the above recommendation should be reconsidered as soon as further data on safety and immunogenicity of the vaccine in pregnant women, or better data on population incidence of hepatitis E and mortality due to this disease become available.

#### **b. Chronic liver disease**

In several clinical case series, patients with pre-existing chronic liver disease have been shown to have an increased risk of severe disease when they develop hepatitis E virus infection.

However, exact frequency of HEV infection and disease in this subgroup of patients is not known. Thus, there are no data on the absolute or relative risk of disease or death due to HEV infection among patients with chronic liver disease.

Immunogenicity and efficacy of hepatitis E vaccine have not been studied in persons with chronic liver disease. The phase III trial of this vaccine specifically excluded patients with chronic liver disease. It did include people with chronic hepatitis B virus infection (healthy carriers), in whom the vaccine was found to be as safe and immunogenic as those without such infection; however, this group cannot be considered as having chronic liver disease. Thus, currently, no data are available on safety, immunogenicity or efficacy of this vaccine in this special group.

**Recommendation:** In view of the increased risk of severe disease associated with HEV infection in this special population group, it would be useful to take steps to prevent HEV infection in

them. However, in view of the lack of safety and immunogenicity data in this group of patients, the Working Group does not currently recommend the routine use of this vaccine in this group of patients.

The Working Group felt that the above recommendation should be reconsidered as soon as data on safety and immunogenicity of the vaccine in patients with chronic liver disease become available.

#### **c. Organ Transplant Recipients and Other Immunosuppressed Persons**

Chronic HEV infections have been recently recognized in the immunosuppressed population, particularly in recipients of solid organ transplants, in European countries and North America. In France, chronic HEV infection was identified in ~3% of solid-organ transplant recipients. These cases have been linked to infection with genotype 3 HEV, except for one recent pediatric case with genotype 4 HEV infection. It remains unclear whether HEV genotypes 1 and 2 are associated with chronicity. Chronic HEV infection may rapidly progress to hepatic fibrosis and cirrhosis. A reduction of immunosuppressive therapy leads to viral clearance in around 30% of cases. Treatment with ribavirin for 3 months is effective in most of the cases, but is contraindicated in some patient groups e.g. kidney transplant recipients.

Safety, immunogenicity and protective efficacy of the available hepatitis E vaccine in immunosuppressed people, including those who are waiting for or have received a solid- organ transplant, have not been studied. This is important since these groups may be less likely to develop specific antibodies because of the underlying disease or because they are receiving immunosuppressive drugs. In any case, if the vaccine is used for transplant recipients, the best time for its administration may be in the pre-transplant phase, before the institution of immunosuppressive drugs.

Also, in the phase III clinical trial of the hepatitis E vaccine, protective efficacy was primarily against disease related to genotype 4 (and to some extent, genotype 1) HEV infection. However, in *in vitro* experiments, the vaccine induced antibodies appeared to bind to and neutralize genotype 3 HEV.

**Recommendation:** In view of lack of data on immunogenicity and safety in this group of patients, and on protective efficacy of the vaccine against genotype 3 HEV infection, the Working Group does not currently recommend the routine use of this vaccine in persons on organ transplant waiting lists at this time.

The Working Group felt that the above recommendation should be reconsidered as soon as data on immunogenicity of the vaccine in this special group become available.

#### **d. Travellers to areas where hepatitis E disease is common**

In developed countries where water supplies are clean, hepatitis E disease is less common. In the 1990s and early 2000s, hepatitis E in these areas mainly occurred among returning travellers after visiting countries with high endemicity. The number of such travel-related cases has gradually decreased over time, even though international travel has increased. Most of these travel-associated cases have occurred among travellers to the Indian subcontinent. The clinical manifestation of disease is usually mild self-limited illness with jaundice. Most cases

were due to infection by HEV genotype 1 but recently travellers to South East Asia have returned with genotype 4 infection.

Whilst many countries do not systematically collect data on travel-related hepatitis E, enhanced surveillance data from England and Wales showed that 28% of cases with hepatitis E confirmed in 2012 were related to travel; the remaining cases were believed to be indigenous. There are no studies of seroprevalence of anti-HEV antibodies among returning travellers to the US or other countries. A study based on the NHANES survey in the US showed a slight elevation of anti-HEV seroprevalence among persons with history of travel abroad than those without such history; however, no further epidemiological information on history of travel-associated illnesses was available for the persons with history of prior travel.

The burden of hepatitis E from international travel is not substantial. Hepatitis E transmission from persons who acquire infection during international travel to family contacts has not been reported. With a recent increase in autochthonous cases with relatively different clinical presentation and severity mainly due to disease occurrence in persons with immune incompetence, travel-related hepatitis E may not be a significant enough problem to warrant targeting for vaccination. Furthermore, risk of hepatitis E infection could be reduced by educating travellers on how to prevent waterborne and foodborne infections.

Hecolin® is efficacious when provided at 0, 1, and 6 months, which is a difficult regimen for travellers who usually do not plan for travel more than 6 months in advance. Immunogenicity and protective efficacy of a shorter-duration (accelerated) schedule, or fewer doses, particularly among previously unexposed persons has not been formally studied. In the phase II and phase III trials, partial protection was observed among those persons who received two doses of the vaccine; however, the data on this aspect are not sufficiently robust.

**Recommendation:** Based on the currently-available limited epidemiologic data that show a low disease burden among travellers, the ability to prevent such infections by standard precautions, and lack of data on protection afforded by short-duration schedules of hepatitis E vaccine, the Working Group does not currently recommend the use of Hecolin® among travellers from low-endemicity areas to high-endemicity areas.

The Working Group recognizes that there may be some special situations where travellers may be (i) at a higher risk of hepatitis E virus infection, such as humanitarian relief workers travelling to areas where an outbreak of hepatitis E is on, or (ii) at a higher risk of serious disease, such as pregnancy. Under such circumstances, each person should be evaluated individually for risks and benefits.

The Working Group felt that the above recommendation should be reconsidered if and when data on immunogenicity and efficacy of shorter vaccine schedules become available.

**e. Prevention and control of outbreaks (including during humanitarian emergencies)**

Many large outbreaks have occurred in developing countries across the Indian Subcontinent, and other parts of Asia and Africa. These outbreaks are waterborne and may be associated with high attack rates. Case-fatality rate is the highest for pregnant women, but a substantial

number of deaths also occur among other persons. Water, sanitation and hygiene (WASH) interventions are the mainstay for prevention and control of hepatitis E outbreaks.

In recent years, some large outbreaks of hepatitis E have occurred in the setting of humanitarian emergencies. In outbreaks among displaced persons/refugees transmission tends to run over a long period with some outbreaks lasting longer than a year (multiple incubation periods). Most outbreaks are caused by genotype 1 HEV and some by genotype 2 HEV. Implementing outbreak control measures, including WASH interventions, in such settings is challenging. Thus, it is pertinent to consider the use of hepatitis E vaccine as a complement to the WASH activities for control of hepatitis E outbreaks, particularly in humanitarian emergencies.

There are no data on the use of hepatitis E vaccine to control hepatitis E outbreaks. The hepatitis E vaccine has, up until the review by the Working Group, only been studied in a 3-dose schedule administered over a 6-month period (0-1-6 month schedule). The implementation logistics and effectiveness of a 3-dose vaccine in an outbreak, particularly in a challenging humanitarian crisis setting, such as in camps for displaced persons, needs further investigation. However, limited data from a phase II and the phase III vaccine trial suggest that two doses of hepatitis E vaccine may provide at least partial protection against hepatitis E disease. There is no information on whether the vaccine can reduce fecal excretion of HEV by persons with clinical disease or subclinical infection, and hence reduce the transmission of HEV infection during outbreaks. Effectiveness of hepatitis E vaccine when administered after a person has been exposed to HEV remains unknown. However, during an outbreak, the vaccine could be expected to work by increasing the proportion of population that is immune to the disease (herd immunity), and thereby reducing both clinical cases as well as disease transmission.

The use of vaccine to control outbreaks of hepatitis E faces certain challenges. These include: (i) the outbreaks are often identified late; (ii) the incubation period of the disease is 2-10 weeks, hence many persons may already be infected and in the incubation period when the outbreak is identified; (iii) immunity induced by the vaccine depends on the number of doses and may take time to develop; (iv) during outbreaks, a proportion of cases occur among children (<16 years) of age who are currently not eligible to receive the available vaccine; and (v) the inoculum of HEV to which people are exposed during outbreaks may be much higher than that encountered during the usual clinical trial situations.

Some outbreaks of hepatitis E (particularly those in humanitarian emergencies and where water quality and quantity cannot be improved rapidly) have been prolonged and have lasted for several months. In such outbreaks, the continued high risk of symptomatic disease within a geographically-limited population outweighs many uncertainties associated with the decision to use hepatitis E vaccine in the general population.

The available data for protection following hepatitis E vaccine are primarily against genotype 4 virus, whereas water-borne outbreaks are caused by genotype 1 or 2 HEV.

**Recommendation:** The Working Group recommends that the use of hepatitis E vaccine during outbreaks of hepatitis E could be considered. If the vaccine is used in this situation, it would be reasonable to vaccinate a large proportion of the affected population as quickly as possible.



Though the vaccine is currently approved only for ages 16 to 65 years, the health authority in charge may consider the use of vaccine in the other age groups. When the vaccine is used in such a setting, every effort must be made to record data and to collect information on vaccine efficacy, adverse events and the possible effect of such vaccine use on the outbreak dynamics.

When use of a vaccine during an outbreak is contemplated, it must be kept in mind that the vaccine is packaged in single dose vials. In view of need for keeping the vaccine within the cold chain, careful calculation and planning are necessary for appropriate transport and storage facilities.

The Working Group felt that the above recommendation should be reconsidered as and when further data on immunogenicity and efficacy of shorter vaccine schedules, on efficacy of the vaccine against genotype 1 or 2 hepatitis E, or on safety and efficacy in children, pregnant women and elderly persons become available.

## **5. Final notes**

The Working Group recognizes that its recommendations are limited by several information gaps in the available data. These information gaps mainly relate to:

1. Information on safety and efficacy of the vaccine in specific subgroups (pregnant women, persons with chronic liver disease, immunosuppressed persons).
2. Information on safety and efficacy of the vaccine in specific age groups (children <16 years and elderly persons >65 years).
3. Epidemiology of hepatitis E, in particular the incidence and mortality of disease in the general population as well as in special population groups.
4. Efficacy of hepatitis E vaccine against disease caused by HEV belonging to genotypes 1, 2 and 3.
5. Efficacy of schedules of hepatitis E vaccine with fewer than three doses or shorter duration.
6. The duration of protection following hepatitis E vaccine and the possible need for boosters.

Thus, as and when data on some of the current information gaps become available, the recommendations for one or more of the situations discussed above will need reconsideration.

Further, the Working Group's recommendations are meant for general use of vaccine. The Group recognizes that there could be special situations where the risk of disease or that of serious disease or mortality could be particularly high, and that these may override other considerations. The Group's recommendations should not preclude the use of this vaccine in these special situations. However, in all such situations, experience with the use of vaccine, including the occurrence of any adverse events, should be documented.

# REPORT OF THE SAGE WORKING GROUP ON VACCINE HESITANCY

*01 October 2014*

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### List of Abbreviations

AFR- WHO African Region  
 AMR- WHO American Region  
 EMR- WHO Eastern Mediterranean Region  
 EUR- WHO European Region  
 GPEI- Global Polio Eradication Initiative  
 GVAP- Global Vaccine Action Plan  
 GACVS- WHO Global Advisory Committee on Vaccine Safety  
 HIC- High Income Country  
 IVIR-AC – WHO Immunization and vaccines related implementation research advisory committee  
 LIC- Low Income Country  
 LMIC- Low and Middle Income Countries  
 NVAC- National Vaccine Advisory Committee (USA)  
 MIC- Middle Income Country  
 SAGE: Strategic Advisory Group of Experts on Immunization  
 SEAR- WHO South East Asian Region  
 UNICEF- United Nations Children's Fund  
 WHO- World Health Organization

The Working Group would like to acknowledge Jörg Meerpohl (German Cochrane Center) as well as Caitlin Jarrett, Maureen O’Leary, Pauline Paterson and Rose Wilson (LSHTM) for their work on the systematic review(s). Further the Working Group would like to thank Noni MacDonald for her lead on drafting this report on behalf of the Working Group.

## Section 1: Introduction

Unlike other medicines, vaccines work at both the individual and community level. While no vaccine is 100% effective, when used broadly in communities, several vaccine preventable diseases could be eliminated and some may be eradicated. High vaccine uptake rates, specific to each vaccine preventable disease, are needed for community-level immunity to be achieved and sustained in order that disease risk can be lowered beyond what would be predicted by vaccine coverage alone. Even in countries with overall high national vaccine uptake rates, there may be clustered pockets or subgroups where the rates of uptake are lower than required for protection of the community. In the past decade, such pockets have been associated with outbreaks or resurgence of measles, mumps, *Haemophilus influenzae* b, pertussis and polio in countries where these diseases had previously been controlled.

At the November 2011 meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, SAGE noted with concern the impact of reluctance to accept immunization on the uptake of vaccines reported from both developed and developing countries. These reports led SAGE to request the establishment of a working group on vaccine hesitancy<sup>1</sup>.

### Background

The evidence demonstrating the benefits of immunization are overwhelming. It is one of the most successful and cost-effective interventions to improve health outcomes. Vaccines have saved countless lives and improved health and well-being around the globe. However, to prevent the morbidity and mortality associated with vaccine preventable diseases and their complications, and optimize control of vaccine preventable diseases in communities, high uptake rates must be achieved. In 2011, SAGE noted the growing recognition of the negative impacts of hesitancy on vaccine uptake rates and program efficiency<sup>2</sup>. Through a survey of SAGE members in 2011, communication with vaccine hesitant populations was identified as one of the new priority topics for SAGE<sup>3</sup>. If the high uptake rates needed for herd immunity are to be achieved and sustained, individual and community hesitation and reluctance to be immunized must be better understood and addressed. SAGE also observed that the problem did not appear to be restricted to one region or subset of the population. For example during the pH1N1 influenza pandemic, SAGE highlighted that while many countries in the Americas successfully deployed influenza pandemic vaccine to the general public, many had difficulty in convincing pregnant women to accept the vaccine. Even when faced with strong evidence of increased morbidity and mortality caused by influenza, many pregnant women hesitated to obtain pandemic influenza vaccination despite the recommendation by their health care provider and their country's immunization program leaders. Even improved access to receive vaccine did not reliably overcome this. Similarly, reluctance to accept measles vaccine in parts of Europe, HPV vaccine in Japan and

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<sup>1</sup> <http://www.who.int/wer/2012/wer8701.pdf>, accessed 16.09.2014

<sup>2</sup> [http://www.who.int/wer/2011/wer8601\\_02.pdf](http://www.who.int/wer/2011/wer8601_02.pdf), accessed 16.09.2014

<sup>3</sup> <http://www.who.int/wer/2011/wer8621.pdf>, accessed 16.09.2014

India, polio vaccine in parts of Nigeria and Pakistan, are just a sample of the episodes that are appearing around the world. Because the root causes of these events are complex and not always straight forward, SAGE also expressed concern that the path forward to address hesitancy was not clear.

Based upon the concerns about hesitancy and its impact on vaccine uptake rates and the performance of national immunization programs, SAGE established the SAGE Working Group on Vaccine Hesitancy in March 2012 with the following terms of reference<sup>4</sup>:

### **Terms of Reference**

- Prepare for SAGE a review and advice on how to address vaccine hesitancy and its determinants.
- Define vaccine hesitancy and its scope
- Undertake a review of vaccine hesitancy in different settings including its context-specific causes, its expression and its impact.
- Suggest one or several indicator(s) of vaccine hesitancy that could be used to monitor progress in the context of the Decade of Vaccines Global Vaccine Action Plan.
- At global, regional and national levels:
  - Perform a landscape analysis of who/what organizations are working on this issue in various settings/countries
  - Identify existing activities and strategies that have had or could have a positive impact including looking at successful strategies that have worked and are not specifically related to vaccines or even medicines;
  - Identify strategies and activities that did not work well;
  - Identify new activities and strategies that could have a positive impact;
  - Prioritize existing and new activities/strategies based on an assessment of their potential impact;
  - Outline the specific role of WHO in addressing vaccine hesitancy;
  - Identify the specific role of regional and country advisory committees.

### **The Working Group on Vaccine Hesitancy was composed of:**

- a) Juhani Eskola, National Institute for Health and Welfare, Finland (Chair of Working Group since April 2014)
- b) Xiaofeng Liang, Chair of Working Group, Chinese Center for Disease Control, China (Member of SAGE until 2014, Chair of Working Group from March 2012 to April 2014)
- c) Arthur Reingold, University of California at Berkeley, U.S.A. (Member of SAGE until 2012)
- d) Mohuya Chaudhuri, Independent Journalist and Documentary Filmmaker, India
- e) Eve Dubé, Institut National de Santé Publique du Québec, Canada

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<sup>4</sup> [http://www.who.int/immunization/sage/sage\\_wg\\_vaccine\\_hesitancy\\_apr12/en/](http://www.who.int/immunization/sage/sage_wg_vaccine_hesitancy_apr12/en/), accessed 16.09.2014

- f) Bruce Gellin, Department of Health and Human Services, U.S.A.
- g) Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa
- h) Heidi Larson, London School of Hygiene and Tropical Medicine, England
- i) Noni MacDonald, Dalhousie University, Canada
- j) Mahamane Laouli Manzo, Ministry of Health, Niger
- k) Dilian Francisca Toro Torres, Congress of the Republic of Colombia (was only able to join the working group proceedings for the first teleconference and had to withdraw for personal reason)
- l) Kinzang Tshering, Jigme Dorji Wangchuck National Referral Hospital, Bhutan
- m) Yuqing Zhou, Chinese Center for Disease Control, China

The Working Group was supported by a SAGE and UNICEF Secretariat, including participation and support from WHO's SAGE Secretariat, the WHO Global Vaccine Safety Group, the WHO Expanded Program on Immunization, the WHO Director General Central communication team, the WHO Polio Department, and WHO regional offices as well as UNICEF headquarters, UNICEF polio communications and the UNICEF AFR regional office.

## **Report Structure**

This Report deals with the deliverables established in the SAGE Terms of Reference for the Working Group. Each Section begins with the deliverables to be addressed followed by the conclusions of the Working Group and then the detailed discussion of the work done to address the deliverables. In the final Section (Section 7), the Working Group's recommendations to SAGE are presented. The Appendices to this report will be posted on the SAGE share point.

## Section 2: General Approach and Methods

The general approach of the SAGE Working Group on Vaccine Hesitancy was guided by the deliverables set out by SAGE. This was accomplished through discussion of 1) commissioned and published relevant systematic reviews of evidence on vaccine hesitancy, including published studies, grey literature, and field reports; 2) models characterizing vaccine hesitancy developed by different organizations; 3) personal observations reported from the field by different organizations and Working Group members; 4) an immunization managers' survey of vaccine hesitancy; 5) a review of systematic reviews of vaccine hesitancy intervention strategies; 6) vaccine hesitancy survey questions extracted from the published and gray literature and developed, in part, with Working Group member input; 7) pilot testing of vaccine hesitancy indicators in Joint Reporting Form (JRF) (2012, 2013) and at Inter-country Support Team South & East and Central African Regional Immunization Managers' meetings in 2013; 8) consultations to discuss hesitancy and its impact with WHO regional offices, UNICEF (HQ and regional offices), the Global Polio Eradication Initiative (GPEI), United States National Vaccine Advisory Committee (NVAC), communications and marketing experts within industry, and other working groups and advisory committees, such as the SAGE Global Vaccine Action Plan (GVAP) Working Group, the SAGE Measles and Rubella Working Group, the Global Advisory Committee on Vaccine Safety (GACVS), and the Immunization and Vaccine related Implementation Research Advisory Committee (IVIR-AC). Other organizations not involved in immunization were also consulted including programs and research groups working on related topics. Attempts were made to draw from experiences from beyond the immunization and the health fields.

The Working Group consulted on the findings and lessons learned from each of these outlined initiatives and embedded the conclusions into their deliberations and recommendations.

In developing a workable model of factors impacting on vaccine hesitancy, literature and reports from other relevant organizations including both published and unpublished findings were reviewed and discussed to inform the final Working Group Vaccine Hesitancy Matrix of Determinants (See Section 3). To ensure a comprehensive approach, the developed Matrix of determinants was reviewed against the findings of the systematic review of determinants, a 2014 review of hesitancy focused on low and middle income countries (LMIC), and the Immunization Program Managers' Survey conducted in 2013.



## Section 3: Definition of Vaccine Hesitancy, its Scope and Vaccine Hesitancy Determinants Matrix

### SAGE Deliverable: *Define vaccine hesitancy and its scope*

The Working Group reviewed vaccine hesitancy definitions and models, discussed the nuances of demand versus hesitancy and the role of communication in hesitancy, and determined that:

#### **Definition: Vaccine Hesitancy**

*Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.*

1. *The scope of vaccine hesitancy does not apply to situations where vaccine uptake is low because of poor availability e.g. lack of vaccine (stock outs), lack of offer or access to vaccines, unacceptable travel/distances to reach immunization clinics, poor vaccine program communication, etc.*
2. *In low uptake situations where lack of available services is the major factor, hesitancy can be present but is not the principle reason for unvaccinated and undervaccinated members of the community. In these settings, improving services is the priority.*
3. *As the Complacency, Convenience and Confidence (“3Cs”) model of vaccine hesitancy determinants succinctly categorized many factors it was embedded in the definition.*
4. *The more complex Working Group Vaccine Hesitancy Determinants Matrix (see below), with determinants in three main categories (contextual, individual and group and vaccine/vaccination specific influences) was more useful for guidance on development of vaccine hesitancy indicators, survey questions, diagnostic tools, and strategies for intervention, and research.*
5. *Concerns about vaccine safety may be associated with vaccine hesitancy. However, it is important not to equate vaccine hesitancy and vaccine safety. Safety is only one driver of vaccine hesitancy. Nevertheless, in situations where vaccine safety is one of the underlying causes of vaccine hesitancy, using appropriate best practices to address concerns over adverse events following immunization, can minimize the potential negative impact that may result.*
6. *Communication is a key tool for success of any immunization program but is not a specific determinant in vaccine hesitancy. However, inadequate or poor communication about vaccines (e.g., why they are recommended and their safety and effectiveness) can contribute to vaccine hesitancy.*
7. *To achieve vaccine demand as per GVAP Strategic Objective 2, not only must vaccine hesitancy be addressed, but communities must be supported in seeing value in vaccines for individuals*

*and for communities and in conveying their vaccine needs and perspectives on how vaccine programs are delivered to key decision makers. However, having communities demand current or new vaccines is a step beyond the scope of SAGE's desire to address vaccine hesitancy and increase vaccine acceptance.*

## **Working Group Considerations on Definition and Scope of Vaccine Hesitancy**

### **Section 3A: Definition**

As there was no established definition of vaccine hesitancy, with input and suggestions from the Working Group, the definition selected as the starting point for discussion in 2012 was:

*Vaccine attitudes can be seen on a continuum, ranging from total acceptance to complete refusal. Vaccine-hesitant individuals are a heterogeneous group in the middle of this continuum. Vaccine hesitant individuals may refuse some vaccines, but agree to others; delay vaccines or accept vaccines but are unsure in doing so.*<sup>5,6</sup>

While highlighting that vaccine hesitant individuals encompass a much larger group and are likely very different to those who outright refuse vaccines, the Working Group determined that this definition was not adequate as it neither defined the scope nor provided any concept of the many factors that influence hesitancy.

The Working Group determined that the definition of vaccine hesitancy and its scope must be practical (i.e. not too long and applicable to populations, subgroups and individuals). It needs to embed the assumption that vaccine(s) are available and affordable. It needs to be highlighted that equivocation on the decision on whether to accept vaccine(s) is the core issue, with many factors impinging on this complex decision i.e. context, time and specific vaccine.

### **Section 3B: Scope**

The Working Group, based upon experience in different geographic settings and the emerging use of the term in the literature, agreed upon vaccine hesitancy being *present when vaccine acceptance in a specific setting is lower than would be expected, given the availability of vaccine services*. Thus vaccine hesitancy is a behavioural phenomenon that is vaccine and context specific and measured against an expectation of reaching a specific vaccination coverage goal, given the immunization services available. The Working Group also recognized that vaccine hesitancy occurs along a continuum between full acceptance, including high demand for vaccine, and outright refusal of some or all vaccines (Figure 1), though acceptance of vaccines is the norm in the majority of populations globally.

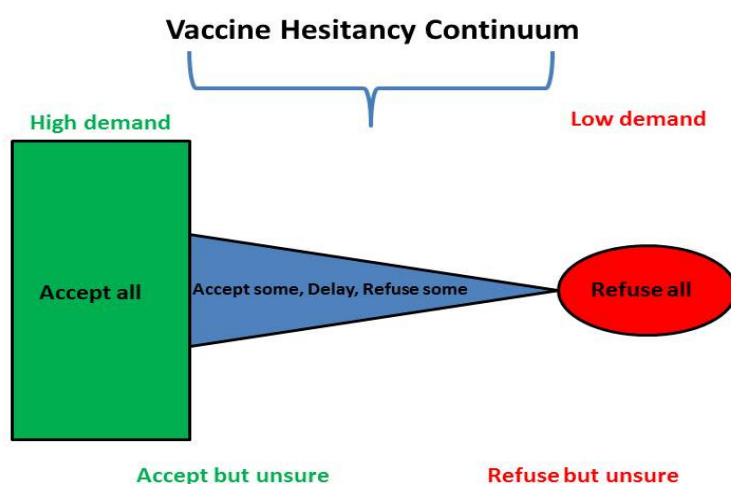
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<sup>5</sup> Opel et al Hum. Validity and reliability of a survey to identify vaccine-hesitant parents. Vaccine. 2011;7:419-25

<sup>6</sup> Benin et al. Qualitative analysis of mother's decision-making about vaccines for infants: the importance of trust. Paediatrics 2006;117:1532-41

The Working Group agreed that although vaccine hesitancy may be present in situations where vaccine uptake is low because of any one of a number of system failures (lack of vaccine, stock-outs, lack of vaccine offer, infeasible travel/ distances to reach immunization clinics, missing vaccine program communication, or curtailment of vaccine services in the presence of conflict, natural disaster or similar situations), it is not the principle driver of unvaccinated or undervaccinated members of the population. These situations where individuals or communities lack the opportunity to accept or refuse vaccine(s) fall outside the scope of the Working Group definition of vaccine hesitancy; thus vaccine coverage estimates cannot be used as a reliable indicator of vaccine hesitancy. In low uptake situations where lack of available services is the major factor, hesitancy can be present but the priority is to address they system failure that limits vaccine access and availability.

**Figure 1: The Continuum of Vaccine Hesitancy between Full Acceptance and Outright Refusal of all Vaccines**



Defining the scope of vaccine hesitancy and differentiating hesitancy from other reasons children/adults are unvaccinated or under-vaccinated is of critical importance in assessment of whether interventions to specifically address vaccine hesitancy in a population or subgroup are or are not needed in order to improve vaccine uptake rates.

### **Section 3C: Vaccine Hesitancy versus Confidence in Vaccines**

The Working Group, in its early meetings, discussed at some length whether hesitancy was the most appropriate word to describe this problem. Concerns were raised that hesitancy has a negative connotation and might send the wrong signal. The most commonly offered alternative in the literature is confidence, a more positive word. However, the Working Group noted that vaccine confidence was too narrow a term, covering only one category of factors that affect vaccine acceptance decisions (see discussion of Models and Matrix below).

### Section 3D: Vaccine Hesitancy and Vaccine Demand

In the Global Vaccine Action Plan, approved by the World Health Assembly in May 2012<sup>7</sup>, Strategic Objective 2 states that “*individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility*” [GVAP p38].

Vaccine hesitancy occurs on the continuum between high vaccine demand and complete vaccine refusal i.e. one who is not demanding available and offered vaccines, but rather is equivocal about ever receiving some or all vaccines in accordance with the recommended schedule (Figure 1). Similarly, a vaccine hesitant community is one that does not accept vaccines at the rate expected, given that services and vaccines are available i.e. lower vaccine demand than expected. At both the individual and community level, if vaccine hesitancy is present, it undermines personal and community responsibility for immunization. Given these characteristics of hesitancy, achieving the GVAP Objective 2 will require better identification, understanding and addressing of both individual and community level vaccine hesitancy, as well as the encouragement of demand.

As noted in the GVAP, achievement of Strategic Objectives 2 will be “*contingent upon all stakeholders having clearly defined and coordinated responsibilities.*” “*Individuals and communities, as recipients of immunization, should do the following: Understand the risk and benefits of vaccines and immunization, viewing this as part of being a responsible citizen. Demand safe and effective immunization programmes as a right from their leaders and government, and hold leaders and government accountable for providing them. Participate in public-health discussions and be involved in key decisions about immunization processes. Participate and contribute to the immunization delivery process and convey the needs and perspectives of their communities to the policy-makers*” [GVAP p95-96].

The working group noted that although it was crucial to address these demand-building approaches as outlined in this GVAP, tackling vaccine hesitancy needs more engagement and tailored approaches, beyond intention for demand generation (see Strategic Objective 2).

Hence, having communities and individuals demand vaccines differs from addressing vaccine hesitancy and increasing vaccine acceptance. The two examples in the box illustrate demand aspects that are beyond addressing hesitancy.

**Two examples of community vaccine demand illustrate the aspect of demand not encompassed in vaccine hesitancy:**

In Uttar Pradesh, India, the community demanded, through the courts, public access to Japanese Encephalitis vaccine to curb annual disease outbreaks associated with high morbidity and mortality (<http://www.rishabhudara.com/sc/view.php?case=100927>).

In Calgary, Canada where access to Human Papilloma Virus vaccine in Catholic schools was precluded in 2008 by a religious ban on in school delivery, citizens’ demand in 2013 successfully overturned this religious ban. [Guichon JR, Mitchell I, Buffler P, Caplan A. Preventive Medicine 2013; 57:409–413].

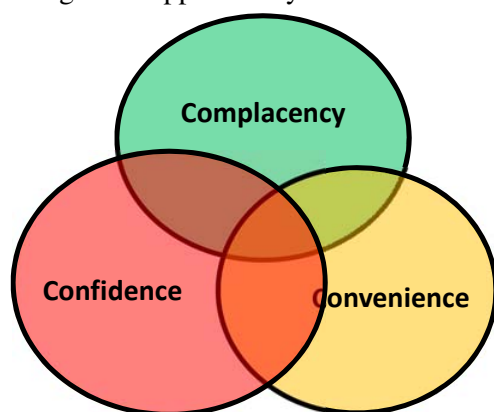
<sup>7</sup> Global Vaccine Action Plan: [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/GVAP\\_doc\\_2011\\_2020/en](http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en), accessed 16.09.2014

As hesitancy undermines demand, to achieve the in GVAP defined vaccine demand goal, countries will need to address hesitancy. High rates of hesitancy mean low demand. Thus the root causes and magnitude of vaccine hesitancy must be determined and addressed at both the individual and community level as a start to increasing demand. However, low rates of hesitancy do not mean that there will be high demand. To achieve high individual and community vaccine demand, context, community and vaccine specific strategies beyond those aimed at addressing hesitancy need to be developed.

### Section 3E: Models of Vaccine Hesitancy: Vaccine Hesitancy Determinants

At its core, vaccine hesitancy is the behaviour that results from the decision-making process and reflects a constellation of factors that may influence the decision to accept some or all vaccines in accordance with the recommended schedule. In further refining the definition of vaccine hesitancy, the Working Group assessed a number of conceptual models for understanding and grouping of vaccine hesitancy determinants (See Appendix A3.1). Models were considered and reviewed for complexity and global applicability. Their factors were considered and assessed for potential usefulness in

informing the development of vaccine hesitancy indicators, survey questions and interventions for use at the global and country levels.



**Figure 2: Confidence, Complacency, Convenience Model of Vaccine Hesitancy**

Review of these models re-enforced that vaccine hesitancy is complex and is not driven by a simple set of individual factors. Two models were determined to be most useful. The Complacency, Convenience and Confidence (“3Cs”) model was intuitive and thus the easiest to grasp (Figure 2). In addition a more comprehensive Working Group Matrix that better captured the complexity of the contextual, individual, and group and vaccine /vaccination-specific influences (Table 1) was developed.

In the “3Cs” model, **confidence** is defined as trust in 1) the effectiveness and safety of vaccines; 2) the system that delivers them, including the reliability and competence of the health services and health professionals and 3) the motivations of the policy-makers who decide on the needed vaccines.

Vaccine **complacency** exists where perceived risks of vaccine-preventable diseases are low and vaccination is not deemed a necessary preventive action. Complacency about a particular vaccine or about vaccination in general is influenced by many factors, including other life/health responsibilities that may be seen to be more important at that point in time. Immunization program success may, paradoxically, result in complacency and ultimately, hesitancy, as individuals weigh risks of vaccines against risks of diseases that are no longer common. Self-efficacy (the self-perceived or real ability of

an individual to take action to vaccinate) also influences the degree to which complacency determines hesitancy.

Vaccine **convenience** is measured by the extent to which physical availability, affordability and willingness-to-pay, geographical accessibility, ability to understand (language and health literacy) and appeal of immunization services affect uptake. The quality of the service (real and/or perceived) and the degree to which vaccination services are delivered at a time and place and in a cultural context that is convenient and comfortable also affects the decision to be vaccinated and could lead to vaccine hesitancy.

The more complex Working Group Determinants of Vaccine Hesitancy Matrix has determinants arranged in three categories: *contextual, individual and group* and *vaccine /vaccination-specific influences* (Table 1). (See Appendix A3.1 for more detailed Matrix).

**Table 1: Working Group Determinants of Vaccine Hesitancy Matrix**

<p><b><u>CONTEXTUAL INFLUENCES</u></b> Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors</p>	<ul style="list-style-type: none"> <li>a. Communication and media environment</li> <li>b. Influential leaders, immunization program gatekeepers and anti- or pro-vaccination lobbies.</li> <li>c. Historical influences</li> <li>d. Religion/culture/ gender/socio-economic</li> <li>e. Politics/policies</li> <li>f. Geographic barriers</li> <li>g. Perception of the pharmaceutical industry</li> </ul>
<p><b><u>INDIVIDUAL AND GROUP INFLUENCES</u></b> Influences arising from personal perception of the vaccine or influences of the social/peer environment</p>	<ul style="list-style-type: none"> <li>a. Personal, family and/or community members' experience with vaccination, including pain</li> <li>b. Beliefs, attitudes about health and prevention</li> <li>c. Knowledge/awareness</li> <li>d. Health system and providers-trust and personal experience.</li> <li>e. Risk/benefit (perceived, heuristic)</li> <li>f. Immunisation as a social norm vs. not needed/harmful</li> </ul>
<p><b><u>VACCINE/ VACCINATION-SPECIFIC ISSUES</u></b> Directly related to vaccine or vaccination</p>	<ul style="list-style-type: none"> <li>a. Risk/ Benefit (epidemiological and scientific evidence)</li> <li>b. Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine</li> <li>c. Mode of administration</li> <li>d. Design of vaccination program/Mode of delivery (e.g., routine program or mass vaccination campaign)</li> <li>e. Reliability and/or source of supply of vaccine and/or vaccination equipment</li> <li>f. Vaccination schedule</li> <li>g. Costs</li> <li>h. The strength of the recommendation and/or knowledge base and/or attitude of healthcare professionals</li> </ul>

The Matrix includes determinants derived from a range of sources: research studies, from experience of Working Group members in the field, from discussions with experts working in the area, from the systematic review of determinants, and the findings from the Working Group's Immunization Managers Survey (Section 4).

Vaccine hesitancy is often equated with vaccine safety concerns. Whereas the Working Group acknowledged that vaccine safety concerns can be factors underlying hesitancy, safety concerns are just one of many determinants of vaccine hesitancy. Nevertheless, specific serious adverse events following immunization (AEFI), such as a death following a vaccination, can trigger hesitancy locally and at a distance if not well managed. Health care workers (HCW) need to be well trained to address serious AEFIs, including investigation, causality assessment, and communication. When AEFIs are well handled, the risk of increasing hesitancy can be minimized. The Vaccine Safety Net facilitates the access of public health authorities, health professionals and the public to reliable information on vaccine safety via the internet<sup>8</sup>.

### Section 3F: Vaccine Hesitancy and Communication

The Working Group discussed whether poor communication was a determinant of vaccine hesitancy. The Working Group concluded that it was a tool not a determinant. While communication is not a specific factor, like confidence, complacency and convenience, when it is poor or inadequate it can negatively influence vaccine uptake and contribute to vaccine hesitancy. Poor quality services of any type, including poor communication, can undermine acceptance.

Poor, inadequate or misguided communication can be a problem in any setting. In HIC with well-resourced vaccine programs, inadequate or poor vaccine communications can increase vaccine hesitancy and outright refusal. For example, in 1999, the reason underlying the decision to minimize thimerosal as a preservative in some vaccines in the USA was poorly communicated. As a consequence, this impacted on public confidence in vaccines and the vaccine system, leading to increased vaccine hesitancy and refusal. In LMIC, scarce communication resources limit the capacity to counter negative information about vaccines and achieve community support for vaccination programs. For instance, the Independent Monitoring Board on Polio Eradication noted deep concern about *"the Global Programme's weak grip on the communications and social mobilization that could not just neutralize communities' negativity, but generate more genuine demand. Within the Programme, communications is the poor cousin of vaccine delivery, undeservedly receiving far less focus. Communications expertise is sparse throughout and needs to be strengthened"*<sup>9</sup>. The WHO African Task Force on Immunization is collaborating with UNICEF on the development of a tool to improve vaccine program communications in the region because these deficiencies, especially during crises with poor quality communication, may result in significant vaccine hesitancy. Thus, regardless of the setting and causes of vaccine hesitancy, poor communication needs to be addressed generally, in addition to developing targeted communication to address hesitancy and improve vaccine uptake.

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<sup>8</sup> Vaccine Safety Net: [http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/), accessed 16.09.2014

<sup>9</sup> WHO Weekly epidemiological record. <http://www.who.int/wer/2013/wer8828.pdf?ua=1>, accessed 16.09.2014



## Section 4: Determinants and Impact of Vaccine Hesitancy in Different Settings

**Deliverable:** *Undertake a review of vaccine hesitancy in different settings including its context-specific causes, its expression and its impact.*

The Working Groups undertook a systematic review of literature on vaccine hesitancy, an immunization managers' survey, discussed examples of hesitancy in populations where measureable improvements had occurred following targeted intervention, and reviewed presentations and materials from other WHO groups, researchers and partners (such as WHO vaccine safety, UNICEF and others). After review and discussion, the Working Group observed that:

1. *Vaccine Hesitancy is:*
  - a) *A global problem that varies between and within countries;*
  - b) *Context, time, place, program and vaccine specific;*
  - c) *Not a new problem but a problem increasingly being recognized;*
  - d) *More likely with:*
    - *new or newly introduced vaccines than with older locally well-accepted vaccines*
    - *mass campaigns than with routine immunization.*
2. *The Impact of Vaccine Hesitancy is*
  - a) *Reflected in lower than expected country vaccine uptake rates and within country subgroup uptake rates, though does not necessarily impact on the country's vaccination coverage if only in subgroups and pockets of unimmunized.*
  - b) *Difficult to assess precisely across the globe and regionally due to country variations in the definition and a lack of data.*
  - c) *A complex and multilayered, social behavioural phenomenon; however, the precise level when vaccine hesitancy has a harmful impact on individuals and communities is dependent on the background epidemiologic picture;*
3. *The Working Group Matrix of Determinants of Vaccine Hesitancy is (see Section 3).*
  - a) *Strongly supported by the systematic review and consistent with other findings.*
  - b) *Determinants may have opposite effects in different settings and regions e.g. higher education has been associated with higher and lower rates of hesitancy. Hence, one cannot assume the influence of a determinant.*
  - c) *While most research on determinants focused on social and cognitive factors, too narrow a research approach may constrict the spectrum of potential strategies conceived to address vaccine hesitancy at the individual, community and population levels.*



*d) While vaccine hesitancy studies with determinants were identified in all regions, the great majority were from the WHO EUR and AMR, with only a few from other regions. Published studies in LMIC were particularly scarce.*

*4. Like a differential diagnosis of a chief complaint in clinical medicine, understanding the Determinants of Vaccine Hesitancy and diagnosis of the root(s) of the problem in each specific setting is fundamental to the development of appropriate and targeted interventions. Moreover, because the evidence-base that supports the effectiveness of various interventions is thin, there is a need to advance this area through evaluation.*

#### **Section 4A: Systematic Review of Vaccine Hesitancy: 2007-2012**

The findings of the commissioned systematic review of the published literature can be found in Larson HJ et al.<sup>10</sup> (See Appendix 4A.1). The review team used the earlier, narrower draft Working Group definition of vaccine hesitancy and a spatial model with vaccine acceptance/hesitancy in middle and many spokes for different determinants (see Section 3, Appendix Figure 3A.2) developed by the Working Group in 2012- 2013. The search focused on routinely recommended childhood vaccines and covered the years 2007- 2012. With duplicates removed, of the slightly over 16,000 articles retrieved from the more than 30,000 articles identified, 1164 were included for full review.

Many factors were found to be associated with vaccine hesitancy, but this review reinforced that there was no simple universal or small group of determinants that influenced hesitancy in all circumstances. The independence and relative strength of each identified factor varied by context, setting and type of vaccine.

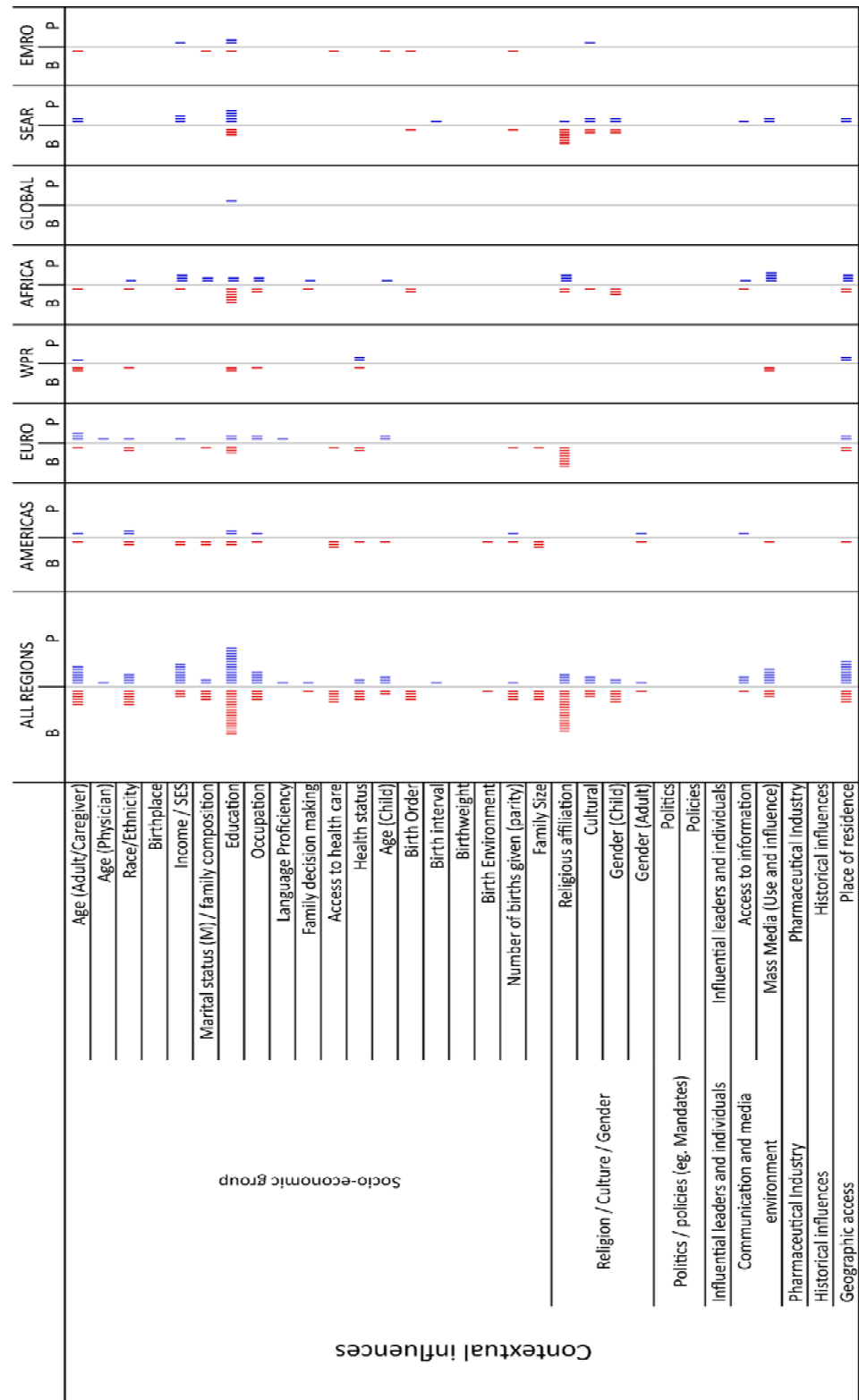
Figure 3 below illustrates barriers (B) and promoters (P) of childhood vaccination uptake, mapped onto the contextual component of the Vaccine Hesitancy Matrix of Determinants by WHO region.

Taking the example of education, the impact of a determinant may differ widely. In contrast to the social determinants of health, where a factor like education drives in one direction, better education resulting in better health, with vaccine hesitancy, higher education may be associated with either lower or higher levels of vaccine acceptance.

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<sup>10</sup> Larson HJ et al. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: A systematic review of published literature, 2007–2012. *Vaccine* 2014, 32: 2150-2159

Figure 3: Barriers (B) and promoters (P) of childhood vaccination by contextual influences



Does education predict vaccine acceptance?: Studies from China, Lebanon, Israel, Bangladesh and USA all identified higher education as a potential barrier to vaccine acceptance, whereas studies from Greece, The Netherlands, Nigeria and Pakistan identified it as a promoter of vaccine acceptance. Low education was cited as a barrier in studies from Nigeria, India, China and Kyrgyzstan, and both as a promoter and barrier to acceptance in the United States. In the DR Congo, both high and low education were barriers. Furthermore, low education had different reported effects in other countries. In India, low literacy was related to low vaccine knowledge but not anti-vaccine attitudes, while in Nigeria and Kyrgyzstan, low literacy was linked to higher likelihood of anti-vaccination attitudes.

These findings regarding education illustrate why individual determinants of vaccine hesitancy must not be viewed in isolation or always assumed to be acting in the same way in different settings. More importantly, the reviews made it clear that multiple factors shape vaccine acceptance. Therefore, in addressing vaccine hesitancy, the critical issue is to determine the principle factors that are collectively contributing as barriers to vaccine uptake and promoters of vaccine hesitancy.

Not all factors in the Working Group Matrix were identified in the systematic review. This may be a reflection of how determinants were selected for study. Most often, selection was based upon core theoretical constructs of classic social cognitive models (e.g. Health Belief Model, Theory of Planned Behaviour). These models do not adequately take into account the influence of broader contextual factors noted in the Working Group Matrix of Determinants of Vaccine Hesitancy. A gap identified was the dearth of studies on populations and subgroups. Most studies focused on addressing individuals not communities. Again, this gap may narrow conceptualization of intervention strategies. The Working Group recognized that while social cognitive determinants are important, in considering the future path of the research community, too narrow a research approach may constrict the spectrum of potential strategies conceived to address vaccine hesitancy at the individual, community and population levels.

As of July 2014, two other systematic reviews of parental vaccine-hesitancy and attitudes towards vaccines had been published<sup>11,12</sup>. The review by Williams focused primarily on HIC and the one by Yaqub on studies from countries in Europe. Of note in the latter study, a paucity of papers from Eastern European countries was observed. Neither review uncovered new determinants for inclusion in the Matrix.

From these reviews, the Working Group concluded that the determinants of vaccine hesitancy in any setting are complex. Vaccine hesitancy is global, but the precise level at which it becomes a problem – disrupting immunization programs and/or contributing to vaccine-preventable disease outbreaks – cannot be precisely determined with current measurement and diagnostic tools. As many of the studies in the systematic review were cross-sectional, extending inferences on vaccine hesitancy behaviour from one setting to another, even in same region, may be problematic and should be done cautiously. More studies, in particular qualitative studies, are needed from all regions in order to better understand

<sup>11</sup> Williams SE. What are the factors that contribute to parental vaccine-hesitancy and what can we do about it? *Hum Vaccin Immunother*. 2014 May 1;10(9)

<sup>12</sup> Yaqub O et al. Attitudes to vaccination: A critical review. *Social Science & Medicine*. 2014; 112

individual and community vaccine uptake behaviour if vaccine hesitancy drivers are to be better understood in specific contexts.

#### **Section 4B: Immunization Managers' Survey on Vaccine Hesitancy**

In April 2013, following the interim report of the Working Group, SAGE recommended that a survey of immunization managers be conducted on vaccine hesitancy in their respective countries to provide a snapshot of the breadth, perceived drivers and importance of vaccine hesitancy globally. The Working Group developed a telephone-based survey designed to qualitatively capture unanticipated responses whilst assessing known determinants of vaccine hesitancy (see Appendix A4.2 for full report).

The survey was carried out in 2013, and consisted of semi-structured interview with 14 closed and open-ended questions. In collaboration with WHO Regional Office advisors, 13 country immunization managers (IM) in the six WHO regions were interviewed – and specifically included high, middle and low-income countries to ensure a breadth of contexts for this vaccine hesitancy assessment.

The study results, not unexpectedly, revealed a wide variation in the reported basis for vaccine hesitancy across these countries. Vaccine hesitancy was identified as a concern in each of the 13 countries surveyed. The impact of vaccine hesitancy on immunization program vaccination uptake was considered as minor in 11 countries, while two noted it to be a major problem. Overall, the qualitative analysis identified religious beliefs as the most often cited determinant of hesitancy. Other commonly noted factors were lack of trust in the health system and/or in the health care provider, vaccine safety concerns, and a lack of perceived benefit of vaccines. Risk of adverse events leading to hesitancy occurred particularly in the context of mass campaigns, and was more likely with newly-introduced than established, more familiar vaccines. In eight of the 13 countries surveyed, interventions were implemented to address the vaccine hesitancy problem, although rigorous evaluation of these interventions had not been done.

The interviews did not identify any new determinants beyond those in the Working Group Matrix and reinforced that hesitancy is a global phenomenon whose impact varies across and within countries. The survey also highlighted that many of these countries lacked the capacity to identify and appropriately address vaccine hesitancy.

A limitation of the study was a lack of consistency in the definition of hesitancy across countries, posed as an open-ended question, and difficulties in quantifying the problem. Further, perceptions of the immunization managers might not represent the reality at the community level. The study also noted that poor service delivery problems can compound hesitancy. The survey also spotlighted the need for tools to diagnose local causes of vaccine hesitancy, as immunization managers are not equipped or trained to do these types of studies, and every country will have its own nuances.

In summary, vaccine hesitancy existed in all 13 countries surveyed. The causes of vaccine hesitancy were variable and context-specific, indicating the need to strengthen the capacity of countries to first identify local context-specific factors of vaccine hesitancy and then develop tailored strategies to address them.

## **Section 4C: Vaccine Hesitancy – Populations, Subgroups, Communities and Individuals**

The Working Group also examined hesitancy within populations and subgroups. Working Group members brought forward examples where subgroups in a population differed in vaccine hesitancy from the main population and then changed their vaccine hesitancy behaviour as the context changed. One example from Israel highlighted this change, where an Orthodox Jewish community began accepting polio vaccine after the wild poliovirus was found in sewage and their local rabbis, who previously had shunned vaccination, started to recommend it<sup>13</sup>. Thus a vaccine hesitant community became vaccine compliant after a contextual change. The kinetics of the H1N1 influenza pandemic in many countries offered numerous examples of variation in vaccine uptake among subgroups in the population (e.g. uptake of vaccine by pregnant women versus uptake by children). As child mortality increased, demand for and acceptance of childhood influenza immunization rose steadily. In contrast, demand for and acceptance by pregnant women in spite of reported deaths from pandemic influenza mirrored these trends in some, but not all countries.

## **Section 4D: Working Group Observations on Determinants and Impact from Materials and Presentations by Experts from GVAP, GPEI, UNICEF, IVIR-AC, NVAC, WHO Regional Offices.**

The Working Group also reviewed presentations and/ or materials from experts from GVAP, GPEI, UNICEF, IVIR-AC, NVAC, WHO Regional Offices and others to see if other determinants not in the Working Group Matrix of Determinants of Vaccine Hesitancy had been raised. No new factors were found, although several determinants not highlighted in the systematic review were noted. The reports did reinforce the findings in the review that a specific determinant may have an opposing effect in different settings, times and contexts. The GPEI highlighted that even when access to vaccination was difficult, many parents in Pakistan tried to have their children immunized. The locals' trust was higher in local health organizations (99% indicated trust) than in international health organizations (70% indicated trust), and was seen as a key factor for polio vaccine acceptance. The presentations from UNICEF, GPEI and IVIR-AC all emphasized the difficulty in accessing vaccine (i.e. convenience as determinant of vaccine hesitancy), even when vaccine outreach programs were in place. Of note, often programs may think that outreach programs address the access barrier, even when they may not (see Bulgaria Roma example page 35). Armed conflict was also noted as a contributor to hesitancy, as it did not only increase access problems, but also added political factors into the mix of determinants of vaccine hesitancy.

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<sup>13</sup> Kallner E. et al. Silent reintroduction of wild-type poliovirus to Israel, 2013 – risk communication challenges in an argumentative atmosphere. *Euro Surv* 2014; 19(7).

## Section 5: Vaccine Hesitancy Monitoring and Diagnosis

**Deliverable:** *Suggest one or several indicator(s) of vaccine hesitancy that could be used to monitor progress (in the context of the Decade of Vaccines Global vaccine Action Plan).*

The Working Group acknowledged that monitoring, diagnosing and segmenting issues that significantly contribute to vaccine hesitancy, needs to be the initial step in order to apply effective, targeted strategies. The Working Group suggests diagnostic tool to measure/diagnose vaccine hesitancy, yet these tools still need further evaluation and validation across different settings.

The Working Group reviewed and pilot tested several indicators and developed a compendium of vaccine hesitancy survey questions, as many countries had expressed need for this. The Guide to Tailoring Immunization Programmes (TIP), developed by WHO EUR, was also reviewed to assess its potential for diagnosing vaccine hesitancy factors in subpopulations.

Two indicators were developed in part to meet the requirement of the GVAP's goal of measuring and monitoring vaccine demand. The first set of indicators developed by the Vaccine Hesitancy Working Group in 2012 was reviewed by the GVAP Working Group. The provided feedback led to a revision of the indicators in 2013.

### Indicators of Vaccine Hesitancy

*Immunization programs need to regularly determine if and where pockets of under-immunized subgroups occur in the country as part of good program management practice. Then, the factors underlying this lower than expected uptake, given the vaccine services, need to be assessed.*

*a) Coverage (uptake rates) and/or immunization drop-out rates, although potentially appealing as proxy measures for hesitancy, are not valid single measures of hesitancy as they encompass non-hesitancy aspects (e.g. access, stockouts, program delivery obstacles, etc) not related to hesitancy.*

*b) Measuring demand for vaccination is problematic. There is no linear relationship between hesitancy and demand-low hesitancy does not necessarily mean communities are demanding vaccines. Addressing demand includes but goes beyond addressing hesitancy.*

*c) The GVAP working group overseeing the revision of the indicators acknowledged that the JRF could provide a practical, routine opportunity to collect information on vaccine hesitancy. WHO/UNICEF regions can decide whether they want to include one or both of the recent indicators into their regional JRF. Adequate translation into languages other than English of the questions and the term "vaccine hesitancy" needs to be ensured.*

*d) Given the limited validation of the relevance of these questions to predict and monitor vaccine hesitancy in a community, the Working Group concluded that only process indicators of vaccine*

hesitancy are feasible at this time and that routinely assessing whether measurements of vaccine hesitancy have been conducted would emphasize the current need to identify vaccine hesitancy in the community when it exists and reinforced this approach to integrate vaccine hesitancy assessments into program assessments until better tools and more resources become available.

e) As vaccine hesitancy is not static and varies by vaccine, context and time, to obtain a clear picture at the country population level may require further refinement of the indicators, building on this JRF work.

Indicators of Vaccine Hesitancy proposed for inclusion in the JRF are:

#### **Process and Etiologic Indicators (2013)**

##### **Etiologic Indicator: Reasons for vaccine hesitancy.**

Question 1:

What are the top three reasons for not accepting vaccines according to the national schedule?

Question 2:

Is this response based or supported by some type of assessment, or is it an opinion based on your knowledge and expertise?

##### **Process Indicator: % of countries that have assessed the level of hesitancy in vaccination at a national or subnational level.**

Question 1: Has there been some assessment of vaccine hesitancy or refusal among the public at national or sub-national level?

Question 2: If yes, please provide assessment title(s) and reference(s) to any publication/report.

These Indicators need to be accompanied by the vaccine hesitancy definition and a note requesting a response to Indicator 2 regardless of the response to Indicator 1.

#### **Vaccine Hesitancy Survey Questions**

Countries using selected questions from the Working Group Compendium of sample Vaccine Hesitancy Questions to measure vaccine hesitancy must bear in mind that:

1. More research is needed to develop, validate and determine the utility of questions on determinants. i.e. are these helpful or should diagnosis of causes best be done using programs such as TIP. The majority of the questions in the survey have not been validated and for those that have, only in HIC.
2. Selecting questions from the compendium supports inter- country comparison of answers.
3. Refusal of vaccination is not the same as vaccine hesitancy which lies on a continuum between acceptance and refusal.

4. *The current survey questions predominantly focus on identifying whether hesitancy is present, not on the determinants of hesitancy.*
5. *Question selection needs to fit the context.*
6. *Question sequencing matters. Leading questions may drive answers in a particular direction and make one factor appear to be more important than it might actually be.*
7. *Context also alters relevancy of specific questions and/or may influence the answers*
8. *Sample questions linked to the Working Group Determinants of Vaccine Hesitancy Matrix were developed.*
9. *Asking specific determinant questions rather than asking for hesitancy concerns must be approached with great caution, as they may trigger hesitancy issues not previously considered by survey participants e.g. bringing to their attention issues around alleged threats by MMR vaccine such as autism.*

### **Diagnosis of Determinants of Vaccine Hesitancy in Specific Subgroups.**

*The 2013 Guide to Tailoring Immunization Programmes (TIP) developed by WHO EUR, based upon evidence from behavioural economics, the medical humanities, psychology, and neuroscience, is an example of a tool that may be useful in understanding and addressing vaccine hesitancy by helping to:*

- a) Identify and prioritize vaccine hesitant populations and subgroups*
- b) Diagnose the demand and supply –side barriers to vaccination in these populations*
- c) Support design of evidence –based responses to vaccine hesitancy appropriate to the setting, context and population.*

*Of Note- TIP does not promote one or more specific intervention strategies. Rather by segmenting the population it helps to validate the diagnosis of the relevant barriers and enablers of vaccine uptake in the subgroup(s); and can guide the development of an intervention tailored to fit the findings, context and available resources for each subgroup.*

*For TIP to be a useful tool globally, the following developments are needed:*

*To apply to vaccine hesitancy:*

- 1. The 2013 TIP needs to be reshaped to better fit the varied needs and levels of expertise in the different regions.*
- 2. TIP vaccine hesitancy=related resources/ expertise/ training are needed to support implementation in WHO regions.*
- 3. Tip needs to be evaluated and assessed in a range of settings in HIC, MIC and LIC.*
- 4. A means to share TIP successes, failures and lessons learned in addressing vaccine hesitancy is needed across regions and globally.*



5. *The TIP approach adapted to address other communicable and non-communicable diseases where behavioural decisions markedly influence outcomes needs to be tested and evaluated.*
6. *For application of TIP to hesitancy and other areas where behavioural decisions are key to health outcomes, to optimize use of resources and minimize costs, pulling together core behavioural insight teams at WHO headquarters and the regional level with the required integrated knowledge and skills of sociologists, behavioural psychologists, anthropologists, experts in social marketing and communication as well as specific disease experts is needed.*

## **Section 5A: Indicators of Vaccine Hesitancy**

One of the Terms of Reference for the SAGE Working Group on Vaccine Hesitancy was “to suggest one or several indicator(s) that could be used to monitor progress on a global and on a national level in the context of the Decade of Vaccines Global Vaccine Action Plan” However, as the Working Group noted in Section 3, vaccine hesitancy and vaccine demand are not synonyms.

The Working Group on Vaccine Hesitancy, therefore focused on developing indicators for assessing vaccine hesitancy. Demand indicators might utilize similar strategies but were beyond the scope of the Vaccine Hesitancy Working Group.

Although coverage and/or immunization drop-out rates are potentially appealing as proxy measures for hesitancy, they encompass non-hesitancy aspects, such as limited access due to vaccines stockouts and other program delivery obstacles not related to hesitancy.

The WHO/UNICEF Joint Reporting Form (JRF)<sup>14</sup> is a questionnaire-based monitoring tool usually completed by national immunization managers designed to examine national immunization coverage, reported cases of vaccine-preventable diseases, immunization schedules and indicators of immunization system performances. This could provide a routine opportunity to capture hesitancy if indicators can be developed. In 2003-2006, the JRF had questions introduced about whether negative publicity concerning vaccines or immunization had been present. While 20% of member states reported the presence of negative publicity, these questions only captured one potential factor that might impact on hesitancy and demand (see Section 3).

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<sup>14</sup> [http://www.who.int/immunization/monitoring\\_surveillance/routine/reporting/reporting/en/](http://www.who.int/immunization/monitoring_surveillance/routine/reporting/reporting/en/), accessed 16.09.2014

## 2012 Trial Indicators

**Indicator 1: % of countries that have assessed (or measured) the level of confidence in vaccination at subnational level.**

Question 1:

Has there been some assessment (or measurement) of the level of confidence in vaccination at subnational level in the past?

Question 2:

If yes, please specify the type and the year the assessment has been done.

**Indicator 2: % of un- and under-vaccinated in whom lack of confidence was a factor or that influenced their decision.**

Question 1:

What is the % of un- and under-vaccinated in whom lack of confidence was a factor that influenced their decision (this applies to all vaccines)?

Question 2:

Was this % measured or estimated?

Question 3:

Any comments or specific issue?

These two indicators were pilot tested in the 2012 JRF in the Americas (PAHO) and the European (EURO) regions. In addition, the two indicators were tested within a self-administered questionnaire distributed at the Inter-country Support Team South & East and Central African Regional Immunization Managers' meetings in 2013 in the African region (AFRO). Pilot testing within these three regions ensured coverage of a broad range of high, middle and low-income countries needed to assess response, comparability and feasibility of the indicators in different settings. The response rate of 14% (13/94) was suboptimal (See Appendix 5A.1 for Report 2012 JRF Indicators). The analysis revealed that 19% of all participating countries had done an assessment of the level of confidence in their country, demonstrating that vaccine confidence was an issue in their country. Of note, lack of vaccine confidence ranged from 0% in Cuba, Dominica, Botswana and Sao Tomé & Príncipe, 1% in German and Brazil, 4% in Guatemala and Jamaica, 5% in Burundi, 8% in DR Congo, 10% in Romania, 18% in Czech Republic to 19% in Uganda. These results demonstrate that the lack of confidence can be significant problem, even in low-income settings, such as Uganda, where rather availability of services, not vaccine confidence might be presumed to be an issue.

Feedback from regions/countries revealed several concerns: a) misreporting, as current surveys did not actually measure vaccine hesitancy, b) surveys may only have been done in one part of a country not reflecting the whole, c) about a lack of a good translation for the term “vaccine hesitancy” in languages other than English and d) confusion about the definition because “access” was included. Many countries called for tools and questions to help them better assess vaccine hesitancy. Based on these concerns, the SAGE GVAP Working Group requested the Working Group to revisit the indicators during its December 2013 face-to-face meeting.

Modifications to the 2013 JRF included: refining the indicators to widen the scope of vaccine hesitancy to include not just confidence but also convenience and complacency, to link with the revised Working Group definition, and inclusion of a narrative description of Working Group definition of vaccine hesitancy in the JRF.

### **Revised JRF Vaccine Hesitancy Indicators 2013:**

#### **2013 Indicators**

##### **Indicator 1: % of countries that have assessed the level of hesitancy in vaccination at a national or subnational level.**

Question 1: Has there been some assessment of vaccine hesitancy or refusal among the public at national or sub-national level?

Question 2:

If yes, please provide assessment title(s) and reference(s) to any publication/report.

##### **Indicator 2: Reasons for vaccine hesitancy.**

Question 1:

What are the top three reasons for **not** accepting vaccines according to the national schedule in the last year?

Question 2:

Is this response based or supported by some type of assessment, or is it an opinion based on your knowledge and expertise?

The indicator questions were accompanied by a narrative on vaccine hesitancy, including the Working Group definition of vaccine hesitancy (Section 3).

The WHO EUR region volunteered again to pilot test the revised vaccine hesitancy indicators in its 2013 JRF. This was sent in January 2014 to the 53 member countries in EUR, who were asked to return the completed forms by 15 April 2014. (See Appendix 5A. for Report on 2013 Indicators)

In brief, more countries (31/45) reported on indicator 1, which is a higher response rate to the indicator than in the JRF 2012 (25/48). Within the 2013 JRF, 10 countries indicated having undertaken an

assessment. This may be due to an increased number of assessments amongst the countries in the EUR region, better understanding of the question due to the inclusion of a revised narrative and/or as a result of the inclusion of both a national and a sub-national assessment in the indicator question in comparison to only a sub-national assessment in 2012. For those countries not responding to indicator 1, it remains unclear if non-response was a proxy for no assessment, lack of understanding, or lack of willingness to answer the question.

With regard to Indicator 2, 36% (16/45) of the countries responded to the question and provided reasons for vaccine hesitancy. The response rate to this newly revised indicator was higher compared to the previous indicator: only 6% (3 out of 48) of the European countries in 2012 had provided a measured or estimated percentage of un- or under-vaccinated in whom a lack of confidence in vaccination was a factor.

The top three reasons for vaccine hesitancy, categorized by the determinants within the Working Group Matrix were 1) beliefs, attitudes, motivation about health and prevention, 2) risk/benefit of vaccines (perceived risks, experiences (heuristics)), and 3) communication and media environment. Major issues were fear of side effects of vaccination and distrust in the vaccine, lack of perceived risk of vaccine-preventable diseases and the influence anti-vaccination reports in the media.

Interestingly, 3 countries mentioned unjustified medical contraindications, medical contraindications, or the child being ill the day of the vaccination as reasons for vaccine hesitancy. The issue of false contra-indications is noted in the Working Group Determinants of Vaccine Hesitancy Matrix under on the role of the health care professional (See Section 3 Table 1 (i.e. in Appendix)).

A plausible reason for the lower response rate on Indicator 2 compared to Indicator 1 may be linked to the current structural format of the indicators. Upon analysing the data, it was found that 67% (14 out of 21) countries that answered “No” to Indicator 1 failed to continue and answer indicator 2. Meanwhile, only one of the ten countries that answered “Yes” to Indicator 1 did not complete Indicator 2. This suggests that countries may have believed that if they answered “No” to Indicator 1, they were not required to continue and complete the remaining questions of the vaccine hesitancy indicator. Further tweaking of the JRF questionnaire is suggested by the Working Group to clarify that both Indicator 1 and Indicator 2 should be completed, regardless of the response in Indicator 1.

Based upon past experiences with the JRF, a time period of approximately 3 years are required to obtain an adequate response rate with newly introduced indicators. With further familiarity and adjustment, the vaccine hesitancy indicators on the JRF may prove to be beneficial in identifying key reasons for vaccine hesitancy. The Working Group acknowledged that the quality of the JRF responses could be enhanced if these are based on national or sub-national survey evidence using questions from the same question bank (see below). Data on vaccine hesitancy collected on an annual basis, pose only a limited burden on countries, could provide information on the global prevalence and monitor potential shifts in the drivers and importance of vaccine hesitancy. Further, the indicators may be a valuable advocacy tool to raise awareness of vaccine hesitancy.

Immunizations programs need to regularly determine if and where pockets of un- or underimmunized subgroups occur in the country as part of good program management practice. This is part of good immunization program practice. To facilitate this, the Working Group, at the request of many countries has assembled a series potential survey questions (see Section 5B).

The revised indicators and the feedback from the JRF 2013 pilot test were presented to the GVAP Working Group in September 2014. Their recommendation was that WHO/UNICEF regional offices should decide whether they wanted to include one or both of the proposed indicators into their regional JRF. The annual JRF indicator 1 at this stage determines if regular assessment of vaccine hesitancy is taking place and serves as a reminder of good program practices. The data deriving from indicator 2 will allow the monitoring of major concerns of immunization managers with regard to vaccine hesitancy and their potential shift over time. Use of country vaccine hesitancy survey findings will in the future lead to improvement of the quality of Vaccine Hesitancy indicators reported on in the annual JRF.

During the meeting of WHO and UNICEF HQ and regional offices to consult on the 2014 JRF, several suggestions were made on how to improve the collection of data using the two proposed indicators. Prerequisite of including the indicators in the JRF was an adequate translation by a knowledgeable interpreter in order to ensure the comprehensibility of questions in languages other than English. Furthermore, the accompanying narrative needs to be very clear to immunization managers to not report on issues beyond vaccine hesitancy e.g. linked to lack of vaccine services or lack of vaccines. Changing the order of the indicators was suggested as this would likely increase response rate to Indicator 2. Within the most 2013 pilot test, countries might have assumed that if they hadn't conducted a measurement of vaccine hesitancy they were not required to move on to the question on the top 3 reasons for vaccine hesitancy.

## **Section 5B: Standard Survey Questions to Assess Vaccine Hesitancy and Its Determinants**

In the feedback from the regions and countries concerning the 2012 JRF Indicators and the Immunization Managers' Survey (Section 4), many countries called for a menu of survey questions to help them assess vaccine hesitancy. A compendium of universally validated survey questions is needed to identify vaccine hesitant populations at the national or subnational level across the globe. Questions are also needed to determine the most prominent factors underlying hesitancy so these can be monitored globally (See Section 3 and 4). A standardized compendium of both survey and determinant questions would further enable intra- and inter-country comparison of the prevalence of and the major determinants leading to vaccine hesitancy and support global assessment.

For **identifying vaccine hesitancy**, the Working Group developed a compendium of three different types of survey questions (see below: Table 2 (Core Closed Questions), 3 (Likert Scale Questions) and 4 (Open Ended Questions)). Some were derived from previously validated questionnaires (HIC only)<sup>15</sup>,

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<sup>15</sup> Freed GL, et al. Parental Vaccine Safety Concerns. *Pediatrics*. April 2010; 125(4):654-659

some came from experts in the field and others were newly proposed. The majority of the proposed general vaccine hesitancy survey questions are aimed at identifying vaccine-hesitant individuals not at identifying determinants of hesitancy.

**Table 2: Potential Vaccine Hesitancy Survey Questions: Version 1.0**

Potential questions to consider in assessing vaccine hesitancy at a community level		
<b>Core Vaccine Hesitancy Survey</b>		
<b>To be asked to parents/caregivers about childhood vaccinations</b>		
1. Do you believe that vaccines can protect children from serious diseases? Yes/ No		
2. Do you think that most parents like you have their children vaccinated with all the recommended vaccines? Y/N		
3. Have you ever been reluctant or hesitated to get a vaccination for your child? Y/N		
4. Have you ever refused a vaccination for your child? Y / N		
<i>a. Please indicate which one(s):</i>		
	Hesitated	Refused
Chicken pox vaccine		
<i>Haemophilus influenza b (HiB) Vaccine</i>		
Hepatitis B vaccine		
Human papilloma virus (HPV) vaccine		
Influenza vaccine		
Polio vaccine		
Measles vaccine		
Meningococcal vaccine		
Mumps vaccine		
Rubella vaccine		

“Pentavalent” or other combination infant vaccine		
Pneumococcal vaccine		
Rotavirus vaccine		
Tetanus, diphtheria pertussis vaccine		
Chicken pox vaccine		

What was/were the reason(s)? *(Use list below to code response)*

Did not think it was needed	Heard or read negative media
Did not know where to get vaccination	Had a bad experience or reaction with previous vaccination
Did not know where to get good/reliable information	Had a bad experience with previous vaccinator/health clinic
Not possible to leave other work (at home or other)	Someone else told me they/their child had a bad reaction
Did not think the vaccine was effective	Someone else told me that the vaccine was not safe
Did not think the vaccine was safe/ concerned about side effects	Fear of needles
Religious reasons	Other (explain)
Other beliefs/traditional medicine	

**5.** Has distance, timing of clinic, time needed to get to clinic or wait at clinic and/or costs in getting to clinic prevented you from getting your child immunized? Y / N  
If yes, please explain

**6.** Are there other pressures in your life that prevent you from getting your child immunized on time? Y / N  
If yes, specify

7. Are there any reasons you think children should not be vaccinated? Y / N

If yes, specify

8. Do you think that it is difficult for some ethnic or religious groups in your community / region to get vaccination for their children? Y / N

If yes, is it because

- a. they choose not to vaccinate?
- b. they do not feel welcome at the health service?
- c. health services don't reach them?

9. Have you ever received or heard negative information about vaccination? Y / N

If yes, please give an example

10. If yes, did you still take your child to get vaccinated after you heard the negative information? Y / N

11. Do leaders (religious, political, teachers, health care workers) in your community support vaccines for infants and children? Please indicate below

Religious Y / N      Political Y / N

Teachers Y / N      Health care workers Y / N

Other specify\_\_\_\_\_



**Table 3: Vaccine Hesitancy 5 point Likert scale questions**

<b>Vaccine Hesitancy 5 point Likert scale questions:</b>					
scale 1 = strongly disagree to-scale 5 = strongly agree					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
L1. Childhood vaccines important for my child's health					
L2. Childhood vaccines are effective					
L3. Having my child vaccinated is important for the health of others in my community					
L4. All childhood vaccines offered by the government program in my community are beneficial.					
L5. New vaccines carry more risks than older vaccines					
L6. The information I receive about vaccines from the vaccine program is reliable and trustworthy.					
L7. Getting vaccines is a good way to protect my child/children from disease.					
L8. Generally I do what my doctor or health care provider recommends about vaccines for my child/children.					
L9. I am concerned about serious adverse effects of vaccines.					
L10. My child/children does or do not need vaccines for diseases that are not common anymore.					

**Table 4: Vaccine Hesitancy Open Ended Survey Questions**

Vaccine Hesitancy Open Ended Survey Questions	
Name of respondent:	Reviewer:
Respondent's Age:_____	Respondent's Gender:_____
Number of children under care of the respondent:_____	
Age of the youngest child under care of the respondent: _____	
<b>Immunization status of the youngest child in the care of the respondent:</b> Fully vaccinated for age/ Partially vaccinated for age/ Unvaccinated	
<b>Question 1:</b> Dear Parent/ Guardian, what are the 3 major reasons why you should immunize your child? Reviewer, please list them below in the order of priority.	
1.	<input type="checkbox"/> Do you consider this as a priority?
2.	<input type="checkbox"/> Do you consider this as a priority?
3.	<input type="checkbox"/> Do you consider this as a priority?
<b>Question 2:</b> Dear Parent/ Guardian, Do you have any worries or concerns when you take your child for immunization? YES/NO If yes, what are they?  Reviewer, please list them below in the order of priority.	
1.	<input type="checkbox"/> Do you consider this as a priority?
2.	<input type="checkbox"/> Do you consider this as a priority?
3.	<input type="checkbox"/> Do you consider this as a priority?
<b>Question 3: (ask this question only for Parent/ Guardians who are known to have accepted immunization in the last 1 year)</b>  Dear Parent/ Guardian, in your family the decision to vaccinate your child (Name XYZ) last week/ month/ year was based on... Reviewer, please list them below in the order of priority.	
1.	<input type="checkbox"/> Do you consider this as a priority?
2.	<input type="checkbox"/> Do you consider this as a priority?
3.	<input type="checkbox"/> Do you consider this as a priority?
<b>Question 4: (ask this question only for Parent/ Guardians who are known to have refused immunization in the last 1 year)</b>  Dear Parent/ Guardian, in your family the decision NOT to vaccinate your child (Name XYZ) last week/	

month/ year was based on... Reviewer, please list them below in the order of priority.

- |    |  |
|----|--|
| 1. | <input type="checkbox"/> Do you consider this as a priority? |
| 2. | <input type="checkbox"/> Do you consider this as a priority? |
| 3. | <input type="checkbox"/> Do you consider this as a priority? |

**Question 5:**

Dear Parent/ Guardian, in your personal opinion, why do some persons refuse to vaccinate their children?  
Reviewer, please list them below in the order of priority.

- |    |  |
|----|--|
| 1. | <input type="checkbox"/> Do you consider this as a priority? |
| 2. | <input type="checkbox"/> Do you consider this as a priority? |
| 3. | <input type="checkbox"/> Do you consider this as a priority? |

**How to use (and how not to use) survey questions to assess vaccine hesitancy**

When countries select questions from these tables for general surveys to monitor hesitancy, several points must be considered 1) refusal is not the same as hesitancy i.e. counting only refusers will not capture hesitancy, 2) causes of hesitancy may be missed, as not all determinants in the Matrix of Determinants of Vaccine Hesitancy are covered by these questions (see below) 3) the overall importance of any one determinant will not necessarily be obvious from the answers, as it may simply be the current one that comes to respondent's mind 4) question sequencing matters. Leading questions may drive answers in a particular direction and make one factor seem more important. The context can also alter the relevance of specific questions and/or may influence the answers. In conclusion, when conducting vaccine hesitancy surveys, care must be taken in question selection and in interpretation of the answers.

**Selecting survey questions to assess the underlying determinants of vaccine hesitancy**

The Working Group developed examples of questions that relate to the factors in the Working Group Determinants of Vaccine Hesitancy Matrix (see Appendix 5.3). As with the above questions, these need to be used with great caution, as they may generate concerns that had not been prevalent prior to asking the question. The general open-ended questions seeking determinants noted above (Table 4) maybe a more positive approach, albeit requiring more skills as well as time to interpret the results.

Of importance, all of the survey questions, whether from the general survey or from the determinant examples, need to be pilot tested and validated in all settings and then refined.

### Section 5C: Diagnosis of Determinants of Vaccine Hesitancy in Specific Subgroups.

As reviewed in Section 4, a multitude of factors can potentially influence parents`/guardians` decision(s) to seek out/accept immunization for themselves or their child. These factors vary with the population subgroup, context, setting, time, and specific vaccine. To address vaccine hesitancy effectively, interventions must target the specific factors in the subgroup of the population that are leading to vaccine hesitancy at that time and in that context. Therefore, beyond assessing if vaccine hesitancy is present in a country, the population immunization uptake data need to be analyzed to detect subgroups with lower than expected coverage rates, given available vaccine services. These subgroups may be linked by geography, culture, socioeconomic and/or other factors. Determination of the factors leading to this hesitancy must be done with care, so that the most appropriate intervention options can be selected. Simply applying a questionnaire using items selected from the Matrix of Determinants of Vaccine Hesitancy Questions (Appendix A5.3) is not adequate and will likely not yield correct diagnosis. Outright refusers of vaccines must be differentiated from the vaccine hesitant. Effective interventions must then be tailored to address the specific factors affecting the subgroup populations` behavioural decisions. Interventions will differ by subgroup, context, setting, vaccine, time, and resources.

In 2011, because of growing concerns about vaccine hesitancy, the European Technical Advisory Group of Experts on Immunization (ETAGE) suggested that WHO EUR develop tools to help countries better address this complex problem. After extensive consultation, EUR developed an evidence- and theory- based behavioural insight framework, the Guide to Tailoring Immunization Programmes (TIP) in 2013<sup>16</sup>. Much of the underpinning of TIP flows from the PSI Delta Marketing Process 7 Steps (see Appendix A5.4 Table A5.4.1), which has proven successful in achieving behavioural change in many low income countries (e.g. in Kenya-in HIV, maternal child health and other programs<sup>17</sup>).

TIP was developed “to provide proven methods and tools that can help national immunization programs design targeted strategies that lead to increased uptake of infant and child vaccination, thereby increasing the immunization coverage rates and curbing the risks of vaccine preventable diseases in the region”.

TIP provides tools to help:

- 1) **identify** and **prioritize** vaccine hesitant populations and subgroups,
- 2) **diagnose** the demand and supply –side barriers to vaccination in these populations
- 3) **design evidence–informed responses** to vaccine hesitancy appropriate to the setting, context and hesitant population.

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<sup>16</sup> <http://www.euro.who.int/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf>, accessed 16.09.2014

<sup>17</sup> <http://www.psikenya.org/index.php?id=44>, accessed 16.09.2014

TIP is not a communication tool but rather a diagnostic guide to define and diagnose behaviourally related concerns such as vaccine hesitancy and then outline appropriate interventions, implement them, and then test and evaluate the outcomes.

In WHO EUR, TIP has now been successfully applied in Bulgaria, Sweden, and the United Kingdom to diagnose and develop targeted interventions for subgroups with lower than expected vaccine uptake. In Bulgaria, TIP diagnostics revealed that for the Roma population, continuing the default intervention to increase vaccine program information and awareness messages was not likely to improve uptake in this subgroup. Neither lack of knowledge and awareness about vaccines nor lack of confidence in the vaccines was the cause of the hesitancy. The major barrier was access to an immunization program that was welcoming to Roma, as the quality of the health worker–caregiver encounter was found to be the most significant determinant of vaccine uptake. These diagnostic findings were used to tailor and target programs designed to address the main cause of Roma vaccine hesitancy.

In Sweden, application of the TIP diagnostic tool to: a) Somali immigrants, b) anthroposophic believers and c) unregistered migrant communities helped Sweden better prioritise the immunization program needs of each community by providing better insight into their preferences and requirements<sup>18</sup>. The United Kingdom had launched a TIP project to address vaccine hesitancy in the Orthodox Jewish communities in Greater London.

Subgroup segmentation of those who are vaccine hesitant can be seen in the Bulgarian example (e.g. the late child, the mobile child, the invisible child, the wary caregiver, the poor child) and the Swedish example (e.g. group conformers, attentive delayers, convenience seekers, promoters of natural immunity). Of note, these subgroups cut across many common profiles used to describe populations, such as socioeconomic status, ethnicity, and religion. In both countries, application of TIP led to customized solutions that specifically addressed the hesitancy problem with available resources. In some instances (a combination of) policy, legal, and communications changes may be needed, once the specific hesitancy problems are identified.

The United Kingdom, Sweden and The Netherlands are tailoring the TIP framework to address intransigence among care providers in dealing with antimicrobial resistance (TAP) i.e. more prudent use of antibiotics. This highlights how the principles in TIP can be applied to other communicable and non-communicable disease areas, where behavioural change is needed to improve outcomes.

More countries in Europe have expressed interest in using TIP in 2014. The influenza team at WHO EUR has begun to adapt the same diagnostic framework for targeting health workers to drive demand for influenza vaccine (TIP-FLU). A case study is underway in Montenegro.

Beyond EUR, use of TIP is being explored in Manitoba, Canada as a means of tailoring their immunization program to increase vaccine uptake among its aboriginal population. Efforts are underway to adapt TIP for LIC settings in collaboration with partners in South Africa.

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<sup>18</sup> <http://www.fhi.no/dokumenter/0ce868ba30.pdf>, accessed 16.09.2014

A major issue constraining wider rollout of TIP is that it requires knowledgeable facilitators with sophisticated expertise. To address this gap, a TIP consultant training program was held in June 2014 and more are planned. In parallel, with financing from the US Centers for Disease Control and Prevention (CDC), a practical TIP field guide for national immunization managers is being developed as a companion to the current 2013 TIP Guide. This more user-friendly document will support the use of TIP in settings where personnel and financial resources are scarce. The 2013 TIP Guide is also being updated, with new examples included, and a more user-friendly step-by-step approach to implementation incorporated.

The Vaccine Hesitancy Working Group has closely followed the development, implementation, use and evolution of the TIP Guide and Program. The Working Group noted that TIP does not support the use of one or more specific intervention strategies, but segmentation of the population to determine the subgroup(s) at risk, the diagnosis of the relevant barriers and enablers of vaccine uptake in the subgroup(s) and development of an intervention tailored to the findings, context and available resources for each subgroup. The Working Group agreed that the principles upon which TIP is based are applicable to all WHO regions. IVIR-AC presenters from Africa, India and Pakistan highlighted the growing importance of and need for community-directed research to better understand hesitancy factors. TIP might be a valuable tool for diagnosing the determinants of vaccine hesitancy in subgroups in these settings, though this will require adaptation.

Given the demand for and demonstrated usefulness of TIP in the WHO EUR region, following the December 2013 meeting, the Working Group was tasked with developing recommendations on how TIP could be adapted for use in a more global context. The Working Group proposed that four major areas be addressed in order to move TIP to a global level:

1. Rework and simplify the document - by region or by level of income (high, middle, lower income countries) to better fit end users' needs- This is being addressed in part by the development of the more practical immunization manager field guide.
2. Develop resources /expertise/training to support implementation of TIP in WHO Regions and countries. A cadre of TIP facilitators is needed. The training program held in June 2014 by WHO EUR is a beginning step to addressing this gap.
3. Ensure each WHO region has local expertise and tool kits adapted to its region to support TIPS-facilitator training which may need to be tailored to fit high, middle and low income settings in different regions. Experience is needed to determine how training can best be adapted to local needs.
4. Develop a means of sharing the lessons learned from TIPS interventions and outcomes, both successes and failures, across regions and globally.

WHO HQ has received funding from the US CDC to expand the use of TIP globally. In collaboration with experts on TIP from WHO EUR and UNICEF, one of the first steps was to look at application of TIP in South Africa. In order to magnify the potential for success of field-testing of TIP there, links

were made to social-behavioural change programs that exist at several universities in South Africa. The pilot test of the TIP framework in South Africa in 2014 was proposed to cover two aspects:

- 1) application of the TIP framework assessing any shortcomings of the methods in this setting and
- 2) application of the tool to see if a meaningful public health impact e.g. higher vaccine acceptance, less vaccine preventable diseases.

The Working Group noted that the success of TIP underlines how application of research evidence from behavioural economics, the medical humanities, psychology, and neuroscience can help decision-makers understand vaccine acceptance decisions. These insights can better equip decision-makers and program managers in tackling vaccine hesitancy. These same principles also appear applicable in addressing communicable and non-communicable diseases in which patient behavioural choices markedly influence outcomes. Behavioural insight methods also have application in outbreak and emergency settings where a rapid and accurate understanding of the populations affected is essential to appropriate planning and response strategy.

Given this breadth of potential for benefit, the integrated knowledge and skills of sociologists, behavioural psychologists, anthropologists, experts in social marketing and communication as well as specific disease experts need to come together to be integrated into core behaviour insights groups at WHO headquarters and at the regional level. Insights can be initially applied to tackling vaccine hesitancy and driving equitable demand for vaccine(s) and then applied to other communicable and non-communicable disease areas where behavioural decisions markedly influence outcomes.

The Working Group also noted that EUR experiences in addressing vaccine hesitancy with this tool need to be evaluated through accumulation and sharing of lessons learned and development of best practices for application of TIP to different subgroups, contexts, vaccines and settings. TIP application to other areas also needs to be evaluated. The Working Group was informed that UNICEF is working with AFRO on a communication document at the request of the WHO African Task Force on Immunization (Regional TAG). Growing immunization communication strengths in AFRO, as recommended by the Independent Monitoring Board for the GPEI, will likely work synergistically with potential TIP- determined interventions.

## Section 6: Strategies to address Vaccine Hesitancy; Research gaps and Landscape Analysis

### Deliverables

- **Identify existing activities and strategies that have had or could have a positive impact including looking at successful strategies that have worked and are not specifically related to vaccines or even medicines;**
- **Identify strategies and activities that did not work well;**
- **Identify new activities and strategies that could have a positive impact;**
- **Prioritize existing and new activities/strategies based on an assessment of their potential impact;**
- **Perform a landscape analysis of who/what organizations are working on this issue in various settings/countries**
- **Outline the specific role of WHO in addressing vaccine hesitancy;**
- **Identify the specific role of regional and country advisory committees.**

To address these deliverables, the Working Group undertook a) a systematic review of strategies to address vaccine hesitancy, b) a review of published reviews on strategies for addressing vaccine hesitancy, c) a review of industry and organizational approaches to shaping behaviours using social marketing principles and further discussion of communication in relationship to social marketing, d) definition of research gaps in vaccine hesitancy and e) a landscape analysis of major actors in vaccine hesitancy:

### Strategies to address Vaccine Hesitancy

*The Working Group determined that while vaccine hesitancy is an important problem that needs to be addressed to help increase vaccine acceptance within a population, overall immunization uptake rates need to be improved using known evidence-based strategies, which may or may not also address hesitancy. The benefits of immunization can be further optimized if, concurrent with evidence-based uptake strategies, vaccine hesitancy factors are determined and specifically addressed.*

*With respect to strategies, the Working Group concluded that:*

- 1. The extensive systematic review of peer reviewed and gray literature, and the review of existing reviews did not identify strategies that specifically overcame hesitancy in any populations.*
- 2. The systematic review of both peer reviewed and gray literature, and the review of existing reviews did identify intervention strategies that improved vaccine uptake. Most studies were observational in design, yielding a low quality of evidence. Nevertheless, increases in vaccine uptake were observed.*



3. *With respect to interventions to increase vaccine uptake, no single strategy or combination of strategies has been applied in all countries (HIC, MIC, LIC) or all contexts with a positive impact. This finding reflected the diversity of drivers related to vaccine hesitancy and reinforced the importance of understanding and addressing local context-specific issues.*
4. *For maintaining and improving vaccine uptake, multi-component strategies appeared to be more effective than single component strategies.*
5. *Interventions with the largest positive effects on vaccine uptake are those that (not in order of importance): a) directly target unvaccinated or under-vaccinated populations; b) aim to increase knowledge and awareness about vaccines and vaccination which have proven to be particularly useful in practice ; c) improve convenience and access to vaccination; d) target specific populations such as the local community and HCW; e) mandate vaccinations or impose some type of sanction for non-vaccination; f) employ reminder and follow-up; and g) engage religious or other influential leaders to promote vaccination in the community.*
6. *Based upon the evidence, integrated, multi-component strategies effective for improving vaccine uptake should be adapted to the context and specific determinants, promoted and evaluated in all immunization programs. Lessons learned about impact on uptake in different settings should be shared.*
7. *With respect to increasing uptake, the paucity of published negative studies identified by the systematic review precluded identification of the strategies that do not work or might work only in a specific setting.*
8. *Using GRADE to assess the quality of the uptake interventions, the few effective vaccine uptake strategies included social mobilisation, mass media, communication tool-based training for health care worker, non-financial incentives, and reminder-recall activities. However, evidence is not available for all settings.*
9. *As neither hesitancy, nor the major factors underlying the hesitancy were assessed prior to or after the uptake intervention, the actual impact of these uptake interventions on hesitancy is unknown. However, some of these uptake interventions might have addressed hesitancy related to specific factors such as a lack of knowledge, cultural norms or complacency if these were present.*
10. *None of the effective vaccine uptake interventions were seen as innovative or promising for global application to address hesitancy in different contexts.*
11. *The early success of the Tailoring Immunization Programmes (TIP)( Section 5 ) recently developed by WHO EUR, built on social marketing principles and behavioural theories suggests that this is a potentially useful strategy to adapt and evaluate in LMIC.*
12. *Utilizing TIP, hesitancy can be addressed by identifying the target population, determining the major factors underlying their hesitancy; tailoring the intervention strategy to address these factors*

*and evaluating the outcome. Doing this concurrently with implementation of uptake intervention strategies might further increase overall vaccine uptake rates.*

*13. Based upon experience from UNICEF, integration of immunization with other health and non-health services may help address complacency and convenience vaccine hesitancy issues in some settings.*

*14. The impact of pain mitigation with immunization on vaccine hesitancy was not included in the systematic review but evidence-based guidelines for addressing pain are available.*

*15. Review of industry and other organizations' approaches to changing behaviour suggests that social marketing techniques may be useful in changing vaccine hesitancy. The WHO –EUR Tailoring Immunization Programmes to address hesitancy is based upon social marketing principles.*

*16. Communication can not only improve knowledge but also influence policy, the environment and realize behavioural changes. Communications is a key component of strategies to address vaccine hesitancy, but communication alone will not resolve every vaccine hesitancy issue. Similarly, correcting poor communication that is contributing to vaccine hesitancy will not necessarily correct vaccine hesitancy.*

*17. Ensuring education and knowledge about vaccines in younger individuals (children, adolescents, young adults) may provide a good opportunity to shape future vaccine acceptance behaviour of parents and adults and minimize the development of hesitancy although evidence of the success of such an approach is needed.*

*18. Based on evidence from the GPEI, discussion of and efforts to address vaccine hesitancy in themselves do not lead to increased vaccine hesitancy.*

*19. Further collaboration between UNICEF and WHO on addressing vaccine hesitancy would be beneficial. As was the case when vaccine safety concerns gained prominence starting in the 1980s until today, countries need to include a capacity that measures and addresses with vaccine hesitancy. WHO HQ and regional expertise to address hesitancy would be a helpful resource for countries.*

## **Vaccine Hesitancy Gaps and Needs: Research Opportunities**

*The Working Group determined that*

*1. The field is young, and as such, there are many gaps in knowledge, diagnosis of the determinants of vaccine hesitancy and effective strategies to address hesitancy in different settings. To accelerate the maturation of the field, a research community should be fostered to share ideas and best practices*

*2. Research on vaccine hesitancy and the most effective strategies for correction is needed at the national, sub-national and subgroup level in HIC, MIC as well as LIC.*

3. *Research questions are likely to evolve as new insights into the complex behavioural phenomenon of vaccine hesitancy become available*

4. *With the evolution of validated, standardized tools and methods, suggested research foci include:*

- a. Prevalence of vaccine hesitancy in different countries, settings and contexts*
- b. Assessments of determinants of vaccine hesitancy – see Appendix 5.3- in different contexts*
- c. Understanding vaccine decision-making*
- d. Designing and piloting of new strategies to address vaccine hesitancy in different contexts, settings, and vaccines including adaptation and evaluation (such as the TIP tool) and the application of individual approaches to diagnosing and responding to vaccine hesitancy to communities.*
- e. Determinants of recrudescence of vaccine hesitancy and appropriate early interventions*

## **Vaccine Hesitancy Evidence, Policy and Programs**

*The Working Group determined that*

1. *As vaccine hesitancy is a complex behavioural phenomenon, and no single best practice intervention to address hesitancy in all its contexts has been found, more nuanced, locally tailored and multi-component approaches are required.*

2. *Evidence- informed policy and programs to address hesitancy need to focus on capacity building for detection of hesitancy, diagnosis of the cause(s) in the subpopulation, then development of tailored strategy to fit, implementation and evaluation of impact on vaccine uptake and then sharing of lessons learned.*

3. *Immunization programs need to regularly determine if and where pockets of vaccine hesitancy exist in their country as part of good program management.*

4. *WHO EUR TIP offers a model for population segmentation, diagnosis of underlying causes of vaccine hesitancy in hesitant subgroups, and tailoring of interventions to address the underlying factors.*

5. *Given that immunization programs should have established close links with civil society organizations, these can be helpful in mobilizing support for immunization, reinforcing that immunizations are a social norm, raising demand for vaccines, and assisting in addressing vaccine hesitancy, depending on the underlying hesitancy factors*

## **Need for Tools and Opportunities to Share Vaccine Hesitancy Lessons Learned**

*The Working Group identified the need:*

*1. To apply the 2013 revised JRF Indicators (Section 5) to facilitate monitoring of vaccine hesitancy at country, regional and global levels; determination of similar and divergent vaccine hesitancy issues and successful interventions across regions and globally.*

*2. For validated, standardized and improved tools to*

- a. document vaccine hesitancy within a country- segmentation of the population (application of TIP modified to fit different settings (Section 5))*
- b. diagnosis factors influencing vaccine hesitancy in specific subgroups (application of TIP adapted to fit different settings (Section 5))*
- c. intervene effectively to address vaccine hesitancy and evaluate the impact of programs such as TIP in different settings, in particular in LIC*

*3. To document best evidence-based practices to diagnose and address vaccine hesitancy in different contexts.*

*4. To establish an interdisciplinary community/network of researchers, health care workers, and public health professionals to, share experience and evidence about best practices for addressing vaccine hesitancy in different settings and contexts.*

## **Landscape Analysis of organizations working on vaccine hesitancy**

*The Working Group determined that*

*1. A number of advisory committees, researchers and organizations have started to study and address the issue of vaccine hesitancy, including defining the problem, gathering information on its determinants and expressions, and suggesting potential intervention strategies to address vaccine hesitancy and mitigate its negative impacts on vaccine uptake. Multiple revisions of the landscape indicate a growth in the field, even over the last two years.*

*2. Inclusion of organizations addressing supply side criteria as well as hesitancy/demand side criteria would be useful to provide a broad oversight of the work being done. Most of the vaccine-related work indicated in the landscape analysis is on supply side criteria, rather than hesitancy /demand-side criteria.*

*3. WHO should encourage collaboration among those identified in the landscape of organisations doing work on vaccine hesitancy. Opportunities are needed for sharing of findings and lesson learned on vaccine hesitancy across and amongst these organizations and to others.*

*4. The landscape analysis of organisations working on vaccine hesitancy found few global vaccine reporting or surveillance systems currently measuring hesitancy/ demand-side indicators, such as vaccine hesitancy. This is not surprising given the acknowledgement of the newness of the issue– and its serious impacts on vaccine uptake and public health outcomes. There are a number of current*

*efforts to pilot survey approaches, as well as media and social media monitoring to detect emerging vaccine hesitancy.*

*5. The landscape of organizations could be used as a resource to facilitate collaboration among researchers and key stakeholders working on vaccine hesitancy.*

## **Section 6A: Intervention Strategies to address Vaccine Hesitancy:**

### **6A.1 Reviews of Intervention Strategies to address Vaccine Hesitancy**

#### **Requested Systematic Review**

The Working Group commissioned a systematic review of intervention strategies to address vaccine hesitancy. Appendix A6A.1 provides the Executive Summary of the commissioned review. A very brief overview of the findings follows:

The review of strategies in the published and gray literature from January 2007 to October 2013 had the following specific objectives:

- 1) Identify and describe the findings of published strategies related to vaccine hesitancy and hesitancy in the use of other health technologies (i.e. reproductive health technologies chosen).
- 2) Map all evaluated strategies to the SAGE Working Group Matrix of Determinants of Vaccine Hesitancy and identify key characteristics.
- 3) Assess relevant evaluated strategies using Grading of Recommendations Assessment, Development and Evaluation (GRADE); relevance was informed by the Population, Intervention, Comparison, outcome (PICO) questions defined a priori by the Working Group and grouped by one of four themes, including: i) Multi-component, ii) Dialogue-based, including dialogue with religious leaders, iii) Reminder/recall-based or iv) Incentive-based.
- 4) Synthesize findings in a manner that informs the design of future interventions and further research.

A major issue that emerged from this analysis was that few studies defined the degree of hesitancy in the population or determined the major factors underlying hesitancy in the study population. Only five studies used the terms ‘vaccine hesitant/hesitancy’. Most studies examined the intervention(s) impact on vaccine uptake or acceptance, not on hesitancy. These studies were retained because issues noted for study matched one or more of the determinants in the Working Group Determinants of Vaccine Hesitancy Matrix. However, the degree of hesitancy in the study population attributable to the specific determinant(s) studied is unknown. Another problem in the review was that interventions that failed in the field have received little attention in the published or grey literature; hence failure of an intervention in one population was likely to not be reported, though success would have been. Hence, the effectiveness of specific interventions in addressing different determinants of vaccine hesitancy in different contexts is unclear.

Thus, despite extensive literature searches from January 2007 to October 2013, only 14% (166/1149) of the peer-reviewed studies and 25% (15/59) of the grey literature evaluated interventions relating to

impact on vaccine uptake. The bulk of the retrieved literature originated from AMR and EUR. Across all regions and literature, the majority of interventions were multi-component in nature, followed by dialogue-based approaches (except EMR, where only multi-component interventions were found). Reminder-recall interventions featured only in higher-income regions (AMR, EUR, WPR), and incentives appeared only in AMR, AFR and SEAR.

Bearing in mind the critical caveats noted above, multi- component interventions were found to be more effective than single component interventions in increasing vaccine uptake in the populations studied. Targeting of populations was also shown to be helpful; underlining the importance of matching the intervention to the cause of poor vaccine acceptance in the population.

Utilizing the GRADE approach to assess quality yielded evidence of moderate confidence in the impact on uptake of social mobilisation, mass media, communication tool-based training for health care worker, non-financial incentives, and reminder-recall activities. However, all studies had weaknesses. Furthermore, as noted above the populations were not well-defined with respect to the presence of either hesitancy or the major determinants underlying hesitancy, making adoption of these to address hesitancy problematic. It is likely however, that some of these uptake strategies might be effective in addressing complacency and convenience hesitancy issues.

A review of successful interventions in reproductive health showed some important parallels. Specifically, dialogue-based interventions, particularly those incorporating a focus on community engagement/social mobilisation and the improvement of health care worker communication, were most effective in improving uptake. Similarly, single-component interventions did not work as well as those that were multi-component. Also, passive interventions (e.g., posters, radio announcements, websites and media releases) that did not have an additional engagement component(s) were less effective. However, as was found in the vaccine hesitancy strategy systematic review, the specific factors underlying poor reproductive health intervention uptake were not well defined in the study populations, making interpretation of effectiveness with different determinants difficult. The Working Group also noted that given that reproductive health decisions are a behavioural phenomenon like vaccine decisions, adaptation of the WHO EUR TIP to address hesitancy surrounding the acceptance of reproductive health interventions ( segmentation of the population to find the reproductive health hesitant subgroups, diagnosis of the major causes of hesitancy in these subgroups and then tailoring the intervention to address the causes) might lead to further improvements in uptake, as has been seen with vaccine hesitancy (See Section 5).

The review found evidence that mandatory immunization requirements can increase vaccine acceptance in some circumstances; however, the Working Group noted that these strategies may be seen as coercive and intrusive and can limit trust. Evidence from the United States indicates that mandating influenza vaccine for health care workers can substantially increase uptake compared to voluntary programs where education, incentives, declination were used. However, in Europe, mandatory healthcare worker immunization requirements vary widely from country to country

suggesting limited acceptance of this type of policy at this time. Mandatory immunization for school admittance might be helpful in some HIC and MIC but would add yet another barrier to access to primary education in LIC; further, mandatory immunization might trigger unintended negative consequences. Thus, mandating immunization as a strategy to address vaccine hesitancy must be approached with great care and caution. The impact of potential negative consequences (e.g. distrust in the immunization program) may outweigh potential benefits such as the increase in vaccination coverage in some settings.

Despite the large body of literature on the many determinants of vaccine hesitancy, most interventions to improve uptake were directed at individual issues such as vaccine/vaccination specific concerns, knowledge gaps, mode of delivery, and role of healthcare professionals; rather than community and subgroup wide concerns. In addition, little attention has been paid to intermediate outcomes such as changes in knowledge, social norms, attitudes and awareness in communities in response to these strategies. Such outcomes might indicate important shifts along the vaccine hesitancy continuum, either away from or towards acceptance, even if they do not necessarily lead to a change in vaccine acceptance. Appreciating where individuals and communities lie on the continuum and what defines this could offer insights to inform intervention design.

## **Review of Published Systematic Reviews**

The Working Group summarized the published reviews on strategies to increase vaccine uptake or vaccine acceptance published between January 2006 and May 2014. Eleven literature reviews or meta-analysis on strategies to increase vaccine uptake or vaccine acceptance in the public or among health care providers were included (see Appendix A6.2). Only two of these reviews directly targeted strategies addressing vaccine hesitancy (defined as voluntary refusal or delay of recommended childhood vaccines while vaccination services are available). In addition, in the United States, the Community Guide recommendations were reviewed, as these regularly include evidence-based recommendations on interventions intended to improve routine delivery of universally recommended vaccinations. The findings of the review of reviews are summarized in Tables in Appendix A6.2.

In brief, this review also found no strong evidence to recommend any specific intervention to address vaccine hesitancy or refusal. The reviewed studies included interventions of diverse content and approaches implemented in different settings and targeting various populations. The number of interventions assessed that were similar enough to allow them to be grouped together for meta-analysis was insufficient to demonstrate effectiveness using recognized validation criteria<sup>19</sup>. In addition, many of the reviewed studies were conducted in the United States with few from LMIC, further limiting global generalization. The reviewed studies that met quality criteria were mostly single-component interventions that are less challenging to evaluate than multi-component interventions, or interventions

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<sup>19</sup> [www.cochrane-handbook.org](http://www.cochrane-handbook.org), accessed 16.09.2014

aiming to change determinants that are difficult to measure (e.g. social norms). Finally, few studies included in the reviews used vaccine uptake or on-time vaccination as an outcome, and even fewer studies directly targeted vaccine hesitant patients.

While acknowledging these caveats, the findings showed that reminders and recall for patients and health care providers help improve vaccine uptake among various groups and in different settings, but there is limited evidence in support of their use to address vaccine hesitancy. There is mixed evidence on the effectiveness of face-to-face communication interventions, health care providers' training interventions, community-based interventions and interventions using mass media. While many communication tools aimed at improving health care provider discussions with vaccine-hesitant parents have been published, few have been evaluated. Whereas communication frameworks often suggest discussing vaccines in a participatory and open manner, a 2013 study by Opel, et al.<sup>20</sup> found that more directive, presumptive discussion styles by healthcare providers were more effective in improving vaccine acceptance in hesitant middle to upper class parents/caregivers studied in Seattle, USA. Interventions using mass media, including the Internet, are appealing but challenging to evaluate and not well-suited to the usual experimental designs. A recent study by Nyhan et al, 2014<sup>21</sup> showed that pro- immunization messaging has differing impacts, depending on the level of vaccine hesitancy among those targeted. Among those who are more strongly negative, and set in their views against vaccines, these messages may have a backfire effect. However, Nyhan's study also showed that pro-vaccine messages reinforce pro-vaccine attitudes. Given that the majority of parents accept vaccines, pro-vaccine messages may be needed to reinforce and support positive sentiment and help prevent emerging hesitancy from expanding.

The value of population segmentation and diagnosis of the determinants of hesitancy noted in the TIP (Section 5) approach, as well as in the Working Group Matrix of vaccine determinants, became even more evident to the Working Group following this systematic review and review of reviews. The Working Group also noted that both the systematic review and the review of reviews emphasized that vaccine hesitancy is a complex and dynamic behavioural phenomenon. Thus it is not surprising that multicomponent rather than single component strategies were found to be more successful, and that no one best strategy was found for any setting.

Future strategies need to address the complexities of vaccine hesitancy in their design and evaluation taking into account the following: 1) target sub-groups who are hesitant and understand their underlying hesitancy drivers; 2) focus on meaningful engagement (i.e. dialogue-based, social mobilisation) that supports realistic action; 3) ensure the intervention(s) address(es) the identified major hesitancy determinants, fits the context, setting and resources; and 4) evaluate the intervention outcomes on hesitancy and on vaccine acceptance and share the lessons learned.

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<sup>20</sup> Opel et al. The Architecture of Provider-Parent Vaccine Discussions at Health Supervision Visits. *Paediatrics* 2013; 132:6 1037-1046

<sup>21</sup> Nyhan et al. Effective messages in vaccine promotion: a randomized trial. *Paediatrics*. 2014 Apr;133(4):e835-42



## 6A.2 Other Strategies

### Pain Mitigation

Mitigation of immunization pain was not addressed in the reviews yet injection pain has been shown to cause distress for infants, children, parents, adults and those giving the injection. Fear of injection can lead to hesitancy. Evidence based guidelines on pain mitigation with immunization have been published<sup>22</sup>. While pharmacological prevention with topical anaesthetics is helpful, it adds expense to immunization. However, other effective strategies for amelioration of pain such as physical intervention with proper holding, needle injection techniques etc, and psychological interventions such as distraction etc, require only training and could be readily applied more widely. Early research in HIC has shown that parents are more comfortable with infant immunization when pain is controlled<sup>23</sup>, but this intervention has not been specifically tested on those in whom vaccine hesitancy is related to fear of pain.

### Intervention Strategies with TIP

The WHO EUR TIP is an approach to identify underlying vaccine hesitancy factors and tailor strategies to address hesitancy based on the context and the resources available (Section 5). Preliminary results suggest that this can be very effective in addressing hesitancy but more evaluation is needed to determine what strategies are most effective in addressing different determinant(s) of hesitancy in different settings. The approach should be adapted and evaluated in a wider range of settings including those in LIC (see Section 5)

### Strategies used in Mass Vaccination Campaigns

As noted in Section 3, mass vaccination campaigns can provoke hesitancy. While neither the systematic review of strategies nor the review of reviews identified research which explicitly looked at hesitancy in the context of mass campaigns, the Working Group did note that *successful* mass campaigns, such as for polio elimination in India (although the reaction to the mass polio campaign approach has also provoked distrust in some countries), polio virus containment in Israel in 2013, Meningococcal A campaigns in several meningitis belt countries in Africa and Meningococcal C outbreak control campaigns in HIC, had a number of common features. In each case, the vaccine preventable disease was well known and feared. Cases were well publicized. Leaders from all levels were actively involved. Communities were directly involved in helping with the campaigns and access to vaccine was made as easy as possible. Social norms of acceptance were publicized. All of these

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<sup>22</sup> Taddio A. et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline (summary). CMAJ. 2010 Dec 14;182(18):1989-95

<sup>23</sup> Taddio et al Impact of prenatal education on maternal utilization of analgesic interventions at future infant vaccinations: a cluster randomized trial. Pain 2014;155(7):1288-92

appeared to increase vaccine acceptance as although hesitancy was not measured, their impact on it is unknown. Of note, these strategies fit with social marketing concepts discussed below. More evaluation of successful mass campaigns is needed to determine if there are particular hesitancy factors that are more common in mass campaigns in particular settings and what strategies are most effective in addressing these.

### **6A.3 Strategies to Address Vaccine Hesitancy: Industry and Organizational Approaches to Shaping Behaviour: Social Marketing and Communication**

Beyond the systematic review and review of reviews of strategies, the Working Group explored private-sector approaches to shaping behaviour, as well as strategies used by other organizations to change behaviour. The Working Group heard from the International Food and Beverage Alliance (IFBA) about marketing strategies used by that industry. The IFBA was established in 2008 when the major food and non-alcoholic beverage manufacturers committed to supporting WHO's 2004 Global Strategy on Diet, Physical Activity and Health. The IFBA representatives noted the sophistication, from a marketing perspective, of the anti-vaccination movement (e.g. branding, focusing on emotions - fear of vaccines - rather than facts). Key industry messages to the Working Group included the following (points particularly relevant to vaccine hesitancy are in *italics*):

- *All that really matters is the power of the story.*
- *Consumers care about benefits, not supporting facts.*
- *Brand = product + compelling story.*
- *Reason leads to conclusions, while emotion leads to action (i.e. change comes from feelings, not facts).*
- *It is important to win the hearts, minds, and now, voice. Due to social media, consumers have a mouth piece and a large portion of media consumption is media generated by other consumers.*
- *The rise of social media has benefits and risks. You can share information on a massive scale at zero cost, but there is less control.*
- *Consumers believe more in messages from other consumers than from big institutions.*
- *It is important to find the intersection of brand topics (what the brand wants to talk about) and audience interests (what existing and desired audiences care about).*
- *Consumer's rationale for decisions may not reflect the true motivation (e.g. give fact-based reasons, but emotional reasons may have in fact driven the behavior).*
- *It is impossible to please all consumers, and some will not like you.*
- *One big idea needs to drive the entire communications strategy. Only one or two messages can be communicated – the rest must be sacrificed.*
- *Communication is increasingly about dialogue back and forth in the context of social media.*
- A communication brief includes: competitive content landscape, target consumer, brand opportunity, communication task, core insight, core essence, functional benefit, emotional benefit, meaningful product truth, brand personality, obtainable brand proposition, key performance indicators. *Effective communication strategies are not simple.*

Some of the messages that particularly resonated with the Working Group included focusing on the benefits of immunization and drawing on the emotional values around child health. Trying to focus on one or two key messages is challenging for a technical organization like WHO and/or country immunization programs, but it is important that pro-vaccine initiatives start driving the conversation, as conversation and dialogue are the new frontier of communication. The Working Group concluded that positive messaging (proactive) was the preferred approach, as opposed to combative messaging (reactive), a currently common strategy. World Immunization Week, in the scope of WHO, is an opportunity to build positive public dialogue around.

Areas of product marketing that are more challenging to apply to vaccination include a) the cost of large marketing campaigns, b) a high proportion of people may have to accept the message for population benefit (herd immunity), c) using the social media approach in areas where not everyone has access, d) the influence of health care workers on vaccine decision making is large, and e) the benefit from vaccines lies in the prevention of a bad event as opposed to a good event happening. In addition, because vaccination programs are about health rather than profit, there are ethical issues such as beneficence and justice. Rather than product competitors, vaccination programs are struggling with the anti-vaccine movement, political groups like the Taliban, and social/cultural norms within certain communities. Furthermore, if lack of trust underlies vaccine hesitancy, it may be vaccine-related or broader distrust in health providers, health system or government and/or politics. Given that trust is so important, immunization communication campaigns done by or in collaboration with a company, a distrusted government, or with substantial finances from industry may cause more mistrust. Community engagement and social mobilization are important components for garnering trust. Where/who the messages come from is important when trust is a driver of hesitancy. As the role of social media in vaccine decision-making is poorly understood, the content of social media needs to be better monitored with respect to vaccine attitudes and the influence of social networks, both for adults and children. Social media interventions need to be embarked on with some caution because of these complexities. Mass communication campaigns may be more useful building or maintaining the pro-vaccination social norms (see Nyhan et al discussed above), while targeted communication interventions might be more effective in addressing some aspects of vaccine hesitancy (segmentation).

Discussion also focused on the role of childhood beliefs about vaccination. Historically, children have not been systematically educated in schools about vaccines, resulting in some in the adult population (i.e. parents and adults) who do not appreciate their benefits to health and societal value for their children and for themselves. While opportunities to learn about vaccines outside of schools exist (e.g. from media, pamphlets, from health care professionals) these routes may miss many in the population. In contrast, older generations understood the value of vaccines because they personally experienced and/or saw the disease impact as children and therefore as adults did not need to be taught about this in school. Now most vaccine preventable diseases have disappeared as a result of high vaccine uptake negating the personal experience route for education. Ensuring education and knowledge about vaccines in younger individuals (children, adolescents, young adults) possibly through school based programs may be a good opportunity to shape future vaccine acceptance behaviour of parents and

adults and minimize the potential for development of hesitancy although more evidence of this is needed possibly from areas like environmental activism, tobacco, exercise behaviour change initiatives. Many children today are highly engaged in social media and peer-group provision of information is very influential, so ensuring education and knowledge about vaccines in younger individuals may be a good opportunity to further shape future vaccine beliefs and behaviours.

The Working Group also reviewed social marketing strategies of several organizations that have successfully translated profit-driven marketing approaches into positive public health impact e.g. marketing of reproductive health services, bed nets, oral rehydration solution, and circumcision. Many of the principles used by these organizations underpin the WHO EUR 2013 TIP discussed in Section 5 which has shown success in addressing hesitancy in different settings in that region. The UNICEF strategies used in the GPEI, such as programs to reach the hard to reach to change behaviours were also examined and need to be considered more closely to determine how they might be applied to other immunization issues beyond polio. UNICEF and others have found that integration of health prevention and intervention services with other needed and desired health and non-health related initiatives both for individuals and for communities has met with good success in some LIC settings. At the ground level, front line health workers, even with limited training, can be taught opportunistically to include immunization in a variety of health and non-health services. This approach may help address some hesitancy factors. Adaption into HMIC settings needs to be explored.

The Working Group further discussed broader communication and social mobilization strategies in terms of their potential application in addressing vaccine hesitancy. The point was strongly made, and reinforced by regional WHO offices, that many countries lack robust immunization communications strategies, and even fewer have specific strategies in place to address vaccine hesitancy. The platforms for messages need to be considered in terms of who is being targeted by media campaigns, insertion in soap operas, worksites etc. But both the messaging and the tools must be based on best current practise and the impact measured in terms of reach and impact on vaccine knowledge and vaccine uptake behaviours. The study of Nyhan et al., referred to earlier, suggests messages tailoring to fit the target audiences is key and reinforced the need to evaluate such strategies to ensure that they have the intended effect and impact. More resources need to be invested in vaccine communication. The Working Group concluded that immunization program every country should have the capacity and financial resources to deal with vaccine risk communication especially in light of the growing number of new vaccines and combinations of vaccines becoming available. Given that many countries have limited resources and capacity to expand existing efforts to monitor emerging hesitancy and develop appropriate strategies, support from regional as well as international partners is needed. For program efficiency, integrating these communication activities with other health promotion areas (e.g. immunization and childcare) may be desirable.

The Working Group reviewed the current communication focus of a) WHO and UNICEF on vaccine hesitancy; b) WHO on safety activities, such as the vaccine safety e-learning module and vaccine safety communications and c) UNICEF on Communications for Development (C4D). The Working Group noted that further collaboration between UNICEF and WHO on vaccine hesitancy interventions and on

communications is needed. The Working Group emphasized that dealing with vaccine hesitancy requires more than communications, and may require legislative, policy, programmatic and educational interventions. As was the case when vaccine safety gained prominence in the 1980s, countries need to build their capacity to monitor and address vaccine hesitancy in a timely manner. The Working Group concluded that every WHO regional office should have a staff member with the relevant expertise and experience needed to diagnose and address vaccine hesitancy to support countries in the region.

One concern raised by some members of the immunization community is the worry that public discussion of hesitancy "legitimizes" it and will make the situation worse i.e. a self-fulfilling prophecy. In addressing this concern, the Working Group noted the importance of reinforcing that immunization is the social norm and also reviewed data from UNICEF and the GPEI on community and individual concerns raised about polio immunization in Nigeria and India. Noteworthy findings were that only 1.2% of children in the polio endemic countries were not vaccinated due to refusal, and the refusal rates were highest where insecurity and social strife were highest. Many of the unvaccinated were children who had been missed i.e. not at home when called rather than having refused the vaccine (although in some settings this was interpreted as a "silent refusal". When organized resistance to polio immunization was present, it was typically based on political opposition to the government or an outside group seen to be supporting immunization and the resistance usually had a dynamic leader at the centre of the movement. Grievances were often linked to lack of other services and amenities (i.e. immunization provided a bargaining chip to leverage access to other services or demanding political actions of government or international players such as "stopping the drones"). Addressing vaccine hesitancy, especially through building the trust of the local leaders can lead to increases in vaccine acceptance in communities and prevent vaccine hesitancy. Thus, the evidence from GPEI does not support the hypothesis that discussing/addressing hesitancy makes the situation worse. Instead, determining the specific factors underlying hesitancy in a subgroup and addressing these factors specifically is key and can help mitigate hesitancy.

## **Section 6B: Vaccine Hesitancy Gaps and Needs: Research Opportunities**

The Working Group noted the complexity of vaccine hesitancy and the many gaps in current knowledge and best practices. Given that hesitancy is context, time, place and vaccine specific, there is need for research in HIC, MIC and LIC in all regions to understand the scope, scale and reasons underlying vaccine hesitancy to inform appropriate responses.

One of the major problems identified in the systematic review of intervention strategies (See Section 6A.1) was the lack of data on vaccine hesitancy levels in the populations where the interventions were tested. A second challenge was the lack of validated and standardized tools to assess and measure vaccine hesitancy rates and underlying hesitancy determinants across settings and between groups, and monitoring trends over time. The survey instruments developed and validated in the United States (See Section 5) but may not be applicable in other HIC or in MIC or LIC. A list of general hesitancy survey questions has been developed by the Working Group (See Section 5) these need to be validated across HMLIC as well as tested in different health care systems, socio-cultural contexts, and vaccine programs, and at the national, sub-national and in some instances the local subgroup level. Special attention also

needs to be paid to differences and similarities between routine delivery of immunization programs and mass campaigns in different settings and contexts.

A third challenge concerns interventions. As noted in the systematic review and review of reviews, most studies did not define hesitancy in the study population and only measured change in vaccine uptake, without determining if the intervention changed hesitancy. Given the paucity of information, if strategies to address vaccine hesitancy are implemented, not only must the population be fully described, but there also must be rigorous evaluation of the impact of the intervention(s) and its (their) components on vaccine hesitancy as well as on vaccine acceptance.

Based upon these three gaps, the following research priorities areas are suggested:

### **1. Prevalence of vaccine hesitancy: some examples of proposed research questions**

- To what extent does vaccine hesitancy exist among vaccinated individuals? What are the most effective ways to identify these vaccine-hesitant individuals? What are their needs?
- In settings where vaccine and vaccination services are otherwise available, at what threshold is “vaccine demand” low enough to suggest that vaccine hesitancy is a problem in a population or sub-group?
- How does vaccine hesitancy among health care professionals impact vaccine acceptance in their patients? What is the level of vaccine hesitancy among health care professionals? What are the most effective ways to assess vaccine hesitancy among health care professionals who are involved in vaccine delivery?
- What is the impact of vaccine hesitancy on vaccine uptake? What is the level of hesitancy that could lead to significant vaccine delays or refusal?
- What is the best proxy marker of vaccine hesitancy in the population? In a subgroup?
- Given that vaccine hesitancy varies across time, place, program (routine vs. mass campaign) and vaccine and is not uniform across a population or subgroup, how best can vaccine hesitancy be quantified and described in a country?

These questions should be answered in a consensus-building approach between researchers, public health and medical/health communities using a common understanding of vaccine hesitancy and its scope (See Section 3).

### **2. Determinants of vaccine hesitancy: some examples of proposed research questions**

- What are the causes of vaccine hesitancy at the individual level (convenience? complacency? confidence?) in different contexts and settings in HIC, MIC and LIC?
  - When and how are parental beliefs and attitudes toward vaccines formed?
  - What is the impact of interactions with health care providers on vaccine hesitancy? Does it differ by the type of health care professional (e.g. physicians, nurses, complementary

- or alternative medicine practitioners, traditional health providers with limited to no professional training) and/or by their work context?
  - What are the main drivers of vaccine hesitancy among health care workers and do these drivers differ from those in the communities they serve?
- To what extent does vaccine hesitancy result from broader socio-cultural and structural influences?
  - To what extent does vaccine hesitancy result from the way that vaccination services are delivered (e.g. mass vaccination campaigns vs. routine programs)?
  - To what extent does vaccine hesitancy result from negative influences of communication and the media environment (e.g. anti-vaccination messaging and the Internet)?
  - To what extent does vaccine hesitancy result from the influence of social networks?
  - To what extent does vaccine hesitancy result from religious beliefs?
  - Does early (school age) education about vaccines change hesitancy perceptions with age? Does this change hesitancy among parents i.e. perhaps learn from their children?

In addition to measuring the prevalence of vaccine hesitancy at the national / sub-national level, more in-depth research should be undertaken to gain a better understanding of the context-specific underlying causes of hesitancy. As shown by the Working Group Determinants of Vaccine Hesitancy Matrix (See Section 3), there are many potential influences on vaccine hesitancy that need to be assessed. In addition to identifying determinants of vaccine hesitancy among sub-groups or populations, it is important to understand *how* and *why* these factors link to vaccine hesitancy.

### **3. Strategies to address vaccine hesitancy: some examples of proposed research questions**

- What is the impact of strategies on vaccine hesitancy using social networks (e.g. peer-to-peer communication stressing fully vaccinated community, use of social media by HCW or vaccine “champion” parents to talk with vaccine-hesitant parents)?
- The emergence of Web 2.0 means that concerns about vaccination information online must expand beyond simply the possibility that people might access information of varying quality. How do people use the current Web? How does such usage influence decision-making processes? What are the implications for communication strategies about vaccination?
- The use of religious and local leaders and prominent citizens in interventions to increase vaccine uptake or reduce vaccine refusal is often recommended, especially in LMIC. What are the best practices? Might there be unintended consequences of such approaches?
- How can communities best be mobilized in support of vaccination i.e. set social norms as pro-vaccination?
- Many communication tools are available for health care providers to discuss with vaccine-hesitant patients. How effective are these and in what settings? What are the best ways to improve communications with patients in HIC, MIC, and LIC?

- How best can a population be segmented into those who are vaccine hesitant and those who are not? How can the determinants be most efficiently diagnosed in order to apply the most appropriate interventions to the designated subgroup? i.e. optimization of TIP
- What communication and social change strategies that have been shown to be effective in changing behaviour in other settings work for vaccine hesitancy?

As vaccine hesitancy is context-, time-, place- and vaccine-specific, research needs to be expanded to capture factors not only at the individual level but also at the community level, the contextual level (politics and policies, communication and media, social norms, influential leaders, etc.) and the organizational level (vaccine and vaccination specifics issues, mode of delivery, etc.) Furthermore, as immunization program managers play a key role in driving vaccine-related policies and activities, their and their staffs' capacities to assess and address vaccine hesitancy in the populations they serve need to be improved. WHO and UNICEF regional offices need a designated vaccine hesitancy person/program with the appropriate skills, expertise and knowledge to address hesitancy. Cross-linkages between programs should be strengthened as vaccine hesitancy is an over arching concept which spans across various immunization-related fields. An integrated approach is needed to ensure consideration of vaccine hesitancy within different work streams. WHO should support development and validation of tools to support immunization program managers in identifying the causes of vaccine hesitancy, in measuring and monitoring vaccine hesitancy, and in responding effectively to the diagnosed drivers of hesitancy in the populations and subpopulations they serve.

In summary, vaccine hesitancy research is needed in all WHO regions in three areas- 1) prevalence of vaccine hesitancy, 2) determinants of hesitancy and 3) interventions to address vaccine hesitancy in HIC, MIC and LIC, as well as within sub groups. Research questions are likely to evolve as new insights into the complex phenomenon of vaccine hesitancy become available.

## Section 6C: Vaccine Hesitancy Evidence, Policy, and Programs

While the need for evidence-informed guidance on policies that have an impact on health system performance is widely accepted<sup>24</sup>, moving evidence into policy and program changes can be challenging. Several articles in 2012<sup>24,25,26</sup> provide models for moving knowledge into policy, programs and practice change in LMIC. The process works relatively well for knowledge translation when evidence is straight forward, the conclusions clear, and the problem well-defined and linear, such as with a drug treatment for a specific disease. However, the more complex the problem the less easy it is to conduct a quality systematic review and use GRADE to assess the quality of the retrieved evidence as was shown in the systematic review of intervention strategies, where comparable studies were few. Furthermore, moving research into practice, even with systematic review of the evidence can be fraught with difficulty. For example, despite overwhelming evidence from systematic reviews, evidence-based

<sup>24</sup> Bosch-Capblanch et al. Guidance for Evidence-Informed Policies about Health Systems: Rationale for and Challenges of Guidance Development Plos Medicine 2012;9(3): e1001185

<sup>25</sup> Lavis et al. Guidance for evidence-informed policies about health systems: linking guidance development to policy development. PloS Med. 2012;9(3):e1001186

<sup>26</sup> Lewin et al. Guidance for evidence-informed policies about health systems: assessing how much confidence to place in the research evidence. Plos Medicine 2012;9: e1001187



guidelines, education programs and public engagement, there are still many patients with undiagnosed and/or mistreated or undertreated hypertension in HIC.

Vaccine hesitancy is a complex behavioural phenomenon, not a “simple” problem, and the evidence does not lead to a single best practice intervention to address hesitancy in all contexts. At this point, the TIP model appears to have promise in guiding the tailoring of interventions to address underlying hesitancy determinants. In general, there is need to focus on capacity building for detection of hesitancy, diagnosis of the cause(s) in the subpopulation, development of tailored strategies, and implementation and evaluation of the impact on vaccine uptake, followed by sharing of lessons learned.

Regional Technical Immunization Advisory Groups (RTAG) as well as National Immunization Technical Advisory Committees (NITAG) need to assess whether issues of vaccine hesitancy are present in their region and country and how these may impact on policy recommendations. The Working Group did not consider a prescriptive approach on the role of either regional or country advisory committees as beneficial given the variations across regions and countries.

#### **Section 6D: Roles and Need for Tools and Opportunities to Share Vaccine Hesitancy Experience and Knowledge**

The Working Group has suggested roles for WHO, partners and member states in addressing vaccine hesitancy in Section 8 – Recommendations.

While vaccine hesitancy has existed ever since vaccines and vaccination programs began, recent acknowledgement that it can influence the impact of vaccination programs has highlighted the need to understand and address it more systematically. Vaccine hesitancy is a complex behavioural phenomenon.

The Working Group identified the need to use the 2013 revised JRF Indicators (Section 5) to facilitate monitoring of vaccine hesitancy at the country, regional and global levels; determination of similar and divergent vaccine hesitancy issues and intervention successes across regions and globally. There is also a need for validated tools to document vaccine hesitancy within a country- segmentation of the population (e.g application of TIP modified to fit different settings suggested (Section 5)); to diagnose factors influencing vaccine hesitancy in specific subgroups and then to intervene effectively to address vaccine hesitancy and evaluate the impact of approaches in different settings. Best evidence-based practices to diagnosis and address vaccine hesitancy in different contexts need to be documented and lessons learned shared. Currently, beyond publication in academic journals, there are no regular opportunities and systems for sharing lessons learned about vaccine hesitancy in different settings.

#### **Section 6E: Vaccine Hesitancy Landscape Analysis- List of key players working on the issue of Vaccine Hesitancy**

Within the Terms of Reference for the SAGE Working Group on Vaccine Hesitancy<sup>4</sup>, one deliverable was to perform a landscape analysis of who/ what organizations are working on vaccine hesitancy in various settings/countries.

The working group developed the following objectives for conducting the landscape of analysis:

- a) Identify organizations working on the issue of vaccine hesitancy in various settings/countries.
- b) Identify those working on the issue of vaccine hesitancy to identify potential partners, donors and collaborators in the field.
- c) Identify the regions where work is being done on vaccine hesitancy and what kind of work is being done in each area. Have those identified state what work their organization is doing to address vaccine hesitancy.

The landscape analysis of organisations working on vaccine hesitancy (Appendix A6C.1) attempted to take a relatively broad view of vaccine hesitancy by including some of the most active specialized vaccine-hesitancy actors in the field, with examples from many different types of organizations at many different levels with the aim of developing a more comprehensive list over time as stakeholders, organizations, institutes and communities respond with suggested additions.

Five categories and four sub-categories of actors were determined to represent the groups working on vaccine hesitancy, including Governments (national and regional), Non-for-profit, Donors, Research-and Multinational Organizations. One further category was included to represent any actor that did not fit in the above categories but was still producing important work related to vaccine hesitancy. Industry was initially not included as its own category in this framework. While the vaccine industry has a major stake in vaccine hesitancy, is keen to combat hesitancy and therefore conducts work on the issue, it was seen as not beneficial to analyze each member of the vaccine industry individually. Instead, the vaccine industry was included as one entity in the 'other' category, so their work and interests as a group could be presented in the landscape analysis.

Seven areas of work and/or interest being carried out by actors working on the issue of vaccine hesitancy were identified, including research, policy recommendation, intervention, education and promotion, collaboration, goal setting and social mobilization. Inclusion/exclusion criteria were outlined by the Working Group. Inclusion criteria included working in at least two of seven areas of interest, specific examples of activities related to vaccine hesitancy. Exclusion criteria included actors promoting vaccine hesitancy or who are part of the anti-vaccination lobby, actors that have not worked on vaccine hesitancy in the last five years.

Two search strategies were used: 1) systematic review of the literature conducted in English and Mandarin over a range of databases and search engines and 2) snowballing technique to obtain unpublished information through personal communication with Working Group members and players identified through the initial literature search, as well as WHO partners familiar with regional/local circumstances to identify organizations relevant to the landscape analysis.(See Report Appendix 6C.1)

The following framework was developed for listing organizations/key players.

Categories		Key Actors	Areas of Work/Interest 1)	Actions 2)	Region	Collaborators and Affiliates
Gov	National					
	Regional					
Not-for-profit						
Donors						
Research	Individual					
	Organisations					
Multinationals						
Other						

1) Including research, policy recommendations, intervention, education/promotion, collaboration, goal setting and social mobilisation.

2) Examples current activities related to the issue of vaccine hesitancy the actor is engaged in.

In brief, the landscape analysis found that a number of advisory committees and organizations have started to address vaccine hesitancy, defining the problem, gathering information on hesitancy and suggesting potential intervention strategies. However, although organisations are starting to view vaccine hesitancy as an important topic, many simply discuss and highlight the issue, without making meaningful contributions (e.g. research, interventions, recommendation). Furthermore, the landscape analysis did not find many global vaccine reporting or surveillance systems currently measuring vaccine hesitancy, although there are a number of groups who are trialling different approaches to measurement.

A wide variety of groups were found, focusing on the promotion of vaccines and therefore addressing vaccine hesitancy in the population. In the future, an organization will need to be responsible for updating the data in the Landscape Analysis.

In summary, there is a growing list of researchers and organizations documenting and/ or studying vaccine hesitancy that are an important resource for addressing the growing needs to measure and address vaccine hesitancy.

## Section 6F: Moving Forward

While vaccine hesitancy is complex and context specific varying across time, place and vaccines, with a myriad of potential underlying determinants, the Working Group emphasized that there are a number of clear paths forward. While more research is needed there are current best practices for addressing hesitancy to follow now.

As part of best practice, immunization programs need to monitor their populations to detect pockets where vaccine up take rates are lower than would be expected with the services available. Often there are clusters of the vaccine hesitant within segment(s) of the population even when overall coverage is high. The WHO EUR TIP model provides an effective strategy to address hesitancy by segmentation of the population into subgroups with higher hesitancy levels, diagnosis of the major underlying factors, then tailoring the intervention to address these factors followed by evaluation of outcomes. Steps are

already underway to adapt TIP for use in LICs and to make the program more user friendly for immunization program managers to use with help from experts with appropriate back grounds.

The systematic review and the review of review of intervention strategies highlighted a number of effective strategies for improving vaccine uptake albeit not all necessarily related to hesitancy. While more work is needed, immunization programs need to incorporate the ones that fit their setting and resources into their program in order to support vaccine uptake. Given that immunization programs should have established close links with civil society organization, these can be helpful in mobilizing support for immunization, raising demand for vaccines and assisting in addressing vaccine hesitancy depending on the underlying hesitancy factors. Social mobilization, possibly through civil organization support, and a quality vaccine communication plan and program are important components for all immunization programs in dealing with hesitancy.

Effectively addressing vaccine hesitancy in addition to these general actions to support vaccine acceptance is part of good housekeeping for a quality immunization program. All immunization programs need to incorporate a plan to measure and address vaccine hesitancy into their country's immunization program. The compendium of vaccine hesitancy survey questions may help inform these surveys and facilitate inter- country comparisons. Sharing of immunization program country findings on hesitancy can lead to improved understanding of vaccine hesitancy and development of best intervention practices according to different major underlying factors in different contexts.

The working group acknowledged the importance of recognizing that addressing the needed behaviour change to overcome vaccine hesitancy is similar to the needed behaviour change required to address other complex communicable and non- communicable problems such as poor population compliance with the diagnosis and management of a chronic disease such as hypertension, diabetes, sexually transmitted infections etc.

As integration of health prevention and intervention services with other needed and wanted health and non-health related initiatives both for individuals and for communities has met with good success in some LIC settings, this strategy can be applied at the ground level. Front line health workers, even with limited training, can be taught opportunistically include immunization into variety of health and non-health services. This may help address some complacency and convenience hesitancy factors and minimize missed opportunities.

The Working Group concluded that the field of vaccine hesitancy is still evolving with a multitude of research activities being conducted by various groups and stakeholders. This will need ongoing evaluation, validation of the tools developed by the Working Group and assessment of future and current research and strategies beyond the realm of the Working Group.

Despite the lack of standardized, validated tools, immunization programs should move forward by implementing strategies to increase vaccination uptake.

## Section 7: Recommendations

Vaccines have saved countless lives. However, to optimize control of vaccine preventable diseases, high immunization coverage rates must be achieved. While hesitancy to accept immunization has occurred since vaccines were first introduced, in the past decade hesitancy has been increasingly recognized as a problem that needs attention if high uptake rates are to be achieved and maintained.

The Working Group defined vaccine hesitancy:

*Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific varying across time, place and vaccines. It includes factors such as complacency, convenience and confidence.*

Following a 2.5 year review of vaccine hesitancy the SAGE Working Group on Vaccine Hesitancy makes the following recommendations:

### 1. General recommendations

**Following conclusions should be acknowledged and disseminated widely:**

- a) Vaccine hesitancy is a complex and rapidly changing global problem that requires ongoing monitoring.
- b) There are many determinants of vaccine hesitancy that are laid out in the Matrix developed by the Working Group.
- c) Concerns about vaccine safety can be linked to vaccine hesitancy, but safety concerns are only one factor that may drive hesitancy.
- d) Addressing vaccine hesitancy within a country and/or subgroup requires an understanding of the magnitude and setting of the problem, diagnosis of the root causes, tailored evidence-based strategies to address the causes, monitoring and evaluation to determine the impact of the intervention and whether vaccine acceptance has improved, and ongoing monitoring for possible recurrence of the problem.
- e) There is no single intervention strategy that addresses all instances of vaccine hesitancy.
- f) In low vaccine uptake situations where lack of access to available services is the major factor, vaccine hesitancy can be present but it should not be the priority of immunization programs to address; improving services and access is the priority.

## **2. Specific recommendations**

### **To WHO:**

- a) Develop core capabilities at headquarters and regional the level for gaining behavioural insights that can be applied in an integrated fashion to many communicable and non-communicable diseases, including to hesitancy. This will require the integrated skills and knowledge of sociologists, behavioural psychologists, anthropologists, experts in social marketing and communication as well as specific disease experts. Efficiency and effectiveness of programs could be optimized, as this recognizes that addressing the needed behaviour change to overcome vaccine hesitancy is similar to the needed behaviour change required to address other complex communicable and non- communicable problems such as poor population compliance with the diagnosis and management of chronic diseases such as hypertension, diabetes, sexually transmitted infections etc.
- b) Engage partners, including civil society organizations, at the global, regional and country levels, to mobilize in support of immunization, its benefits to individuals and for communities.
- c) Cross-linkages between programs should be strengthened as vaccine hesitancy is an overarching concept which spans across various immunization-related fields. An integrated approach is needed to ensure consideration of vaccine hesitancy within different work streams. The landscape of organisations active in the field of vaccine hesitancy needs to be maintained and updated as a resource to facilitate collaboration and facilitate the establishment of global networks of researchers and stakeholders working on vaccine hesitancy.
- d) If beyond their scope, WHO should identify the suitable partners to take on the planning and implementation for vaccine hesitancy related work.

### **To UNICEF:**

- a) Given their vast experience in the field of polio with expertise in civil society organization, in communications and in behavioural change, UNICEF should continue their work with member states and ensure competencies in the field of vaccine hesitancy. Although much attention is given to the experiences from LIC, the lessons learned that apply to vaccine hesitancy need to be shared with HIC and MIC. This applies in particular to the findings obtained from addressing issues around polio vaccination.

**To WHO and UNICEF:**

- a) Create an organizational structure to address and coordinate vaccine hesitancy and demand issues at HQ level:
  - 1. Vaccine hesitancy work is not done in isolation but is intertwined, hence should be taken into consideration by all departments working in the field of immunization and beyond.
  - 2. Regular synthesis, digestion and sharing of vaccine hesitancy monitoring, intervention, prevention, training and research findings globally and regionally should be ensured.
  - 3. Regular updating and dissemination of best practices in management of and training for addressing vaccine hesitancy in HIC, MIC and LIC should be facilitated.
  - 4. One of potentially other useful tools is the WHO EUR TIP model which should be adapted for global use. Necessary support for training the trainers should be provided. Countries should be supported in using TIP and sharing their lessons learned as its effectiveness needs to be monitored, in particular LIC and MIC.
  - 5. The pilot testing and validation of the sample survey questions linked to the Matrix of determinants in various contexts needs to be undertaken and coordinated jointly.
- b) Consider the implementation of one or both of the proposed indicators into the regional JRFs
  - 1. The proposed etiological indicator will allow the monitoring of the three major concerns of immunization managers in regard to vaccine hesitancy by year and their potential shift over time.
  - 2. The proposed process JRF indicator determines if regular assessment for vaccine hesitancy is taking place. Use of country vaccine hesitancy survey findings will in the future lead to improvement of the data reported on in the annual JRF. Beyond assessment of process, the indicator serves as a reminder of good program practices and an advocacy tool.
  - 3. The data deriving from the indicators will be assessed by the GVAP Working Group. These analyses may lead to further refinement of the indicators.

**To WHO, UNICEF, other international organisations and partners:**

- a) Build regional capacity to support country progress on vaccine hesitancy.
- b) Ensure opportunities for community input into vaccine hesitancy strategies for prevention, diagnosis, intervention and monitoring to ensure that they resonate with communities.

- c) As steps are taken to improve vaccine program communications in LMIC, ensure that these also facilitate an understanding of vaccine hesitancy and the role communication may or may not play in driving and addressing hesitancy.
- d) Create and /or facilitate opportunities for sharing lessons learned about vaccine hesitancy on a regular basis.
- e) Work together to develop, validate and/or promote the use of tools to address vaccine hesitancy in different setting in HIC, MIC and LIC, including tools on monitoring, diagnosis, intervention, evaluation of impact, cost and community acceptability.
- f) As integration of health prevention and intervention services with other needed and wanted health and non-health related initiatives both for individuals and for communities has met with good success and needs to be applied more widely, immunization needs to be included. This can help address some complacency and convenience hesitancy factors.
- g) Encourage and support research on vaccine hesitancy:
  - i. Research on prevalence, determinants, effective intervention strategies, prevention, recrudescence and early intervention especially in LMIC but also in HIC.
  - ii. Expand research to capture factors not only at the individual level, but also at the community, contextual (politics and policies, communication and media, social norms, influential leaders, civil society organizations etc.), and organizational levels (vaccine and vaccination specifics issues, mode of delivery, etc) in HIC, MIC and LIC settings.

**To regional and country immunization advisory committees:**

- a) Give consideration to vaccine hesitancy issues in their region or country.
- b) Assist with dissemination of the deliverables developed by the Working Group.

**To member states:**

- a) Incorporate a plan to measure and address vaccine hesitancy into their country's immunization program as part of good program practices; the compendium of vaccine hesitancy survey questions may help; use of questions from the compendium facilitates inter-country comparisons, though the survey questions still remain to be validated throughout different settings.



- b) Within the immunization program and beyond, undertake education and training of health care workers to empower these to address vaccine hesitancy issue in patients and parents.
- c) Given their impact on the patient, vaccine hesitant behaviours within HCWs should be addressed.
- d) Ensure education on vaccination and immunization in general, and addressing vaccine hesitant patients in particular, by inclusion relevant training into academic curricula of nursing, medical and other health care professional students.
- e) Ensuring education and knowledge about vaccines in younger individuals provides a good opportunity to further shape future vaccine beliefs and behaviour.
- f) As part of good immunization program practice, civil society organizations need to be involved in supporting vaccine programs, in enhancing demand for vaccine and in helping to address vaccine hesitancy depending upon the underlying factors.
- g) Regularly share country information, research and lessons-learned on vaccine hesitancy among member states. Practices and interventions, ideally evidence-informed, need to be documented, evaluated and shared.
- h) The systematic review and the review of review of intervention strategies highlighted a number of effective strategies for improving vaccine uptake albeit not all necessarily related to hesitancy. While more work is needed, immunization programs need to incorporate the ones that fit their setting and resources into their program in order to maintain or increase vaccination uptake.