World Health Organization

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

# SAGE

## November 2013

### Strategic Advisory Group of Experts
### 5-7 November 2013

### CCV, Geneva

# SAGE November 2013

This booklet contains key background documents for the meeting of the Strategic Advisory Group of Experts on Immunization (SAGE), 5-7 November 2013.

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

**http://www.who.int/immunization/sage/meetings/2013/november**

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

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Version: 17 October 2013

World Health Organization

**Draft Agenda**
**Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)**
**5 - 7 November 2013**
**CCV/CICG, Geneva**

**Tuesday, 5 November 2013**

| Time | Session | Purpose of session, target outcomes and questions for SAGE | |
|---|---|---|---|
| 9:00 | **Welcome - introduction**<br><br>J. Abramson, Chair of SAGE | | 20 min. |
| **9:20** | **Global report from Director, IVB – Session 1**<br><br>Global report including key updates and challenges from regions, J.-M. Okwo-Bele, WHO, 30 min.<br><br>Discussion: 1 hr. | **FOR INFORMATION** | 1h 30 min. |
| **10:50** | **Coffee/tea break** | **Break** | **30 min.** |
| 11:20 | **Report from GAVI – Session 2**<br><br>Report from the GAVI Alliance, S. Berkley, GAVI Alliance, 20 min.<br><br>Discussion: 20 min. | **FOR INFORMATION** | 40 min. |

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| 12:00 | **Reports from other Advisory Committees on Immunization - Session 3**<br><br>Report of the Expert Committee on Biological Standards (ECBS), E. Griffiths, Chair of ECBS, 10 min.<br><br>Discussion: 10 min.<br><br>Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min.<br><br>Discussion on GACVS report and specific discussion on vaccination of pregnant and lactating women: 40 min. | **FOR INFORMATION AND DISCUSSION** | 2h |
| **13:10** | **Lunch** | **Break** | **1h** |
| 14:10 | **Reports from other Advisory Committees on Immunization - Session 3, (Contd.)**<br><br>Report of the Immunization Practices Advisory Committee (IPAC), S. Deeks, Chair of IPAC, 10 min.<br><br>Discussion: 10 min.<br><br>Report of the Immunization and Vaccine related Implementation Research (IVIR-AC) Advisory Committee, R. Breiman, Chair of IVIR, 10 min.<br><br>Discussion: 20 min. | | |
| 15:00 | **Global polio eradication initiative - Session 4**<br><br>Major developments and progress in polio eradication and issues for SAGE decisions and discussions.<br>B. Aylward, WHO, 10 min.<br><br>Discussion: 10 min.<br><br>Progress of Polio Eradication and Endgame Strategy Plan : detection and interruption of poliovirus transmission. H. Jafari, WHO, 20 min.<br><br>Discussion: 30 min. | **FOR DISCUSSION AND DECISION**<br><br>For decision:<br>• Optimal schedule for 1 IPV dose<br>• Strategic framework for responding to type 2 virus detection post-OPV2 cessation<br>• Recommendation for a WHA resolution in 2014 on accelerated IPV introduction, based on the progress toward a global supply and financing strategy<br><br>For discussion:<br>• Strategy to ensure bOPV access to all OPV-using countries | 3h 30 min. |

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| | | • Criteria to assess global readiness for global OPV2 withdrawal | |
| **16:10** | **Coffee/tea break** | **Break** | **30 min.** |
| 16:40 | **Global polio eradication initiative - Session 4, (Contd.)**<br><br>Planning for OPV2 withdrawal: the report from the Polio Working Group. E. Miller, Chair of SAGE Polio Working Group, 20 min.<br><br>Discussion: 60 min.<br><br>IPV supply, financing and introduction strategy in priority countries. M. Zaffran, WHO, 10 min.<br><br>Discussion: 20 min.<br><br>Post-OPV2 cessation type II poliovirus outbreak response strategy. C. Maher, WHO, 10 min.<br><br>Discussion: 20 min. | | |
| **19:00** | **Cocktail** | | |

**Wednesday, 6 November 2013**

| Time | Session | Purpose of session, target outcomes and questions for SAGE | |
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| 8:30 | **Decade of Vaccines - Global Vaccine Action Plan (GVAP) Monitoring - Session 5**<br><br>The GVAP annual progress report: the process, data sources and data quality, Secretariat of the Decade of Vaccines Working Group, T. Cherian, WHO, 20 min.<br><br>Summary of GVAP implementation progress,<br>R. Martin, Member of the Decade of Vaccines Working Group, 20 min.<br><br>Recommendations for corrective actions, N. Arora, Chair of the Decade of Vaccines Working Group, 20 min.<br><br>Discussion: 90 min. | **FOR DECISION**<br><br>SAGE will be expected to produce an independent first report on progress with the Decade of Vaccines Global Vaccine Action Plan.<br><br>Specially, SAGE will be asked to:<br>- Review the DoV WG "Assessment report on DoV progress" based on:<br>• the review of the "annual report on the Decade of Vaccines progress" prepared by the DOV secretariat,<br>• Information provided by other partners' annual reports on Decade of Vaccines progress.<br>- Make recommendations on any necessary changes to the formulation of the indicators, operational definitions and/or the processes for data collection.<br>- Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed.<br>- Provide recommendations and corrective actions for Members States, regions, partners, donor agencies or other parties regarding DoV GVAP implementation in a "SAGE Assessment report on the Decade of Vaccines progress" which will be the basis of the "progress report" for the WHO Board and World Health Assembly. | 2h 30 min. |
| **11:00** | **Coffee/tea break** | **Break** | **30 min.** |
| 11:30 | **Pandemic and pre-pandemic influenza vaccine - Session 6**<br><br>Update on H7N9 epidemiologic situation and vaccine development, W. Zhang, WHO, 10 min.<br><br>Discussion: 10 min.<br><br>Review of evidence on H5N1, J. Bresee, Member of the influenza Working Group, 15 min. | **FOR INFORMATION AND FOR DECISION**<br><br>For information<br>An update on the epidemiology of H7N9 and progress on vaccine development will also be provided. SAGE will be asked to discuss information to be collected on H7N9 cases of emerging virus in order to facilitate policy recommendations | 1h 30 min. |

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| | Conclusions and recommendations form the influenza Working Group on the H5N1 stockpile and on pre-pandemic use of H5N1 vaccine, L. Miller, Chair of the influenza Working Group, 15 min.<br><br>Discussion: 40 min. | For decision<br>In the context of the Pandemic Influenza Preparedness framework, review the previous recommendations on the establishment and use of an H5N1 vaccine stockpile<br><br>Review the current recommendations on inter-pandemic use of H5N1 vaccines. | |
| **13:00** | **Lunch** | **Break** | **1h** |
| 14:00 | **Measles and rubella elimination - Session 7**<br><br>Update on progress and challenges in achieving measles and rubella targets.<br>P. Strebel, WHO, 15 min.<br><br>Discussion: 30 min.<br><br>Recommendations for introducing rubella vaccine into the routine vaccination schedule and determining the target age range for measles and combined measles-rubella SIAs.<br>P. Figueroa, Chair of the Measles and Rubella Working Group, 20 min.<br><br>Discussion: 40 min<br><br>Recommendations for vaccination of health workers,<br>S. Reef, Member of the Measles and Rubella Working Group, 10 min.<br><br>Discussion: 25 min. | **FOR DISCUSSION AND DECISION**<br><br>For discussion:<br>• Global status report<br>• Report from each Region<br>• How to get back on track towards global and Regional targets<br><br>For decision:<br>• Use of combined measles-rubella vaccine for both routine doses<br>• Criteria to guide countries on expansion of the target age range measles and measles-rubella SIAs<br><br>For decision:<br>• Vaccination of health workers | 3h |
| **16:20** | **Coffee/tea break** | **Break** | **30 min.** |
| 16:50 | **Measles and rubella elimination - Session 7 (Contd.)**<br><br>Prioritizing the research agenda for measles and rubella<br>W. Moss, Member of the Measles and Rubella Working Group, 15 min.<br><br>Discussion: 25 min. | For discussion:<br>• List of priority research topics | |

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| 17:30 | **Smallpox vaccines - Session 8**<br><br>WHO Smallpox vaccine emergency stockpile and production, A. Costa, WHO, 10 min.<br><br>Review of efficacy and safety of smallpox vaccines, H. Meyer, Paul Ehrlich Institute, Germany, 15min.<br><br>Conclusions and recommendations from the Expert Consultation, Y. Al-Mazrou, Chair of the Expert Consultation, 15 min.<br><br>Discussion: 50 min. | **FOR DECISION**<br><br>The last case of Smallpox occurred in 1977. In 1980 the World Health Assembly declared this disease eradicated. A global stockpile of vaccines, held in Switzerland, was created with donations from Member States.<br><br>In 2004 Previous the Ad-Hoc Orthopoxvirus Committee, recommended that the stockpile should consist 200 million doses. The current physical WHO stockpile is ~ 2.4 million doses, and the virtual stockpile consists of 31 million doses.<br><br>In order for WHO to make an informed decision (risk-benefit) on which vaccines to stock and to be able to give advice to countries on their stockpile, WHO would like SAGE to answer the following questions:<br><br>Which vaccine should be recommended to be used during an outbreak of smallpox? (vaccine used during the eradication, vaccine produced in tissue cell, or further attenuated vaccines).<br>–Composition of stockpile<br>–Size of stockpile<br><br>What groups should be prioritized to be vaccinated while faced with limited vaccine supply?<br>–Age groups, risk factors/safety aspects, vulnerable populations, ethical considerations<br>–Which vaccine should be given?<br><br>Which vaccine should be recommended for preventive use? Who should be targeted and with which immunization schedule? (First aid responders, army, police, health workers) | 1h 30 min. |
| 19:00 | **End of day** | | |

**Thursday, 7 November 2013**

| Time | Session | Purpose of session, target outcomes and questions for SAGE | |
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| 8:30 | **Immunization supply chain & logistics : key challenges and future direction - Session 9**<br><br>A story about the supply chain challenges in country, J. Vandelaer, UNICEF, 10 min.<br><br>The key supply chain challenges, J. Vandelaer, UNICEF, 10 min.<br><br>Mechanisms in place to address some of the challenges and key take-home messages, D. Chang-Blanc, WHO, 10 min.<br><br>Discussion: 30 min. | **FOR INFORMATION**<br><br>The purpose of this session is to highlight the ongoing constraints faced by country supply chains for vaccines, and provide evidence of the mounting challenges of introducing more vaccines into currently stretched systems. It will provide insight as to how WHO and UNICEF are enhancing their collaboration to support countries strengthen their immunization supply chain systems for the future. | 1h |
| 9:30 | **Sentinel site surveillance - Session 10**<br><br>Strategic review of the IB-VPD surveillance network: key findings, conclusions and recommendations, C. Broome, informal Technical Advisory Group Chair, 15 min.<br><br>Strategic review of the rotavirus surveillance network: key findings, conclusions and recommendations, G. Kang, informal Technical Advisory Group Co-Chair, 15 min.<br><br>Moving forward after the strategic review: Next steps & future vision, T. Cherian, WHO, 10 min. | **FOR DISCUSSION**<br><br>To seek SAGE guidance on the results of a strategic review of the global rotavirus and invasive bacterial vaccine preventable diseases (IB-VPD) sentinel hospital networks, both of which use a case-based approach with laboratory confirmation of cases;<br><br>To seek SAGE advice on the utility of these global coordinated surveillance networks to provide data for public health decision makers;<br>To seek SAGE guidance on the suitability of these networks as platforms for surveillance for other VPDs. | 1h 30 min. |
| **10:10** | **Coffee/tea break** | **Break** | **30 min.** |
| 10:40 | **Sentinel site surveillance – Session 10 (Contd.)**<br><br>Discussion: 50 min. | **FOR DISCUSSION** | |
| **11:30** | **Closing** | | |
| **12:00** | **End of meeting** | | |

World Health Organization

**Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization**
**5 – 7 November 2013**
**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: June 2010

# DECLARATION OF INTERESTS FOR WHO EXPERTS

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

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

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed.

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

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

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

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

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|---|
| Name:<br>Institution:<br>Email: |

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

_____

_____

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

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

**EMPLOYMENT AND CONSULTING**

***Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?***

1a Employment Yes Í No Í

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

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

2a Research support, including grants, collaborations, sponsorships, and other funding Yes Í No Í

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) Yes Í No Í

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

**INVESTMENT INTERESTS**
***Do you have current investments (valued at more than US $5000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.***

3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes Í No Í

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) Yes Í No Í

**INTELLECTUAL PROPERTY**
**.**
***o you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?***

4a Patents, trademarks, or copyrights (including pending applications) Yes Í No Í

4b Proprietary know-how in a substance, technology or process Yes Í No Í

**PUBLIC STATEMENTS AND POSITIONS** (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? Yes Í No Í

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? Yes Í No Í

**ADDITIONAL INFORMATION**

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? Yes Í No Í

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes Í No Í

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? Yes Í No Í

6d Have your received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? Yes Í No Í

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes Í No Í

7. **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)*
Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, Yes Í No Í

manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?

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

| **Nos. 1 - 4:**<br>**Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.** | **Name of company, organization, or institution** | **Belongs to you, a family member, employer, research unit or other?** | **Amount of income or value of interest (if not disclosed, is assumed to be significant)** | **Current interest (or year ceased)** |
|---|---|---|---|---|
| | | | | |
| **Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details** | | | | |

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

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

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

Date: _____ Signature_____

World Health Organization

**CONFIDENTIALITY UNDERTAKING**

1. Commercial, academic and other research institutions and individual scientists often submit or present for discussion by committees or groups of the WHO Department of Immunization, Vaccines and Biologicals on research, products and processes (hereafter referred to as "Information") which the institutions and individuals consider proprietary. To help ensure the appropriate use by WHO of such Information whilst protecting the institutions' or individual's proprietary rights, WHO undertakes to release such Information only to persons who have signed this agreement.

2. Information submitted by such institutions or individuals through WHO to committees or groups for review, discussion or comment, whether at meetings, on internet-based collaborative workspaces, during telephone conferences or otherwise, shall be regarded by the Undersigned as confidential, unless clearly stated otherwise, by the institution, individual concerned and/or the WHO Secretariat.

3. The Undersigned undertakes to treat such confidential Information as proprietary information and agrees not to make copies of it, nor to disclose or use the same in whole or in part.

4. If requested to do so, the Undersigned agrees to return to WHO any and all Information identified as confidential.

5. The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that the Information:

   (a) was known to him/her prior to any disclosure to him/her by the institution or individual or WHO;

   (b) was in the public domain at the time of disclosure by the institution or individual;

   (c) becomes part of the public domain through no fault of the Undersigned; or

   (d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality to the institution, individual or WHO.

6. This Confidentiality Undertaking is valid during the entire time the Undersigned participates in the work of the committee or group, in whatever capacity, and for a period of ten (10) years thereafter.

Date:……

Signature……...

Name……
(print or type)

CONFIDENTIALITY1.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Management of Conflict of Interest**

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

World Health Organization

**CURRENT SAGE WORKING GROUPS**

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

**Terms of Reference**

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

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

2. Propose key recommendations to SAGE for updating the 2003 position paper on IPV and consolidating it with other relevant documents (including the 2006 supplement to the IPV position paper) into one vaccine position paper on routine polio immunization covering both IPV and OPV and giving consideration to the ongoing polio eradication efforts.
3. Advise SAGE on technical guidance to WHO and the GPEI for the development and finalization of the overall polio eradication 'endgame strategy' to reduce long-term risks associated with OPV and to accelerate wild poliovirus eradication, including:

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

**Composition**

*SAGE Members*

- Elizabeth Miller, Chair of Working Group. Health Protection Agency, UK
- Hyam Bashour, Damascus University, Syria. (SAGE member until April 2011)
- Zulfiqar Bhutta, The Aga Khan University, Pakistan (Joined the Working Group in March 2012)
- Peter Figueroa, University of the West Indies, Jamaica

*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. WHO Initiative for vaccine research/global malaria programme joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)**

**Terms of reference**

JTEG provides advice to WHO 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 influenza vaccines and immunization (established August 2010)**

**Terms of Reference**

Objectives of the Working Group:

1. Prepare for a SAGE evidence-based review and updating of WHO recommendations on the use of seasonal influenza vaccine (e.g. priority target groups) with a particular focus on low and middle-income countries and with a view to update the 2005 WHO influenza vaccine position papers.
2. Prepare for a SAGE discussion on coverage goals for seasonal influenza vaccination to be proposed to the WHA to update the coverage goals contained in the 2003 resolution.
3. Identify essential gaps in evidence that may impede SAGE's ability to update the recommendations on the use of influenza vaccines and propose coverage targets.
4. Provide advice about pandemic vaccine preparedness.

**Composition**

*SAGE Members*

- Elizabeth Miller, Chair of Working Group. Health Protection Agency, London, UK
- Jon Abramson, Wake Forest University School of Medicine, USA
- Art Reingold, University of California, USA. (Joined the Working Group after the SAGE meeting in November 2010) (SAGE member until November 2011)
- Claire-Anne Siegrist, University of Geneva, Switzerland

*Experts*

- William Kwabena Ampofo, Noguchi Memorial Institute for Medical Research, Ghana
- Joseph Bresee, Centers of Disease Control, USA
- Janet Englund, Seattle Children's Hospital, USA
- Randeep Guleria, All India Institute of Medical Sciences, India
- Yu Hongjie, Chinese Center for Disease Control and Prevention, People's Republic of China
- Michael Pfleiderer, Paul-Ehrlich-Institut, Germany
- David Salisbury, Department of Health, UK (SAGE member until April 2010)
- Barry Schoub, National Institute for Communicable Diseases, South Africa

**4. 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., QUIVER 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
- 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 April 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

**5. 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*

- Xiaofeng Liang, Chair of Working Group, Chinese Center for Disease Control, China
- Juhani Eskola, National Institute of Health and Welfare, Finland

*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

**6. SAGE Working Group on Varicella and Herpes Zoster Vaccines (established – May 2012)**

**Terms of Reference**

The Working Group will be asked to review the evidence, identify the information gaps, and guide the work required to address the information gaps and formulate proposed recommendations in preparation for a SAGE review of the use of varicella and herpes zoster vaccines. This will then lead to an updating the current (1998) varicella vaccine position paper.

The Working Group will specifically be asked to identify and review:

- data regarding the global prevalence and burden of disease caused by varicella and herpes zoster according to country development status
- issues related to varicella and herpes zoster surveillance
- the safety, effectiveness and immunogenicity profile of varicella and herpes zoster vaccines including that of vaccine combinations such as MMRV
- the duration of protection following immunization
- the impact of co-administration of varicella and herpes zoster vaccines with other vaccines
- the impact of varicella vaccination on immunocompromised individuals
- country experiences with introduction and use of varicella vaccines (in countries with information that allows a robust analysis)
- the potential for widespread childhood vaccination to reduce natural boosting through varicella virus circulation in the community and increase the risk of zoster in the adult and elderly population
- evidence on the cost-effectiveness of different approaches, in particular in low and low-middle income countries (as per WHO guidelines)
- additional critical issues that need to be considered in updating the current vaccine position paper.

The review of vaccine safety will consider of a review by the Global Advisory Committee on Vaccine Safety, and that on cost-effectiveness will link with the Immunization and Vaccines related Implementation Research (IVIR) Advisory Committee (formerly known as QUIVER).

**Composition**

*SAGE Members*

- Jon Abramson, Chair of Working Group, Department of Paediatrics, Wake Forest University School of Medicine, USA

- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

*Experts*

- Marc Brisson, Département de Médecine Sociale et Préventive, Laval University, Canada
- Raina MacIntyre, School of Public Health and Community Medicine, University of New South Wales, Australia (was nominated in February 2013 replacing Sin Yun Cheah)
- Philip LaRussa, Division of Pediatric Infectious Diseases, Department of Pediatrics, Columbia University, USA
- Hanne Nøkleby, Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway
- Bolutife Ayokunnu Olusanya, Department of Ophthalmology, University College Hospital, Nigeria
- Jane Seward, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, USA
- Claudia Vujacich, Foundation for Infectious Diseases, FUNCEI, Argentina
- Dapeng Yin, National Immunization Programme, Chinese CDC, China
- Sin Yun Cheah, Health Sciences Authority, Singapore (resigned from the group in February 2013)

**7. 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 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 new-borns

- 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*

- Elizabeth Miller (Working Group Chair), Health Protection Agency, UK
- Claire-Anne Siegrist, Department of Pediatrics, University of Geneva, Switzerland
- 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

**8. SAGE Working Group on non-specific effects of vaccines (established March 2013)**

**Terms of Reference**

WHO's Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence concerning the possible non-specific effects of vaccines included in the routine infant immunization schedule.

Preparatory to such a review of the evidence by SAGE in 2013, it is necessary to:

- systematically review all published and grey literature concerning epidemiological studies addressing "non-specific" effects of BCG, measles and, DTP-containing vaccines on survival/all-cause mortality in children under five years of age and,
- critically appraise the evidence using the WHO Strategic Advisory Group of Experts (SAGE) guidelines.

The Working Group will be asked to determine if the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Guidance for the development of evidence-based vaccine related recommendations.

The Working Group will specifically be asked to:

1. Review and provide guidance on the protocol for two independent systematic reviews (one on epidemiological studies and one on immunological factors) on the evidence of selected vaccines on child survival/ deaths by all causes in children less than 5 years of age.
2. Review the available evidence that addresses the effect of BCG, DTP and measles-containing vaccines on survival/all-cause mortality in children less than five years of age and, the outcomes of the above mentioned reviews and related GRADE tables.
3. Determine if the current evidence on non-specific effects of vaccines is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation.

**Composition**

*SAGE Members*

- Terry Nolan (Chair of the Working Group), Head, University of Melbourne School of Population and Global Health, Melbourne, Australia
- Zufiqar Bhutta, Department of Paediatrics & Child Health, The Aga Khan University Medical Center, Karachi, Pakistan
- Kate O'Brien, Center for American Indian Health, Johns Hopkins Bloomberg School Public Health, Baltimore, USA

*Experts*

- Christine Stabell Benn, Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Denmark
- Mike Brennan, Senior Adviser, Global Affairs. AERAS, Washington D.C., USA
- Stephen Evans, Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine, UK
- Paul Fine, Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK
- Brad Gessner, Scientific Director, Association pour la Medicine Preventive (AMP), Ferney-Voltaire, France
- Diane Griffin, University Distinguished Service Professor Alfred and Jill Sommer Chair W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health; Professor, Medicine and Neurology, Johns Hopkins University School of Medicine, USA
- Jaleela Sayed Jawad, Head of Immunization Group and EPI Manager Ministry of Health, Manama, Bahrain
- Martin Mermikuwu, Professor of Pediatrics, University of Calabar, Nigeria
- Walter A. Orenstein, Professor of Medicine, Infectious Diseases, Emory University, USA
- Dipika Sur, Deputy Director, National Institute of Cholera and Enteric Diseases, Kolkata, India

**9. 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
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**10. 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**

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**11. SAGE Working Group on Japanese encephalitis vaccines (In process of establishment)**

**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.

**Expertise needed**

- Expertise in JE epidemiology and control strategies
    - Epidemiology/Surveillance
    - Clinical
    - Virology
- Expertise in immunogenicity, efficacy and safety of available JE vaccines
    - Epidemiology/Surveillance
    - Immunology
    - Regulatory
    - Program management

**Strategic Advisory Group of Experts (SAGE) on Immunization**
**5 - 7 November 2013**
**Geneva, Switzerland**

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Organisation mondiale de la Santé

# Weekly epidemiological record
# Relevé épidémiologique hebdomadaire

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## Meeting of the Strategic Advisory Group of Experts on immunization, April 2013 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 9–11 April 2013 in Geneva, Switzerland. This report provides a summary of the discussions, conclusions and recommendations.[2]

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

The report focused on: (i) the Global Vaccine Action Plan (GVAP) roll-out; (ii) the strengthening of routine immunization and efforts to integrate immunization and other child health interventions; and (iii) the changing epidemiology of measles. The report also covered, inter alia, the proposed development of preferred product characteristics for shaping upstream vaccine research and development, advisory processes at regional and global levels with emerging issues and agenda items on the horizon, and the establishment of the cholera vaccine stockpile expected to be operational by mid-July 2013.

SAGE recognized the importance of the GVAP as the new global framework for immunization services at all levels. The GVAP implementation requires concrete actions at regional and national level to strengthen immunization systems. SAGE acknowledged the regional commitment and shared responsibilities in this regard. Much support is still required to assist countries in establishing a well-function-

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

[2] The complete set of presentations and background materials used for the SAGE meeting of 9–11 April 2013 together with summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2013/april/en/index.html; accessed in April 2013.

## Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2013 – Conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 9 au 11 avril 2013 à Genève (Suisse). Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

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

Le rapport s'est concentré sur: i) la mise en place du Plan d'action mondial pour les vaccins (GVAP); ii) le renforcement de la vaccination systématique et des efforts visant à intégrer la vaccination et d'autres interventions en faveur de la santé de l'enfant; et iii) l'évolution de l'épidémiologie de la rougeole. Par ailleurs, le rapport a porté entre autres sur l'élaboration proposée des caractéristiques préférées pour les produits afin d'orienter en amont la recherche-développement des vaccins, les processus consultatifs aux niveaux régional et mondial avec en ligne de mire les points à l'ordre du jour et problèmes émergents, et la création d'un stock de vaccins anticholériques qui devraient être opérationnels d'ici la mi juillet 2013.

Le SAGE a reconnu l'importance du Plan d'action mondial pour les vaccins en tant que nouveau cadre mondial pour les services de vaccination à tous les niveaux. La mise en œuvre du Plan d'action exige la prise de mesures concrètes aux niveaux régional et national afin de renforcer les systèmes de vaccination. Le SAGE a pris acte de l'engagement régional et des responsabilités partagées à cet égard. Les pays ont encore besoin d'un

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

[2] La série complète des communications et des documents de travail de la réunion du SAGE tenue du 9 au 11 avril 2013, ainsi que les résumés des déclarations d'intérêts fournies par les membres de ce groupe sont disponibles à l'adresse suivante: http://www.who.int/immunization/sage/meetings/2013/april/en/index.html; consulté en avril 2013.

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ing immunization system and aligning their multi-year plans with the GVAP. The concept of extending the current system from childhood immunization programmes to one with enhanced flexibility, able to respond to changing epidemiology and spanning all ages, needs to be embraced. Sustainable funding for immunization services is a continuing challenge, especially with increasing demands on national budgets from competing health priorities such as non-communicable diseases. Middle-income countries continue to struggle to afford new vaccines, and new coordinated regional initiatives for pooled procurement, such as that in the Eastern Mediterranean Region, are welcomed.

SAGE noted that many developing countries have weak primary health care systems which have difficulty in delivering quality vaccination and other health services. They are unable to sustain high coverage with essential vaccines or to effectively integrate new vaccines into their national vaccination and maternal and child health programmes. The majority of unvaccinated children globally are concentrated in 10 low-income countries with weak health systems which are priority countries for international support.

SAGE emphasized the importance of measles immunization coverage and its role as a flagship reflecting the successes and failures of the immunization system. Noting this, it is a concern that many countries in all regions report outbreaks with the disease shifting to older age-groups, and ongoing difficulties with vaccine coverage and data quality.

After reviewing country experiences, SAGE noted an increase in the proportion of measles cases in older age groups, particularly adolescents and adults, and the increased risk of complications of measles when it occurs in adults (e.g. encephalitis). SAGE reaffirmed the principle that measles immunization strategies should be adapted to the country's control goal, the epidemiological situation, and the programme's capacity to achieve high coverage. In particular, measles supplementary immunization activities (SIAs) should be tailored to cover all susceptible age groups as indicated by the age distribution of measles cases and vaccine coverage gaps. SAGE noted the funding constraints for measles elimination and encouraged countries and partners to support implementation of strategies that are responsive to the current measles susceptibility profile. Countries need to be proactive in identifying their susceptible populations. Systematic support for strengthening the national immunization programme, if necessary including high quality SIAs, will be needed to enable countries to achieve elimination targets. As previously stated, SAGE highlighted the imperative to integrate rubella with measles in the programme and the need to address susceptibility gaps to both rubella and measles simultaneously. SAGE complimented the commitment of the South-East Asia Region and endorsed the regional technical advisory group's proposal to the

appui important pour mettre sur pied des systèmes de vaccination pleinement opérationnels et aligner leurs plans pluriannuels sur le Plan d'action mondial. Il faut intégrer le concept d'extension du système actuel pour passer des programmes actuels de vaccination de l'enfant à un qui soit plus souple, puisse réagir à l'évolution de l'épidémiologie et couvre tous les âges. La pérennité du financement des services de vaccination est un défi continuel, notamment alors que les budgets nationaux doivent de plus en plus faire face à d'autres priorités sanitaires comme les maladies non transmissibles. Les pays à revenu intermédiaire continuent de lutter pour trouver les moyens de se procurer les nouveaux vaccins, et de nouvelles initiatives régionales coordonnées pour l'achat groupé, comme celle mise en œuvre dans la Région de la Méditerranée orientale, sont les bienvenues.

Le SAGE a constaté que, dans de nombreux pays en développement, la faiblesse des systèmes de soins de santé primaires rend difficile la prestation de services de vaccination et d'autres services de santé de qualité. Ils ne sont pas en mesure de maintenir une couverture élevée par les vaccins essentiels ou d'intégrer efficacement de nouveaux vaccins dans leurs programmes nationaux de vaccination et de santé de la mère et de l'enfant. La majorité des enfants non vaccinés dans le monde vivent essentiellement dans 10 pays à faible revenu dans lesquels les systèmes de santé laissent à désirer et qui sont considérés comme prioritaires pour l'aide internationale.

Le SAGE a souligné l'importance de la couverture par la vaccination antirougeoleuse, qui sert de figure de proue aux succès et aux échecs du système de vaccination. C'est d'ailleurs pourquoi il est préoccupant que de nombreux pays, toutes Régions confondues, signalent des flambées épidémiques, la maladie sévissant dans des groupes plus âgés, de même que des difficultés persistantes en matière de couverture vaccinale et de qualité des données.

Après avoir passé en revue les expériences des pays, le SAGE a constaté une augmentation de la proportion de cas de rougeole dans des groupes plus âgés, en particulier les adolescents et les adultes, ainsi que le risque accru de complications lorsque cette maladie se manifeste chez les adultes (encéphalite, par exemple). Il a réaffirmé le principe selon lequel les stratégies de vaccination antirougeoleuse devaient être adaptées à l'objectif de lutte du pays, à la situation épidémiologique et aux capacités du programme à instaurer une couverture élevée. En particulier, les activités de vaccination antirougeoleuse supplémentaires (AVS) devraient être façonnées de façon à couvrir tous les groupes d'âge vulnérables tels qu'ils ressortent de la répartition des cas selon l'âge et des lacunes de la couverture vaccinale. Le SAGE a pris acte des contraintes financières gênant l'élimination de la rougeole et encouragé les pays et les différents partenaires à soutenir la mise en œuvre de stratégies répondant au profil actuel de vulnérabilité. Les pays doivent se montrer proactifs en matière de recensement des populations vulnérables. S'ils veulent atteindre les objectifs en matière d'élimination, un soutien systématique devrait leur être apporté pour renforcer les programmes nationaux de vaccination, au besoin en organisant des AVS de qualité. Comme indiqué précédemment, le SAGE a souligné qu'il était impératif d'intégrer la rubéole et la rougeole dans le même programme et nécessaire de s'attaquer simultanément aux lacunes qui rendent sensibles à ces deux maladies. Le SAGE a félicité la Région de l'Asie du Sud-Est pour son engagement et a approuvé la proposition du groupe consultatif technique régio-

Regional Committee to set a target date for measles elimination.

Access and service delivery to insecure internal populations and refugee populations is a challenge for many countries and regions. Financial and technical support should be offered to countries which host refugee populations, to sustain vaccination coverage in these groups.

SAGE is concerned that there is insufficient coordination and integration of current vaccine initiatives with other critical health programmes which frequently compete for scarce health resources and miss opportunities for synergistic action to strengthen national vaccination programmes and health systems in a sustainable cost-effective way. Routine immunization services need to be continuously strengthened and integrated with other primary health care interventions, such as the newly launched integrated Global Action Plan for Pneumonia and Diarrhoea. Immunization services should be made responsive to local epidemiology, and strategies and structures need to be developed to expand services to older age groups.

SAGE noted the significant efforts by WHO, the GAVI Alliance and many partners, as well as countries themselves, to improve coordination and integration of services, but that far more needs to be done to strengthen the national immunization systems and to integrate programmes such as the Global Polio Eradication Initiative (GPEI) into routine services. SAGE plans to review the measures being taken by WHO, GAVI and other partners to improve coordination and integration of vaccination programmes and other health programmes, and assess what additional measures can be identified to strengthen national vaccination programmes and health systems to ensure universal vaccine and health care coverage.

SAGE noted with concern the differences in mortality estimates for certain diseases, including some vaccine-preventable childhood diseases, from the Institute for Health Metrics and Evaluation (Global Burden of Disease 2010 project) compared to official WHO estimates. These discrepancies threaten to have a detrimental impact on vaccine advocacy and support for the GVAP, and create confusion at the country policy level. While recognizing the recent efforts to bring the scientific community together around this subject, SAGE expressed concern about slow progress and underscores the need for transparency regarding the data and methods, and global consensus on estimates based on best evidence. Adequate resourcing of WHO for these efforts should become a global priority.

## Report from the GAVI Alliance

The report provided an update on: (i) the processes and timelines for developing the next Vaccine Investment Strategy (for the period 2015–2020) beyond existing commitments, (ii) the preliminary Board discussions regarding GAVI's potential role in supporting the GPEI,

nal au Comité régional de fixer une date cible pour l'élimination de la rougeole.

L'accès et la prestation des services aux populations vivant dans des zones d'insécurité et aux réfugiés représentent toujours un défi dans de nombreux pays et régions. Un soutien technique et financier devrait être proposé aux pays qui accueillent des populations de réfugiés, afin de pouvoir maintenir la couverture vaccinale dans ces groupes.

Le SAGE craint une coordination et une intégration insuffisantes entre les initiatives actuelles en matière de vaccin et d'autres programmes de santé essentiels entrant souvent en concurrence lorsqu'il s'agit de ressources limitées pour la santé; des occasions d'agir en synergie pour renforcer les programmes nationaux de vaccination et les systèmes de santé de façon économique et efficace seraient ainsi perdues. Les services de vaccination systématique doivent être renforcés en permanence et s'intégrer aux autres interventions de soins de santé primaires, comme le nouveau Plan d'action mondial intégré pour la pneumonie et la diarrhée. Les services de vaccination devraient être plus réactifs à l'épidémiologie locale, et des stratégies et structures doivent être mises en place pour les étendre aux groupes de population plus âgés.

Le SAGE a constaté les efforts importants déployés par l'OMS, l'Alliance GAVI et de nombreux autres partenaires, ainsi que par les pays eux-mêmes, pour améliorer la coordination et l'intégration des services, tout en notant qu'il fallait en faire bien davantage pour renforcer les systèmes nationaux de vaccination et intégrer des programmes tels que l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) dans les services systématiques. Il prévoit d'examiner les mesures prises par l'OMS, l'Alliance GAVI et d'autres partenaires pour améliorer la coordination et l'intégration des programmes de vaccination avec d'autres programmes de santé et déterminer les mesures supplémentaires à prendre pour renforcer les programmes nationaux de vaccination et les systèmes de santé, afin de garantir la couverture universelle de la vaccination et des soins de santé.

Le SAGE a constaté avec préoccupation les différences dans les estimations de la mortalité pour certaines maladies, y compris des maladies de l'enfance évitables par la vaccination, établies par l'Institut de métrologie sanitaire et d'évaluation (projet Charge mondiale de morbidité 2010) par rapport aux estimations officielles de l'OMS. Ces divergences risquent d'avoir un impact négatif sur les campagnes de sensibilisation et le soutien au Plan GVAP et de créer une confusion au niveau décisionnel dans les pays. Tout en reconnaissant les efforts déployés récemment pour rassembler la communauté scientifique autour de cette question, le SAGE s'inquiète de la lenteur des progrès et souligne la nécessité de la transparence pour les données et les méthodes, ainsi que d'un consensus mondial autour d'estimations fondées sur les données les plus probantes. La mobilisation de ressources suffisantes pour aider l'OMS dans cet effort devrait devenir une priorité mondiale.

## Rapport de l'Alliance GAVI

Le rapport complète une mise à jour sur: i) le processus et le calendrier d'élaboration de la nouvelle stratégie d'investissement dans les vaccins (pour la période 2015-2020) au-delà des engagements existants, ii) les discussions préliminaires du Conseil concernant le rôle potentiel de l'Alliance GAVI à l'appui

including supporting inactivated polio vaccine (IPV) introduction and potential innovative financing instruments for mobilizing resources, and (iii) the preparations for the next GAVI replenishment round in 2014.

SAGE welcomed GAVI's efforts in using its potential support for the GPEI to strengthen routine immunization programmes and integration with other maternal, newborn and child intervention programmes. While recognizing a resource constrained environment, SAGE encouraged GAVI to consider vaccines and strategies identified by disease elimination programmes and encourage flexibility in support to these programmes. In particular, SAGE stressed that consideration should be given to the funding of measles immunization for older age groups. The work on strengthening cold chain logistics, health systems, data quality and surveillance, and on strengthening health systems beyond immunization was noted and appreciated. SAGE encouraged GAVI to continue to explore ways in which its mechanisms can support graduating countries and partner activities for low-middle income countries to obtain better and fairer pricing of vaccines.

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

A report of the December 2012 GACVS meeting was presented.[3] SAGE acknowledged the detailed review and the recommendations of GACVS on the safety profile of varicella vaccines, risk of narcolepsy and Guillain-Barré syndrome with influenza vaccines, and the safety of dengue vaccines.

SAGE suggested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy. SAGE stressed that the development of guidelines for the use of vaccines in pregnant women needs to be accelerated and recognized that while GACVS is focusing on specific vaccines, more generic guidance about the use of different vaccines in pregnant women should be developed by SAGE to complement this work.

## Report from the Immunization Practice Advisory Committee (IPAC)

A report of the April 2013 IPAC meeting was presented. SAGE endorsed IPAC's ongoing contributions to the development of the "Reaching Every Community" toolkit and to the immunization session checklist. SAGE supported these additional tools and validated IPAC's proposal to pilot test the tools before wide-spread implementation. SAGE noted the importance of including the private sector in consideration of addressing missed vaccination opportunities, as this is often overlooked. SAGE acknowledged that the "Reaching Every Community" tool is not designed for areas which are inaccessible due to dangerous insecurity; as such,

[3] See No. 6, 2013, pp. 65–70.

de l'IMEP, notamment l'aide à l'introduction du vaccin antipoliomyélitique inactivé (VPI) et des instruments financiers novateurs susceptibles d'être utilisés pour la mobilisation de ressources, et iii) les préparatifs en vue de la prochaine reconstitution des fonds de l'Alliance en 2014.

Le SAGE a salué les efforts déployés par l'Alliance GAVI qui utilise son soutien potentiel à l'IMEP pour renforcer les programmes nationaux de vaccination et les intégrer à d'autres programmes de santé de la mère, du nouveau-né et de l'enfant. Conscient de la situation d'austérité en matière de ressources, le SAGE a néanmoins encouragé l'Alliance à étudier les vaccins et stratégies retenus par les programmes d'élimination des maladies et à accroître la flexibilité dans le soutien à ces programmes. Il a, en particulier, souligné qu'il fallait envisager de financer la vaccination antirougeoleuse dans les groupes de population plus âgés. Il a pris note avec satisfaction des activités en matière de renforcement de la logistique de la chaîne du froid, des systèmes de santé, de la qualité et de la surveillance des données, et du renforcement des systèmes de santé au-delà de la vaccination. Le SAGE a encouragé l'Alliance à continuer d'étudier les moyens de mettre à profit ses mécanismes pour aider les activités nationales et celles des partenaires dans les pays à revenu intermédiaire de la tranche inférieure à se qualifier pour obtenir une tarification meilleure et plus juste des vaccins.

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

Un rapport sur la réunion de décembre 2012 du GACVS a été présenté.[3] Le SAGE a pris acte de l'examen détaillé et des recommandations du GACVS relatives au profil d'innocuité des vaccins contre la varicelle, au risque de narcolepsie et de syndrome de Guillain-Barré en lien avec les vaccins antigrippaux et à l'innocuité des vaccins contre la dengue.

Le SAGE a suggéré que les recommandations futures relatives à l'innocuité du vaccin contre la dengue soient liées à la stratégie de mise au point de ce vaccin. Il a souligné que l'élaboration de lignes directrices pour l'utilisation des vaccins chez la femme enceinte devait être accélérée et a reconnu que, si le GACVS se concentrait sur certains vaccins en particulier, le SAGE devrait élaborer, pour compléter ces travaux, des orientations plus générales sur l'utilisation des différents vaccins chez la femme enceinte.

## Rapport du Comité consultatif sur les Pratiques vaccinales (IPAC)

Un rapport sur la réunion d'avril 2013 de l'IPAC a été présenté. Le SAGE a entériné les contributions en cours du Comité pour la mise au point de l'outil «Atteindre toutes les communautés» et pour l'établissement de la liste de vérification pour les séances de vaccination. Il a soutenu la mise au point de ces outils supplémentaires et validé la proposition par le Comité d'un essai pilote avant la généralisation de ces outils. Il a noté l'importance de faire participer le secteur privé à l'examen de la question des occasions de vaccination manquées, ce point étant souvent sous-estimé. Le SAGE a reconnu que l'outil «Atteindre toutes les communautés» n'est pas destiné aux zones inaccessibles pour des raisons d'insécurité; des travaux supplé-

[3] Voir N° 6, 2013, pp. 65-70.

further work on identifying best practices in such extreme circumstances needs to be undertaken.

SAGE noted that programmatic guidance by IPAC will be required to support the GPEI, including the withdrawal of OPV2 and the introduction of IPV as recommended by SAGE.

## Dengue vaccines

Dengue causes an estimated 100 million symptomatic cases, 2.1 million severe cases, and 21 000 deaths annually, with the geographic spread and burden of the disease growing dramatically in the last 30 years because of spread of the mosquito vector.

There are no licensed vaccines or antiviral drugs to prevent or treat this disease. Hospitalizations are often due to systemic vascular permeability that can lead to severe dengue, which is a life-threatening condition. In response to this growing health threat, WHO has recently published the *Global strategy for dengue prevention and control, 2012–2020*.[4]

There are unique challenges for dengue vaccine development, including a lack of animal disease models, absence of immunological correlates of protection, and a potential immunopathological component in severe disease, as previous infection with dengue is a risk factor for severe disease upon secondary infection by a heterologous dengue virus. There are currently 5 vaccine candidates in human trials, all of which are tetravalent vaccines designed to protect against all 4 dengue serotypes; 3 are chimeric live attenuated vaccines and 2 are inactivated or subunit vaccines. Several other vaccine candidates are in the preclinical stage of development.

SAGE reviewed the results of the Phase IIb trial of the lead vaccine candidate, a tetravalent live attenuated vaccine. The vaccine was shown to be safe and immunogenic against dengue viruses 1, 2, 3 and 4. The overall vaccine efficacy was 30.2% (95% confidence interval: 13.4–56.6). The exploratory intention to treat analysis suggested efficacy for dengue viruses 1, 3, and 4. No efficacy was demonstrated for dengue virus 2.

A review of points for consideration for vaccine introduction highlighted the importance of country-adapted immunization and delivery strategies, a robust surveillance system, and integration with sustained vector control.

SAGE noted that dengue was an important global health issue, as it causes a major health burden in many countries and regions. Dengue is the source of significant social and economic cost, and outbreaks exert strain on already weak health-care systems. The varying virus transmission patterns in different settings and populations means that different age groups may be affected, including adults, adolescents and children.

The burden of disease needs to be better documented. In particular, dengue is underreported in Africa although more outbreaks have been reported in the past few years. SAGE strongly supported systematic stan-

[4] See http://www.who.int/denguecontrol/9789241504034/en/

## Vaccins contre la dengue

La dengue est responsable, selon les estimations, de 100 millions de cas symptomatiques, 2,1 millions de cas graves et 21 000 décès chaque année, la charge de la maladie et son étendue géographique ayant augmenté de façon spectaculaire ces 30 dernières années en raison de la propagation du moustique vecteur.

Il n'existe pas de vaccin ou de médicaments antiviraux homologués pour prévenir ou traiter cette maladie. Les hospitalisations sont souvent dues à une perméabilité vasculaire systémique, qui peut entraîner une dengue sévère, potentiellement mortelle. Face à cette menace croissante pour la santé, l'OMS a publié récemment la Stratégie mondiale de lutte contre la dengue 2012-2020.[4]

La mise au point d'un vaccin contre la dengue se heurte à des difficultés particulières, notamment l'absence de modèles animaux, l'inexistence de corrélats immunologiques de la protection et une composante immunopathologique potentielle pour la forme sévère, des antécédents d'infections par le virus de la dengue constituant un facteur de risque d'apparition d'une forme sévère lors d'une nouvelle infection par un virus hétérologue. Il existe actuellement 5 vaccins candidats en phase d'essai chez l'homme; il s'agit dans tous les cas de vaccins tétravalents conçus pour conférer une protection contre les 4 sérotypes de la dengue; 3 sont des vaccins chimères vivants atténués et 2 des vaccins inactivés ou sous-unités. Plusieurs autres vaccins en sont au stade préclinique.

Le SAGE a passé en revue les résultats de l'essai de phase IIb du principal vaccin candidat – un vaccin vivant atténué tétravalent. Il s'est avéré sûr et immunogène contre les virus de la dengue 1, 2, 3 et 4, avec une efficacité générale de 30,2% (intervalle de confiance à 95%; 13,4-56,6). L'analyse exploratoire a indiqué une efficacité contre les virus 1, 3 et 4 mais n'a en revanche démontré aucune efficacité contre le virus 2.

Un examen des points à examiner en vue de l'introduction du vaccin a souligné l'importance de stratégies d'immunisation et de vaccination adaptées à chaque pays, d'un système de surveillance solide et de l'intégration avec une lutte antivectorielle durable.

Le SAGE a noté que la dengue était à l'échelle mondiale un problème de santé important car elle est à l'origine d'une charge de morbidité majeure dans de nombreux pays et régions. Source de coûts économiques et sociaux importants, les flambées sollicitent des systèmes de santé déjà faibles. Comme les modes de transmission du virus varient selon les contextes et les populations, différents groupes d'âge peuvent être touchés: adultes, adolescents et enfants.

La charge de morbidité doit être mieux documentée. En particulier, la dengue est sous-notifiée en Afrique même si des flambées plus nombreuses y ont été signalées ces dernières années. Le SAGE a fortement soutenu la surveillance systématique stan-

[4] Voir http://www.who.int/denguecontrol/9789241504034/en/.

dardized surveillance to improve reporting of cases and understanding of dengue epidemiology.

SAGE encouraged the development of the 5 dengue vaccine candidates currently in clinical trials, particularly those with user-friendly schedules in the field. SAGE was reassured that the cost of some of the candidates should not be prohibitive. As a dengue vaccine approaches licensure, SAGE requested that independent, comprehensive cost-effectiveness and other economic analyses be undertaken, taking account of the disease epidemiology, cost of illness and health services, and the impact on households and poverty. Careful consideration will be given to data needs for global recommendations and post-registration studies on safety and effectiveness, as already discussed in WHO-led consultations, and may be needed for country decision-making.

## Polio eradication

SAGE commended the GPEI on remarkable continued progress made towards decreasing wild poliovirus transmission in the remaining endemic areas, especially in view of significant difficulties. The programme has also intensified systematic preparations for the withdrawal of oral polio vaccine type 2 (OPV2) along several key workstreams. SAGE recognised that the need to introduce IPV in up to 130 countries that use OPV over a relatively short period of time represented a major and unprecedented challenge.

SAGE noted with concern the extraordinary challenges the GPEI has faced due to the recent serious security problems encountered in Pakistan and Nigeria. Security concerns are now the key impediment to achieving progress in SIA quality in the remaining endemic areas. SAGE strongly supports ongoing initiatives in both countries to respond to and resolve the security problems affecting the polio programme. The programme should ensure that the negative impact of impaired security and access on the sensitivity of surveillance is assessed and responded to promptly.

SAGE applauded the promising recent effort in the Middle East to engage Islamic scholars and religious leaders and establish an Islamic leader task force to assist in communicating with local religious and community leaders in the remaining endemic areas. There is hope that these efforts will lead to improved and safer access of vaccination teams to children, and increase community acceptance of OPV and other EPI vaccines.

Programme updates provided to SAGE, as well as subsequent SAGE discussions, highlighted the crucial importance of involving local communities, to the maximum extent possible, in working with immunization field staff in devising and implementing innovative ways to resolve critical access and security problems. Strong efforts must be made to include women and engage women's groups in polio work, wherever possible.

dardisée afin d'améliorer la notification des cas et de mieux comprendre l'épidémiologie de cette maladie.

Le SAGE a encouragé la mise au point de 5 vaccins candidats actuellement au stade des essais cliniques, en particulier ceux dont le calendrier d'administration est facile à appliquer sur le terrain. Il s'est assuré que le coût de certains des vaccins candidats ne devrait pas être prohibitif. Étant donné qu'un vaccin est proche de l'homologation, le SAGE a demandé que des analyses indépendantes complètes du rapport coût/efficacité et d'autres aspects économiques soient entreprises en tenant compte de l'épidémiologie de la maladie, du coût de celle-ci sur les services de santé, et de l'impact sur les ménages et sur la pauvreté. Une attention particulière sera portée aux données nécessaires pour l'établissement de recommandations mondiales, et des études d'innocuité et d'efficacité posthomologation seront peut-être nécessaires pour la prise de décisions au niveau des pays, comme cela a déjà été évoqué dans le cadre des consultations menées par l'OMS.

## Éradication de la poliomyélite

Le SAGE a félicité l'IMEP des progrès continuels remarquables réalisés pour faire baisser la transmission du poliovirus sauvage dans les zones d'endémie restantes, compte tenu en particulier des difficultés rencontrées. Le programme a également intensifié les préparations systématiques en vue du retrait du vaccin antipoliomyélitique oral de type 2 (VPO2) en suivant plusieurs axes de travail essentiels. Le SAGE a reconnu que la nécessité d'introduire dans un délai relativement court le VPI dans les pays utilisant le VPO, dont le nombre peut atteindre 130, représentait un défi majeur et sans précédent.

Le SAGE a noté avec préoccupation les extraordinaires difficultés auxquelles est confrontée l'IMEP en raison des graves problèmes de sécurité rencontrés récemment au Pakistan et au Nigéria. Les préoccupations en matière de sécurité sont désormais le principal obstacle à l'amélioration de la qualité des AVS dans les zones d'endémie qui subsistent. Le SAGE soutient avec force les initiatives en cours dans les 2 pays pour résoudre les problèmes de sécurité qui affectent le programme. Celui-ci devra veiller à évaluer l'impact négatif éventuel des problèmes de sécurité et d'accès sur la sensibilité de la surveillance et à prendre rapidement des mesures.

Le SAGE s'est félicité des efforts prometteurs menés récemment au Moyen-Orient afin d'associer les chefs religieux et dignitaires islamiques et de constituer un groupe spécial islamique pour faciliter la communication avec les responsables communautaires et religieux locaux dans les zones d'endémie restantes. Ces efforts devraient, espère-t-on, permettre d'améliorer et de sécuriser l'accès des équipes de vaccination aux enfants, et mieux faire accepter le VPO et les autres vaccins du PEV par les communautés.

Les informations actualisées sur les programmes qui ont été communiquées au SAGE ainsi que les discussions qui en ont découlé au sein du Groupe ont mis en lumière l'importance cruciale de faire participer le plus largement possible les communautés locales aux travaux du personnel de vaccination sur le terrain pour mettre en place des moyens novateurs visant à résoudre les problèmes contigus d'accès et de sécurité. Des efforts importants doivent être faits pour engager, chaque fois que possible, les femmes et leurs associations dans les activités contre la poliomyélite.

SAGE noted the complexity involved in establishing vaccination requirements for travellers from endemic areas under the International Health Regulations (IHR), and encouraged the review of this issue by an Expert Review Committee under the IHR in 2014 to explore the potential value of establishing such requirements, especially in view of the WHA resolution declaring polio eradication as a programmatic emergency for global public health.

SAGE noted that the proposed timeline leading to final OPV2 withdrawal (which may occur as early as April 2016) is ambitious but both achievable and urgently needed to ensure the success of the programme. Initiating and then completing OPV2 withdrawal as soon as feasible is essential to: reduce the disease burden caused by circulating vaccine-derived poliovirus; avoid global programme fatigue and control programme cost; shorten the overall timeline towards the GPEI goal through the sequential removal of Sabin strains in order to boost global immunity against the remaining wild virus serotypes; and, potentially, to accelerate wild virus eradication in any areas of residual transmission.

SAGE agreed with the activities towards OPV2 withdrawal, as outlined by the SAGE polio working group. This will require SAGE to review suggested IPV schedules, a draft type 2 virus response protocol for the period after OPV2 cessation, and a draft IPV supply and financing strategy, at the next meeting in November 2013. 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.

SAGE highlighted several important remaining caveats for the programme to successfully achieve OPV2 withdrawal according to the timeline presented. These include the need to develop more detailed workplans for each of the main workstreams on critical OPV2 withdrawal pre-requisites, and the preparation of contingency plans for responding to possible delays or other problems.

It will be imperative also to involve, inform and work with countries as soon as possible, to assure their participation in a globally accelerated agenda for IPV introduction, followed by replacement of tOPV with bOPV for routine immunization, with a specified deadline for cessation of tOPV use in those places that have not until that point switched to bOPV (i.e. globally synchronized withdrawal of OPV2). 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.

SAGE recognized the importance of sustained funding to cover all aspects of the new 'polio endgame', including the supply and financing of IPV, as well as other costs associated with OPV2 withdrawal at country level.

Le SAGE a pris acte de la complexité que suppose l'établissement des exigences en matière de vaccination pour les voyageurs en provenance des zones d'endémie aux termes du Règlement sanitaire international (RSI), et il a appelé à ce que la question soit examinée par un comité d'experts dans le cadre du RSI en 2014, lequel serait chargé d'étudier l'utilité éventuelle de ces prescriptions, en tenant compte notamment de la résolution de l'Assemblée mondiale de la Santé déclarant que l'éradication de la poliomyélite est une urgence programmatique pour la santé publique mondiale.

Le SAGE a noté que le calendrier proposé pour le retrait définitif du VPO2 (qui pourrait intervenir dès avril 2016) est ambitieux mais réalisable et surtout nécessaire d'urgence pour garantir le succès du programme. Il est essentiel en effet de commencer à retirer le VPO dès que possible, puis d'achever ce retrait, afin de réduire la charge de morbidité entraînée par les poliovirus circulants dérivés d'une souche vaccinale; d'éviter l'usure du Programme mondial et le coût de la lutte; de raccourcir le délai final pour la réalisation de l'objectif de l'IMEP, par le retrait progressif des souches Sabin pour renforcer l'immunité au niveau mondial contre les sérotypes restants de virus sauvage; et, si possible, d'accélérer l'éradication du virus sauvage dans toute zone où subsisterait une transmission résiduelle.

Le SAGE a approuvé les activités en vue du retrait du VPO2, ainsi qu'elles ont été décrites par le groupe de travail sur la poliomyélite. Cela suppose qu'il examine les calendriers proposés pour l'introduction du VPI, un projet de protocole de réponse au virus de type 2 pour la période suivant le retrait du VPO2, et un projet de stratégie de financement et d'approvisionnement en VPI à la prochaine réunion de novembre 2013. Le SAGE a préconisé l'organisation d'une séance d'information technique sur les principales questions liées au retrait du VPO2 lors de l'Assemblée mondiale de la Santé de 2014, avant une éventuelle résolution de l'Assemblée de la Santé en 2015 sur une date cible pour le retrait du VPO2 de tous les programmes de vaccination systématique dans le monde entier.

Le SAGE a émis plusieurs avertissements importants si l'on veut que le programme réussisse à retirer le VPO2 selon le calendrier présenté. Il faudra notamment élaborer des plans de travail plus détaillés pour chacun des principaux axes de travail sur les conditions préalables au retrait du VPO2, et préparer des plans d'urgence pour faire face à des retards possibles ou autres problèmes.

Il faudra également informer les pays, les associer et travailler avec eux dès que possible pour obtenir leur participation au programme accéléré d'introduction du VPI dans le monde, suivi du remplacement du VPOt par le VPOb pour la vaccination systématique, une date butoir étant fixée pour la cessation de l'utilisation du VPOt dans les lieux qui ne seront pas encore passés au VPOb (c'est-à-dire un retrait du VPO2 synchronisé au niveau mondial). Il faudrait mettre en place des capacités suffisantes au niveau mondial pour fournir un appui technique et programmatique aux pays, afin de les aider à planifier et à mettre en œuvre toutes les activités liées au retrait du VPO2 et à l'introduction du VPI.

Le SAGE a reconnu l'importance d'un financement durable pour couvrir tous les aspects de la nouvelle «phase finale», notamment la fourniture et le financement du VPI, ainsi que des autres dépenses associées au retrait du VPO2 dans les pays. Le déficit

The remaining funding gap continues to pose a threat to the comprehensive approach required for the timely and complete implementation of endgame strategies.

SAGE appreciated the report on finalizing the 'legacy' component of the GPEI 2013–2018 Strategic Plan, and agreed that a systematic effort to document lessons learnt by the GPEI, particularly in terms of accessing chronically unreached populations, will be extremely valuable and will inform future development initiatives as well as eradication plans. Legacy planning should consider how the GPEI infrastructure and innovation could be used to strengthen routine health services. Such an initiative could be started in places where polio has been eliminated. 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. Strengths and weaknesses should be assessed. SAGE noted that, as the programme is still ongoing, a term like 'transition planning' may be preferable to 'polio legacy planning', better reflecting the transition to a world free of polio and transition of activities to other immunization and disease prevention efforts.

## Yellow fever vaccination

A report was presented from the SAGE working group on yellow fever (YF) vaccines; the group was tasked with reviewing the evidence and making recommendations to SAGE with a view to updating the 2003 WHO position paper on the use of YF vaccines. An extensive background paper was provided; it was in particular informed by 2 systematic reviews on, respectively, whether there is a need for booster doses of YF vaccine every 10 years after primary vaccination, and on the risk of serious adverse effects following immunization in the elderly.

Based on currently available surveillance data, SAGE concluded that vaccine failures are extremely rare and do not cluster as time increases after immunization. A single dose of YF vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease and a booster dose of YF vaccine is not needed. Surveillance in endemic countries and clinical studies may possibly identify specific risk groups (such as infants or HIV-infected patients) that could benefit from a second primary or booster dose. SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against YF.

Regarding the use of YF vaccine in people over 60 years of age, SAGE noted that while the risk of YF vaccine-associated viscerotropic disease in persons ≥60 years of age is higher than in younger groups, the overall risk remains low. Vaccination should be recommended based on a careful risk–benefit assessment comparing the risk of acquiring yellow fever disease versus the risk of a

du financement subsistant fait peser une menace sur l'approche globale requise pour mettre en œuvre dans les délais et complètement les stratégies de la phase finale.

Le SAGE a accueilli avec satisfaction le rapport sur la mise au point définitive de l'élément «reconversion» du plan stratégique 2013-2018 de l'IMEP, et convenu qu'un effort systématique pour tirer les enseignements de l'initiative, en particulier en ce qui concerne l'accès aux populations chroniquement mal desservies, serait extrêmement utile et orientera, pour l'avenir, les initiatives de développement et les plans d'éradication. La planification de la reconversion devrait envisager la façon dont les infrastructures et les aspects novateurs de l'IMEP pourraient être mis à profit pour renforcer les services de santé généraux. Une telle initiative pourrait être mise en place là où la poliomyélite a été éliminée. Pour documenter la «planification de la reconversion», il conviendrait de faire appel aux contributions des communautés et des agents de santé en première ligne pour connaître leur expérience du programme contre la poliomyélite, savoir ce qu'il a représenté pour eux et de quelle façon les enseignements tirés pourraient servir à améliorer encore les programmes de santé et de vaccination systématique. Il faudrait évaluer les points forts et les faiblesses. Le SAGE a fait observer qu'étant donné que le programme se poursuit, un terme comme «planification de la transition» serait peut-être préférable, et refléterait mieux la transition vers un monde exempt de poliomyélite et la transition des activités vers d'autres efforts de vaccination et de prévention de la maladie.

## Vaccination contre la fièvre jaune

Un rapport du groupe de travail du SAGE sur les vaccins antiamarils a été présenté. Le groupe avait été chargé d'examiner les données factuelles et de faire des recommandations au SAGE en vue d'actualiser la déclaration OMS de 2003 sur l'utilisation des vaccins antiamarils. Un document d'information très complet a été soumis, basé notamment sur 2 études systématiques, visant à déterminer s'il est nécessaire d'administrer des doses de rappels du vaccin antiamaril tous les 10 ans après la primovaccination et concernant aussi le risque d'effets secondaires graves consécutifs à la vaccination chez les personnes âgées.

Sur la base des données de surveillance actuellement disponibles, le SAGE a conclu que les échecs du vaccin étaient extrêmement rares et n'augmentent pas en nombre avec le temps écoulé depuis la vaccination. Une dose unique de vaccin antiamaril suffit à conférer une immunité durable et une protection à vie contre la fièvre jaune et il est inutile d'administrer une dose de rappel. La surveillance dans les pays d'endémie et des études cliniques pourraient peut-être permettre de préciser les groupes à risque (tels que les nourrissons ou les patients infectés par le VIH) qui auraient intérêt à se faire vacciner une deuxième fois ou à avoir une dose de rappel. Le SAGE a demandé à l'OMS que le RSI revoie les dispositions relatives à la période de validité des certificats internationaux de vaccination antiamarile.

Concernant l'utilisation du vaccin antiamaril chez les personnes de >60 ans, le SAGE a constaté que, si le risque de fièvre jaune vaccinale (maladie viscérotrope) chez les personnes ≥60 ans est plus important que dans les groupes plus jeunes, le risque général reste faible. La vaccination devrait être recommandée sur la base d'une évaluation soigneuse du rapport risque/avantage, en comparant le risque de contracter la fièvre jaune et le risque

potential serious adverse event following immunization for persons ≥60 years of age who have not been previously vaccinated and for whom the vaccine is recommended. Further research is needed to better quantify the risk for vaccine recipients who are ≥60 years of age and who reside in or travel to a yellow fever endemic area.

YF vaccine is not recommended for individuals who are severely immunocompromised for a range of clinically recognized reasons. YF vaccination may be offered to asymptomatic HIV-infected persons with CD4+ counts ≥200 cells/mm³ who require vaccination. There is limited clinical study data on safety and immunogenicity of YF vaccine when used in HIV-infected children. However, available data are reassuring on safety, including from a secondary analysis of safety in a mass vaccination campaign in Brazil, although the vaccine may be less immunogenic in these children. In addition, YF vaccine has been used in routine immunization programmes where HIV-infected children have been vaccinated with no safety concerns noted. SAGE therefore recommended that the vaccine may be administered to all clinically well children through immunization programmes, and that HIV testing is not a pre-requisite for vaccination in this setting.

In situations where the risk of YF disease is high and mass vaccination campaigns are undertaken, limited data has not so far indicated safety concerns for HIV-positive adults and children who are immunized in this context. SAGE therefore recommends that for mass immunization campaigns there is no requirement to establish HIV status as a prerequisite for vaccination. Additional data on safety and immunogenicity of YF vaccine, including persistence of immunity in HIV-positive adults and children should be obtained.

There are limited data on the use of YF vaccine in pregnant and lactating women. Current data do not suggest a risk of viscerotropic or neurologic disease in mothers or their fetus/newborn after immunization and there is no evidence of congenital abnormalities due to YF vaccine. There were 3 cases of virus transmission shown in lactating mothers.

Vaccination is nevertheless recommended if indicated for pregnant or breastfeeding women travelling to endemic areas when travel cannot be avoided or postponed. Both pregnant women and nursing mothers at high risk of yellow fever disease should thus be counseled regarding the benefits and potential risks of vaccination so that they can make an informed decision about vaccination. For lactating women, the benefits of breastfeeding infants far outweigh those of other nutritional alternatives.

Limited data are currently available on the safety and immunogenicity when YF vaccine is simultaneously administered with other vaccines. Although several studies have indicated that the YF and measles vaccines can be simultaneously administered without any effects on safety and immunogenicity, a single study of simulta-

de réaction postvaccinale indésirable potentiellement grave pour des personnes ≥60 ans qui n'ont pas été précédemment vaccinées et pour qui le vaccin est recommandé. De nouvelles recherches sont nécessaires afin de mieux quantifier le risque pour les personnes vaccinées ≥60 ans susceptibles de résider dans des zones d'endémie de la fièvre jaune ou de s'y rendre.

Le vaccin antiamaril n'est pas recommandé chez les personnes sévèrement immunodéprimées pour toute une série de motifs cliniques reconnus. La vaccination antiamarile peut être proposée aux personnes infectées par le VIH asymptomatiques, dont la numération des CD4+ est ≥200/mm³ et qui doivent être vaccinées. On ne dispose que de données limitées venant d'études cliniques sur l'innocuité et l'immunogénicité du vaccin antiamaril utilisé chez les enfants infectés par le VIH. Toutefois, les données disponibles sont rassurantes quant à l'innocuité, notamment d'après une analyse secondaire de ce paramètre lors d'une campagne de vaccination de masse effectuée au Brésil, même si l'immunogénicité du vaccin est peut-être moindre chez ces enfants. En outre, le vaccin antiamaril a été utilisé dans le cadre de programmes de vaccination systématique où des enfants infectés par le VIH ont été vaccinés sans que des problèmes particuliers d'innocuité n'aient été observés. Le SAGE a donc recommandé d'administrer le vaccin à tous les enfants bien portants, dans le cadre des programmes de vaccination, le test de dépistage du VIH n'étant pas une condition préalable à la vaccination dans ce cadre.

Dans les situations où le risque de fièvre jaune est élevé et où des campagnes de vaccination de masse sont entreprises, les données limitées n'ont jusqu'ici pas indiqué de problème particulier d'innocuité pour les adultes et les enfants VIH-positifs vaccinés dans ce cadre. Le SAGE recommande donc que, lors des campagnes de vaccination de masse, il ne soit pas exigé de déterminer le statut sérologique à l'égard du VIH comme condition préalable à la vaccination. Il faudrait obtenir des données supplémentaires sur l'innocuité et l'immunogénicité du vaccin antiamaril, y compris la persistance de l'immunité chez des adultes et des enfants VIH-positifs.

On ne dispose que de données limitées sur l'utilisation du vaccin antiamaril chez les femmes enceintes et allaitantes. Les données actuelles ne suggèrent pas de risque de maladie viscérotrope ou neurologique chez les mères ou le fœtus/le nouveau-né après la vaccination et il n'y a pas de signe d'anomalies congénitales dues au vaccin antiamaril. On a compté 3 cas de transmission du virus chez les mères allaitantes.

La vaccination est néanmoins recommandée si elle est indiquée pour les femmes enceintes et allaitantes se rendant dans des zones d'endémie quand elles ne peuvent ni éviter ni différer leur voyage. Il faut donc la conseiller tant aux femmes enceintes qu'aux mères allaitantes exposées à un risque élevé de fièvre jaune en tenant compte des avantages et des risques potentiels de la vaccination, afin qu'elles puissent prendre la décision de se faire vacciner ou non en toute connaissance de cause. Pour les femmes allaitantes, l'allaitement au sein présente de loin beaucoup plus d'avantages que toute autre solution d'alimentation.

On ne dispose actuellement que de données limitées sur l'innocuité et l'immunogénicité du vaccin antiamaril administré simultanément avec d'autres vaccins. Bien que plusieurs études aient montré que les vaccins antiamarils et antirougeoleux puissent être administrés simultanément sans effets sur l'innocuité et l'immunogénicité, une seule étude portant sur l'admi-

neous administration of YF and measles, mumps and rubella (MMR) vaccines in infants suggest that immunogenicity may be compromised for both YF vaccine and the rubella and mumps components of MMR vaccine. Separating MMR and YF vaccine administration by 30 days mitigated the effect. To date, there is insufficient evidence to change current recommendations and SAGE recommended that additional studies should be undertaken on the simultaneous administration of YF and other vaccines, to further inform immunization programmes.

The control strategy for YF should include sound epidemiologic surveillance, and delivery of YF vaccine through a complementary and optimized combination of routine immunization and mass preventive campaigns. Reactive campaigns should be conducted in response to yellow fever outbreaks if there is inadequate vaccination coverage within the population.

SAGE recommended that all countries with areas at risk should set time-defined objectives for the introduction of YF vaccine into their immunization programmes and to establish regional plans for controlling yellow fever.

## Non-specific effects of vaccines on mortality

SAGE previously requested that WHO review the evidence concerning the possible non-specific mortality effects of vaccines included in the routine infant immunization schedule. SAGE has now established a working group to review data on non-specific effects and consider whether current evidence is sufficient to merit adjustments in policy recommendations, or may warrant further scientific investigation and if so, to outline a path towards obtaining unequivocal evidence that would inform future robust, evidence-based adjustments in immunization policies, if warranted. SAGE recognized that there have been previous reviews on this topic by WHO committees, including reviews by the GACVS between 2000 and 2008.

SAGE was asked to review the protocols for 2 systematic reviews to assess the possible non-specific effects of vaccines: one regarding the epidemiological mortality studies and the other on human immunological studies of non-specific effects of vaccine on mortality in children <5 years of age.

SAGE noted that there are new published studies on non-specific mortality effects of vaccines and that there is a growing scientific debate on this topic. SAGE supported the proposed literature review that includes documentation of the current and proposed studies in the field. SAGE insisted that the reviewers should make efforted to include all available evidence and access all relevant data sets.

SAGE stressed that the primary focus of the working group will be to review the epidemiology on childhood mortality. The immunological review of human data will be performed to provide an additional source of evidence if the epidemiological review supports the

nistration simultanée du vaccin antiamaril et du vaccin antirougeoleux, anti-ourlien et antirubéoleux (ROR) chez le nourrisson semble indiquer que l'immunogénicité pourrait être compromise tant pour le vaccin antiamaril que pour les valences rubéole et oreillons du ROR. Un intervalle de 30 jours entre le vaccin ROR et le vaccin antiamaril limite cet effet. À ce jour, on ne dispose pas de données probantes suffisantes pour modifier les recommandations actuelles et le SAGE a préconisé d'entreprendre de nouvelles études sur l'administration simultanée du vaccin antiamaril et d'autres vaccins afin de mieux orienter les programmes de vaccination.

La stratégie de lutte contre la fièvre jaune devrait comporter une surveillance épidémiologique solide et l'administration du vaccin antiamaril dans le cadre d'une association complémentaire et optimisée de la vaccination systématique et des campagnes de prévention de masse. Des campagnes devraient être organisées pour réagir en cas de flambées de fièvre jaune si la couverture vaccinale est insuffisante dans la population concernée.

Le SAGE a recommandé que tous les pays présentant des zones à risque pour la fièvre jaune fixent des objectifs dans le temps pour l'introduction du vaccin antiamaril dans leurs programmes de vaccination et établissent des plans régionaux de lutte contre la maladie.

## Effets non spécifiques des vaccins sur la mortalité

Le SAGE avait précédemment 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. Il a maintenant créé un groupe de travail chargé d'examiner les données sur ces effets et de déterminer si, actuellement, elles suffisent pour justifier des ajustements dans les recommandations sur la politique vaccinale ou pourraient légitimer des recherches scientifiques plus poussées et, dans ce cas, de définir les moyens d'obtenir des données incontestables afin de pouvoir apporter des ajustements solides, fondés sur des données scientifiques probantes, aux politiques de vaccination le cas échéant. Le SAGE a constaté que certains comités OMS, y compris le GACVS, avaient déjà examiné la question à plusieurs reprises entre 2000 et 2008.

Le SAGE a été prié de revoir les protocoles de 2 examens systématiques pour évaluer les effets non spécifiques possibles des vaccins: l'un portant sur les études de mortalité épidémiologique et l'autre sur les études en immunologie humaine des effets non spécifiques des vaccins sur la mortalité des enfants de <5 ans.

Le SAGE a constaté que de nouvelles études avaient été publiées sur les effets non spécifiques des vaccins sur la mortalité et que le débat scientifique sur cette question prenait de l'ampleur. Il est favorable à l'examen proposé de la littérature incluant la documentation sur les études actuelles et projetées dans ce domaine. Il a insisté sur le fait que les examinateurs devraient s'efforcer de prendre en compte toutes les données disponibles et d'avoir accès aux bases de données pertinentes.

Le SAGE a souligné que le groupe de travail devait se concentrer essentiellement sur l'étude de l'épidémiologie de la mortalité chez l'enfant. L'examen immunologique des données chez l'homme sera effectué afin de fournir une source de données supplémentaires, si l'examen de l'épidémiologie révèle la néces-

need for further scientific investigation. SAGE advised that the reviews should focus on mortality as an outcome, and that the vaccines under review should be limited to BCG, DPT and measles, without including high titre measles vaccines, additional vaccines or animal studies at this point. SAGE also noted that the immunological studies should focus primarily on specific immune markers identified in previous studies as being affected by these vaccines.

## Vaccine hesitancy

Vaccine hesitancy and refusal is not a new phenomenon, although more attention has been paid to it in recent years. The concept of vaccine hesitancy is reflected in the GVAP as the value of vaccines to individuals and communities. Vaccine hesitancy occurs when an individual delays or refuses to accept a vaccine that is otherwise available; it exists on a spectrum, with some people accepting selected vaccines, and some refusing all vaccines. There are, of course, several other causes of non-vaccination such as access, supply limitations and cost.

SAGE was presented with a definition and framework for vaccine hesitancy that relates to issues of confidence (e.g. trust), complacency (e.g. perceived risk of disease), and convenience (e.g. health systems). There are many contextual influences, individual/social group influences, and vaccine-specific and vaccination-specific issues. Examples include influence of the media, experience with past vaccination, and knowledge of vaccine-preventable diseases. There is a need to identify the key determinants in each specific situation to determine the best strategy to address it. A literature review was carried out to assess the causes and impact of vaccine hesitancy, identifying studies from all WHO regions. The number of articles published in the last 5 years has doubled, many of which focus on human papillomavirus and influenza vaccines. Factors that were identified in the review as related to vaccine hesitancy could serve either as promoters or barriers, depending on the context.

In a preliminary review of strategies implemented to address vaccine hesitancy, it was found that few strategies in the published literature have been evaluated for effectiveness. Most evaluations of strategies are limited to outcomes such as knowledge and awareness, but the relationship between knowledge, awareness and impact is unclear. The published literature is limited, especially from regions where the majority of the world's children live. A review of the grey literature will be performed drawing in particular on the experience with strategies used to address polio vaccine refusal. More broadly, lessons can also be drawn about refusal of other health interventions and strategies to address it.

The impact of vaccine hesitancy on immunization programmes is not fully understood, in part because of the lack of metrics, and the lack of investigation in most countries. SAGE recognized the importance of measuring vaccine hesitancy with feasible readily applicable

sité d'investigations scientifiques plus poussées. Le SAGE a préconisé que les examens se concentrent sur la mortalité en tant que résultat et que l'examen se limite au BCG, au DTC et au vaccin antirougeoleux, à l'exclusion des vaccins antirougeoleux à titre élevé, d'autres vaccins ou d'études animales pour le moment. Il a également noté que les études immunologiques devraient avant tout porter sur les marqueurs immunitaires spécifiques repérés lors d'études antérieures et affectés par ces vaccins.

## Hésitation à l'égard des vaccins

L'hésitation à l'égard des vaccins et le refus de ceux-ci ne sont pas un phénomène nouveau même si l'on y a accordé davantage d'attention ces dernières années. Ce concept d'hésitation se retrouve dans le Plan d'action mondial pour les vaccins au niveau de la valeur accordée aux vaccins par les individus et les communautés. On observe le phénomène lorsqu'un individu retarde ou refuse un vaccin disponible; elle est variable, certaines personnes acceptant certains vaccins et d'autres refusant tous les vaccins. Il existe, bien sûr, plusieurs autres causes à la non-vaccination, telles que des problèmes d'accès, de limitation de l'offre et de coût.

On a proposé au SAGE une définition et un cadre pour l'hésitation à l'égard des vaccins qui relient les problèmes de confiance, de sous-estimation de la menace (risque perçu de la maladie, par exemple) et de commodité (par exemple systèmes de santé). On observe de nombreuses influences contextuelles, des influences de l'individu/du groupe social et des problèmes liés spécifiquement à la vaccination ou aux vaccins. On citera par exemple l'influence des médias, les expériences antérieures de vaccination et la connaissance des maladies évitables par la vaccination. Il est nécessaire de recenser les principaux déterminants dans chaque situation particulière afin de déterminer la meilleure stratégie pour y répondre. Un examen de la littérature a été effectué pour évaluer les causes et l'impact du phénomène, des études ayant été recensées dans toutes les Régions de l'OMS. Le nombre d'articles publiés au cours des 5 dernières années a doublé, beaucoup étant consacrés aux vaccins contre le papillomavirus humain et contre la grippe. Les facteurs identifiés dans l'étude comme liés à cette hésitation pourraient servir de promoteurs ou d'obstacles selon le contexte.

Lors de l'examen préliminaire des stratégies mises en œuvre pour remédier à l'hésitation à l'égard des vaccins, on a constaté que, dans la littérature publiée, il y avait peu de stratégies dont l'efficacité avait été évaluée. La plupart des évaluations se limitent aux effets tels que la connaissance ou la sensibilisation, mais le lien entre les connaissances, la sensibilisation et l'impact reste absent. La littérature publiée est limitée, notamment dans les régions où vivent la majorité des enfants du monde. Une revue de la littérature grise sera effectuée, en se basant en particulier sur les stratégies utilisées pour lutter contre le refus du vaccin antipoliomyélitique. Plus généralement, des enseignements peuvent aussi être tirés du refus d'autres interventions sanitaires et des stratégies utilisées pour y remédier.

L'impact du phénomène sur les programmes de vaccination n'est pas entièrement compris, notamment faute de métrologie et de recherche dans la plupart des pays. Le SAGE a reconnu l'importance qu'il y avait à mesurer ce facteur au moyen d'indicateurs facilement applicables et constaté que les indicateurs

indicators, noting that the SAGE proposed GVAP indicators for vaccine hesitancy are currently being field tested and will be reviewed.

SAGE recognized that research is needed in this area, including the need to develop evidence-based strategies and to assess and quantify the impact of hesitancy on immunization programmes overall. In many settings training of researchers in behavioural research and capacity building will be needed to sensitize countries to the issues around vaccine hesitancy.

SAGE recognized that the working group had completed a significant amount of background work which provided a valuable contribution to understanding vaccine hesitancy, and stressed that vaccine hesitancy remains a major concern in all regions and all countries in different populations and at different times. SAGE recommended that the working group reconsider the name and definition of vaccine hesitancy to avoid confusion and ensure that hesitancy is discussed with a common understanding. 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".

SAGE endorsed the effort to review successful interventions in health-related fields beyond immunization, aiming at improving confidence and increasing demand. SAGE supported the development of diagnostic tools to identify the context-specific cause(s) of hesitancy and to differentiate hesitancy from the many other reasons why children are not vaccinated or under-vaccinated. Such tools would help guide strategies to address the underlying causes.

SAGE recommended that interviews with immunization managers could be useful to understand challenges on the ground in a variety of contexts. There was agreement there should be recommendations for evidence-based strategies, for which different methodologies could be used, such as probe studies. While these strategies have so far focused on responding to vaccine hesitancy, attention should also be paid to where vaccine hesitancy could potentially become a problem following introduction of new vaccines or new services. Recommendations should be developed with regard to demand creation and proactive interventions. SAGE recommended close linkages and interaction with key WHO and UNICEF initiatives to address the unvaccinated or under-vaccinated groups and relevant interventions.

### *Haemophilus influenza* type b (Hib) immunization schedules

Following a session on this topic during the SAGE meeting in November 2012, SAGE asked that a revised summary of the evidence, including GRADE tables, be presented to SAGE in April 2013.

SAGE was requested to consider the optimal Hib immunization schedules for children in different epidemiological settings. SAGE was informed by: (i) 3 sys-

du GVAP, proposés par le SAGE dans ce domaine, étaient actuellement expérimentés sur le terrain et seront examinés.

Le SAGE a reconnu que des recherches sont nécessaires dans ce domaine, avec notamment la nécessité d'élaborer des stratégies fondées sur des données factuelles et d'évaluer et de quantifier l'impact de l'hésitation sur les programmes de vaccination dans leur ensemble. Dans de nombreuses situations, une formation des chercheurs en recherche comportementale et un renforcement des capacités seront nécessaires pour sensibiliser les pays à ces questions.

Le SAGE a reconnu que le groupe de travail avait effectué un travail de fond important qui apportait une contribution précieuse à la compréhension du problème; il a insisté sur le fait que l'hésitation vis-à-vis des vaccins restait une préoccupation majeure dans toutes les régions et tous les pays quelles que soient les populations et les époques. Il a recommandé que le groupe de travail reconsidère la terminologie et la définition pour éviter toute confusion et veiller à ce que tous les interlocuteurs soient d'accord lorsqu'ils s'expriment sur la question. Le SAGE a suggéré que la définition comporte le libellé «lorsque l'acceptation d'un vaccin ou d'un programme de vaccination par une communauté est plus faible que prévu compte tenu des informations fournies et des services disponibles».

Le SAGE a approuvé les efforts visant à examiner les interventions efficaces dans des domaines de santé au delà de la vaccination, à améliorer la confiance et à accroître la demande. Il a soutenu la mise au point d'outils de diagnostic permettant de déterminer la ou les causes d'hésitation selon le contexte, et de différencier celles-ci des nombreuses autres raisons faisant que les enfants ne sont pas ou pas suffisamment vaccinés, et qui pourraient aider à orienter utilement les stratégies.

Le SAGE a estimé que des entretiens avec les responsables de la vaccination pourraient être utiles pour mieux comprendre les difficultés sur le terrain dans divers contextes. Il a convenu que des recommandations pour l'établissement de stratégies fondées sur des données factuelles devraient être élaborées, différentes méthodologies pouvant être utilisées telles que des études par sondage. Si ces stratégies se sont concentrées jusqu'ici sur les réponses à apporter au problème, il faudrait également diriger l'attention là où les réticences pourraient devenir un problème après l'introduction de nouveaux vaccins ou de nouveaux services. Des recommandations devraient être mises au point pour la création de la demande et des interventions proactives. Le SAGE a recommandé des liens et des échanges étroits avec les principales initiatives de l'OMS et de l'UNICEF pour remédier à la non-vaccination ou à la sous-vaccination et autres interventions pertinentes.

### Calendriers de vaccination contre *Haemophilus influenza* type b (Hib)

Suite à une séance sur le sujet au cours de sa réunion de novembre 2012, le SAGE a demandé qu'un résumé révisé des données factuelles, avec des tableaux GRADE, lui soit présenté en avril 2013.

Le SAGE était invité à examiner les calendriers de vaccination optimaux contre le Hib pour les enfants dans différents contextes épidémiologiques. Il a été saisi: i) de 3 études systé-

tematic reviews on Hib immunization schedules (2 reviews of RCTs, and 1 of observational studies), (ii) a Cochrane review on Hib combination vaccines (iii) a descriptive review of Hib disease and Hib vaccination in England and Wales, (iv) a review of the long term impact of Hib vaccine in 35 countries which had introduced the vaccine > 5 years ago, (v) a global review of the epidemiology of Hib disease in children, (vi) a systematic review of Hib vaccine herd effects and (iv) <100 published and unpublished reports of Hib vaccine impact. The outcomes of these reviews were used to refine the assumptions and parameters of a Hib vaccine schedules model, particularly in relation to duration of protection, herd immunity and efficacy/effectiveness of various Hib vaccine schedules.

Selecting the optimal schedule for Hib-containing vaccines is a complex process which needs to take into consideration the following: (i) efficacy and effectiveness of various Hib vaccine schedules; (ii) age-distribution of Hib disease; (iii) vaccine presentation (monovalent Hib vaccine versus combined with other antigens); (iv) potential to administer all recommended doses on time and achieve high coverage and; (v) contact opportunities for provision of other health interventions and other vaccines. In addition, other elements require consideration including: (i) interplay between carriage rates in the pre-vaccine era and reduction of carriage and potential for natural boosting after vaccine introduction; (ii) herd immunity and the force of infection; and (iii) changes in Hib disease epidemiology over time since introduction of Hib vaccine in the country.

SAGE recommended that any one of the following Hib immunization schedules may be used: 3 primary doses without a booster (3p+0); 2 primary doses plus a booster (2p+1); and 3 primary doses with a booster (3p+1). The interval between doses should be at least 4 weeks if 3 primary doses are given, and at least 8 weeks if 2 primary doses are given. Booster doses may be administered at 11 months or during the second year of life. The age at first dose should be determined based on the local epidemiology, vaccine presentation (Hib monovalent vaccine versus combination) and how this fits into the overall routine immunization schedule. In most developing countries the first dose should be given at 6 weeks of age or soon thereafter. Hib vaccine is not required for healthy children after 5 years of age as almost all of the Hib disease occurs prior to this age. In countries where the majority of severe Hib disease burden is in young infants, it is more beneficial to provide 3 doses of vaccine early in life. In some settings (e.g. where the greatest disease morbidity and mortality occur later, in the presence of herd immunity, or where rate reductions of disease are not fully sustained after the routine use of Hib vaccine), it might be advantageous to give the 3rd dose as a booster dose or to add a 4th dose as a booster to a 3-dose primary schedule at an age appropriate to local epidemiology.

matiques sur les calendriers de vaccination anti-Hib (2 études portant sur des essais contrôlés randomisés et 1 étude d'observation); ii) d'une étude Cochrane sur les vaccins anti-Hib en association; iii) d'une étude descriptive de la maladie due au Hib et de la vaccination anti-Hib en Angleterre et au Pays de Galles; iv) d'une étude sur les répercussions à long terme du vaccin anti-Hib dans 35 pays qui l'ont introduit il y a >5 ans; v) d'une étude mondiale sur l'épidémiologie du Hib chez l'enfant; vi) d'une étude systématique des effets du vaccin anti-Hib sur l'immunité collective; et vii) de <100 rapports publiés et non publiés sur l'impact du vaccin anti-Hib. Les résultats des études susmentionnées ont été utilisés pour affiner les hypothèses et les paramètres concernant les modèles de calendriers de vaccination anti-Hib, en particulier eu égard à la durée de protection, à l'immunité collective et à l'efficacité/performance des divers calendriers.

Le choix d'un calendrier optimal pour les vaccins à valence Hib est un processus complexe qui doit prendre en considération les points suivants: i) l'efficacité et la performance des divers calendriers de vaccination anti-Hib; ii) la répartition de la maladie due au Hib selon l'âge; iii) la présentation du vaccin (vaccin anti-Hib monovalent ou vaccin associant d'autres antigènes); iv) la possibilité d'administrer toutes les doses recommandées dans les délais et d'obtenir une couverture élevée; et v) les possibilités de contact pour la fourniture d'autres interventions sanitaires et l'administration d'autres vaccins. De plus, d'autres éléments doivent être pris en compte, à savoir: i) l'interaction entre les taux de portage pendant la période précédant la vaccination et la réduction du portage et des possibilités de renforcement de l'immunité naturelle après l'introduction de la vaccination; ii) l'immunité collective et la force de l'infection; et iii) les changements intervenus dans l'épidémiologie du Hib dans le temps depuis l'introduction du vaccin anti-Hib dans le pays.

Le SAGE a recommandé que chacun des 3 calendriers anti-Hib suivant pouvait être utilisé: primovaccination avec 3 doses sans rappel (3p+0); primovaccination avec 2 doses plus 1 rappel (2p+1); et primovaccination avec 3 doses plus 1 rappel (3p+1). L'intervalle entre les doses devrait être d'au moins 4 semaines si l'on administre 3 doses et d'au moins 8 semaines si l'on administre 2 doses pour la primovaccination. Les doses de rappel peuvent être administrées à 11 mois ou au cours de la deuxième année de vie. L'âge d'administration de la première dose devrait être déterminé sur la base de l'épidémiologie locale, de la présentation du vaccin (vaccin monovalent ou en association) et de la façon dont elle s'inscrit dans le calendrier général de la vaccination systématique . Dans la plupart des pays en développement, la première dose devrait être administrée à l'âge de 6 semaines ou peu après. Le vaccin anti-Hib n'est pas exigé pour les enfants en bonne santé après 5 ans car la plupart des cas surviennent avant cet âge. Dans les pays où l'essentiel de la charge de morbidité grave due au Hib concerne les jeunes enfants, il est plus efficace d'administrer 3 doses de vaccin tôt dans la vie. Dans certaines situations (par exemple là où la plus forte charge de morbidité et la mortalité interviennent plus tard, en présence d'une immunité collective, ou parce que la réduction de l'incidence de la maladie ne persiste pas pleinement après l'utilisation systématique du vaccin anti-Hib), il pourrait être avantageux d'administrer la troisième dose sous forme de rappel ou d'ajouter à un âge adapté selon l'épidémiologie locale, une quatrième dose sous forme de rappel au calendrier de 3 doses pour la primovaccination.

SAGE identified the following knowledge gaps that require further research: (i) impact on immunological responses and disease outcomes of 4 week versus 2 month intervals between primary doses, when only 2 primary doses are administered, especially in developing countries; (ii) impact of different schedules with and without the use of booster doses on immunological responses and disease outcomes when different schedules are used, especially in developing countries; (iii) duration of protection in different epidemiological settings using different schedules; (iv) possible lower effectiveness of Hib vaccines when combined with acellular pertussis vaccines; (v) population impact of Hib vaccine in settings with high HIV prevalence.

SAGE welcomed and endorsed the use of the Hib vaccine schedules model developed by the London School of Hygiene and Tropical Medicine and presented during this meeting. It is designed to provide a simple tool to assist countries in choosing appropriate schedules by illustrating the impact of different vaccination regimens on invasive Hib disease in different epidemiological scenarios.

SAGE emphasized the importance of establishing and maintaining high quality surveillance for Hib disease, in order to monitor the impact and changes in disease epidemiology over time. Some countries have observed a small increase in disease incidence several years after vaccine introduction but these increases have been small relative to the overall Hib disease reductions following vaccine introduction. When increases in the incidence of Hib cases are observed, investigation should be initiated promptly and include documentation of the age, Hib vaccination status, time since last Hib doses, and HIV status of cases.

SAGE noted with concern that despite the issuance of a WHO recommendation in 2006 calling for the universal introduction of Hib vaccines in routine immunization programmes and the demonstrated impact of the vaccine, 9% (17/194) of the member states have still not yet introduced the vaccine. SAGE urged policy makers in these countries to support the introduction of Hib vaccines.

## Malaria vaccines

Malaria continues to make a significant contribution to the global disease burden, with an estimated 660 000 deaths (range 490 000–836 000) in 2010. New tools are needed to combat the disease, as currently effective measures such as long-lasting insecticidal nets and artemisinin-based combination therapies are threatened by insecticide and drug resistance. There are currently several *Plasmodium falciparum* malaria vaccines in clinical trials, most of which are targeted at the pre-erythrocytic and blood stages of the parasite; there is only one *P. vivax* vaccine currently in clinical trials. The lead malaria vaccine candidate RTS,S/AS01 is being studied in a Phase III multi-centre efficacy trial conducted in 11 centres in 7 African countries. With over 12 months of follow-up post dose 3, the according-to-protocol vaccine efficacy against all clinical malaria episodes was estimated at 55.1% (95% CI, 50.5-59.2) in

Le SAGE a recensé les lacunes des connaissances qui imposent des recherches plus poussées: (i) l'impact sur la réponse immunologique et l'issue de la maladie lorsque les 2 doses de la primovaccination sont administrées à un intervalle de 4 semaines au lieu de 2 mois, notamment dans les pays en développement; (ii) l'impact des différents calendriers avec ou sans dose de rappel sur la réponse immunologique et l'issue de la maladie, en particulier dans les pays en développement; (iii) la durée de protection dans différentes situations épidémiologiques selon que l'on utilise divers calendriers; (iv) l'efficacité éventuellement plus faible des vaccins anti-Hib lorsqu'ils sont associés aux vaccins anticoquelucheux acellulaires; (v) l'impact dans la population du vaccin anti-Hib dans les situations de forte prévalence du VIH.

Le SAGE s'est félicité de l'utilisation du modèle de calendriers de vaccin anti-Hib mis au point par la *London School of Hygiene and Tropical Medicine* présenté lors de la réunion. Il s'agit d'un outil simple pour aider les pays à choisir les calendriers adaptés en illustrant l'impact des différents schémas de vaccination sur l'infection invasive à Hib, selon différents scénarios épidémiologiques.

Le SAGE a souligné l'importance d'établir et de maintenir une surveillance de qualité de la maladie à Hib, afin de surveiller l'impact sur l'épidémiologie de la maladie et son évolution dans le temps. Certains pays ont observé une légère augmentation de l'incidence plusieurs années après l'introduction du vaccin mais ces augmentations ont été faibles par rapport à la baisse générale qui a suivi l'introduction du vaccin. Lorsque des augmentations d'incidence du Hib sont observées, il conviendrait d'entamer rapidement des investigations et d'étudier notamment l'âge, le statut vaccinal vis-à-vis du Hib, le temps écoulé depuis les dernières doses de vaccin administrées et le statut sérologique vis-à-vis du VIH des sujets.

Le SAGE a noté avec préoccupation que, malgré la publication d'une recommandation de l'OMS en 2006 appelant à l'introduction universelle des vaccins anti-Hib dans les programmes de vaccination systématique et l'impact démontré du vaccin, 9% des États Membres (17 sur 194) n'ont toujours pas introduit celui-ci. Le SAGE a prié instamment les décideurs de ces pays d'appuyer l'introduction des vaccins anti-Hib.

## Vaccins antipaludiques

Le paludisme continue de contribuer fortement à la charge mondiale de morbidité avec, selon les estimations, 660 000 décès (490 000-836 000) en 2010. De nouveaux outils sont nécessaires pour lutter contre la maladie, étant donné que les mesures efficaces actuellement disponibles, telles que les moustiquaires à imprégnation durable et les combinaisons thérapeutiques à base d'artémisinine sont menacées par la résistance aux insecticides et aux médicaments. Plusieurs vaccins contre le paludisme à *Plasmodium falciparum* en sont actuellement au stade des essais cliniques, la plupart ciblant les stades sanguins et préérythrocytaires du parasite; il n'y a pour l'instant qu'un seul vaccin contre *P. vivax* au stade des essais cliniques. Le principal vaccin candidat contre le paludisme, le RTS,S/AS01, est actuellement étudié dans le cadre d'un essai d'efficacité multicentrique en phase III mené dans 11 centres de 7 pays africains. Avec >12 mois de suivi après l'administration de la troisième dose, l'efficacité du vaccin selon le protocole contre tous les

the 5–17 month age group and 33.0% (95% CI 26.4-38.9) in the 6–12 weeks age group. The Joint Technical Expert Committee (JTEG), which reports jointly to SAGE and the Malaria Policy Advisory Committee (MPAC), has reviewed available data from the Phase III trial for potential policy implications. There was a substantial difference between the efficacy results in the 2 age groups, though possibly confounded by transmission intensity and a differential contribution of cases from various sites between the age groups that could affect the overall efficacy estimates. Remaining questions include how efficacy changes with time since vaccination, transmission intensity, and seasonality, as well as the impact of co-administration with pentavalent vaccine, maternally acquired antibody, prior hepatitis B vaccination, and age or prior exposure to malaria. The lead malaria vaccine candidate will be evaluated as an addition to, and not as a replacement for existing preventive, diagnostic and treatment measures. Pending all data and analyses being available by 2015, and depending on the regulatory submission timings, malaria vaccine policy recommendations will be made in the last quarter of 2015 during a joint session of SAGE and MPAC.

épisodes palustres cliniques a été estimée à 55,1% (IC à 95% 50,5-59,2) dans le groupe d'âge 5 17 mois et à 33,0% (IC à 95% 26,4-38,9) dans le groupe d'âge 6-12 semaines. Le Comité conjoint d'experts techniques (JTEG), qui rend compte à la fois au SAGE et au Comité consultatif de la Politique antipaludique (MPAC), a passé en revue les données disponibles à l'issue de cette phase III pour en étudier les répercussions possibles au plan des politiques. Il a observé une différence substantielle dans les résultats concernant l'efficacité entre les 2 groupes d'âge, peut-être due toutefois à l'intensité de la transmission et à un nombre de cas différents selon les groupes d'âge dans les différents sites qui ont pu se répercuter sur les estimations générales de l'efficacité. Certaines questions subsistent, notamment comment évolue l'efficacité avec le temps écoulé depuis la vaccination, avec l'intensité de la transmission et avec le caractère saisonnier ainsi que l'impact de l'administration concomitante du vaccin pentavalent, des anticorps transmis par la mère, des antécédents de vaccination contre l'hépatite B et de l'âge ou de l'exposition préalable au paludisme. Le principal vaccin candidat sera évalué en vue de l'ajouter aux mesures de prévention de diagnostic et de traitement existantes et non de s'y substituer. En attendant que la totalité des données des analyses soient disponibles d'ici 2015, et en fonction des délais de soumission réglementaires, des recommandations relatives à une politique en matière de vaccin antipaludique seront formulées au dernier trimestre de 2015 lors d'une session conjointe du SAGE et du MPAC.

SAGE was also updated on the Malaria Vaccine Technology Roadmap originally launched in 2006 and focused on *P. falciparum*, the under-5 year age group, and prevention of severe disease and death. Changing malaria epidemiology has rendered parts of the 2006 Roadmap out of date, and it is currently being revised. The updated version includes consideration of both *P. falciparum* and *P. vivax*. The updated strategic goals include both a focus on the traditionally targeted at-risk groups in endemic areas, and on transmission reduction that could enable elimination in multiple settings. Two sets of WHO Preferred Product Characteristics (PPCs) will be developed in 2013-2014 and will provide technical guidance for vaccine developers at early stages of vaccine research and development to address both of these strategic goals. Innovation is still greatly encouraged. PPCs are not static exit criteria and will not replace standard policy or pre-qualification processes.

Le SAGE a également actualisé la feuille de route sur la technologie du vaccin antipaludique présentée à l'origine en 2006 et axée sur *P. falciparum*, le groupe d'âge des <5 ans, ainsi que la prévention des cas graves et des décès. L'évolution de l'épidémiologie du paludisme fait que certaines parties de la feuille de route de 2006 sont dépassées et elle est actuellement en cours de révision. Dans la version actualisée, on prend en compte à la fois *P. falciparum* et *P. vivax*. Des objectifs stratégiques révisés portent à la fois sur les groupes traditionnellement à risque des zones d'endémie et sur une réduction de la transmission qui pourrait permettre l'élimination dans de nombreux contextes. Deux séries de caractéristiques préférées par l'OMS pour les produits (PPC) seront mises au point en 2013-2014 afin de proposer des orientations techniques aux fabricants de vaccins dès les stades précoces de la recherche-développement, afin de prendre en considération ces 2 objectifs stratégiques. L'innovation est toujours vivement encouragée. Les PPC ne sont pas des critères de sortie définis une fois pour toutes et ne remplaceront pas les processus de préqualification ou les politiques normatives.

SAGE reaffirmed that malaria vaccine development remains a global imperative. SAGE recognized that countries will be under much political pressure to introduce a malaria vaccine when available. Because early results suggest that the vaccine is partially efficacious, and efficacy may differ by age group and transmission intensity, careful guidance from WHO will be essential so that countries can make appropriate decisions about introduction. SAGE strongly supported modeling and cost-effectiveness studies, which will have a critical role to play. SAGE recommended that in addition to the traditional parameters included in models, there be consideration of a potential interaction with different levels of use of existing preventive measures, and other factors that might alter vaccine efficacy. SAGE further

Le SAGE a réaffirmé que la mise au point d'un vaccin antipaludique restait un impératif mondial. Il a reconnu qu'une fois disponible, les pays subiraient des pressions politiques considérables pour le mettre en circulation. Les premiers résultats laissant entendre que le vaccin n'est que partiellement efficace et que l'efficacité peut varier d'un groupe d'âge à un autre et selon l'intensité de la transmission, il sera indispensable que l'OMS formule des orientations rigoureuses à l'intention des pays afin que ceux-ci puissent prendre les décisions qui s'imposent quant à l'introduction du vaccin. Le SAGE est très favorable à des études de modélisation et du rapport coût/efficacité qui auront un rôle essentiel à jouer. Il a recommandé qu'en plus des paramètres traditionnels pris en compte par ces modèles, on envisage une interaction potentielle avec les différents niveaux d'utilisation des mesures de prévention existantes et

suggested that consideration be given to analyses on the role of maternal antibody transfer, and nutritional and HIV status. SAGE strongly supported the extended follow-up of Phase III study participants as well as investigation of various immunization schedules, including a novel 6-month visit and consideration of use of the 9-month visit. SAGE was very supportive of Phase IV studies, which are critical to determine the duration of protection and for pharmacovigilance. SAGE strongly acknowledged the need for ongoing malaria surveillance, noting the changes in epidemiology already occurring within regions and the possible impact of vaccination on the age pattern of morbidity, herd immunity, as well as the possible, unconfirmed relationship between transmission intensity and vaccine efficacy.

SAGE emphasized the need to evaluate the acceptability of the vaccine and community communication strategies, given the partial efficacy of the vaccine, in order to avoid undermining confidence in all vaccines.

SAGE strongly endorsed the early engagement between WHO and regulatory authorities regarding the lead malaria vaccine candidate, particularly with countries which may soon be asked to consider licensure of a malaria vaccine product. SAGE was encouraged by the interaction with the European Medicines Agency and would support a flexible approach when the agency reviews the product, to include consideration of the public health impact as part of the evaluation. 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. ■

d'autres facteurs susceptibles de modifier l'efficacité du vaccin. Le SAGE a en outre suggéré d'envisager des analyses sur le rôle du transfert des anticorps maternels, de l'état nutritionnel et du statut sérologique vis-à-vis du VIH. Il a vivement encouragé un suivi prolongé des participants à l'étude en phase III ainsi que des investigations sur les divers calendriers de vaccination, y compris une nouvelle visite à 6 mois et un recours éventuel à une visite à 9 mois. Le SAGE est très favorable aux études en phase IV, qui sont essentielles pour déterminer la durée de la protection et pour la pharmacovigilance. Il a reconnu sans réserve la nécessité d'une surveillance permanente du paludisme, notant les changements qui interviennent déjà dans l'épidémiologie à l'intérieur des Régions et l'impact possible de la vaccination sur les groupes d'âge touchés, la morbidité, l'immunité collective, ainsi qu'une relation éventuelle non confirmée entre l'intensité de la transmission et l'efficacité vaccinale.

Le SAGE a souligné la nécessité d'évaluer l'acceptabilité du vaccin et les stratégies de communication dans la communauté, compte tenu de l'efficacité partielle du vaccin de façon à éviter une remise en cause de la confiance dans les vaccins en général.

Le SAGE a approuvé la collaboration précoce entre l'OMS et les autorités de réglementation concernant le principal vaccin candidat contre le paludisme, en particulier avec des pays qui pourraient rapidement être appelés à envisager l'homologation d'un produit vaccinal antipaludique. Il a été encouragé par les échanges avec l'Agence européenne du Médicament et serait favorable à une approche souple lorsque l'Agence examinera le produit, afin de prendre en considération l'impact sur la santé publique dans le cadre de l'évaluation. Le SAGE a noté l'utilité des PPC pour ceux qui mettent au point le vaccin et les bailleurs de fonds, et a proposé d'offrir la possibilité de contribuer à l'établissement de futurs PPC à un stade précoce pour tout vaccin considéré comme important pour la santé publique dans le cadre de son mandat mondial de santé publique. ■


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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 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 | Pending | 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 SAGE November 2012 meeting, SAGE further requested ECBS to prepare guidance for national regulatory authorities on studies needed to support evidence-based off-label use of vaccines which 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. |
| General | SAGE noted the important potential of immunization programmes for strengthening the overall health system, suggesting that good examples be documented and shared. | Action | Nov 2011 | Ongoing | An analysis of health systems impact of new vaccine introduction was presented to SAGE in April 2012. SAGE endorsed revised principles for adding a vaccine to a national immunization system while strengthening the immunization and health systems and endorsed the proposal that the 2005 WHO Vaccine Introduction Guidelines be updated to assist decision-makers and managers with identifying and taking opportunities to strengthen the health system through new vaccines introduction.<br><br>The Vaccine introduction guidelines are now updated and in print |
| General | SAGE recommended that ways to improve curricula for medical personnel should be explored. | Action | Nov 2008 | Ongoing | The African region started to work with academia to develop a pre-service curricula for nursing and medical staff. Annual courses for medical and nursing staff take place in collaboration with Network for education and support in immunization (NESI).<br>An evaluation of the impact of pre/service training and curricula changes is ongoing in 9 countries in AFRO. An evaluation was conducted in late 2011 and a draft report has been prepared but it is not available for wider circulation yet. It first needs approval from countries involved. A report was expected for early 2013 yet this report was not recieved by October 2013. |
| 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 | 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. TIP was implemented in Bulgaria and on three projects in Sweden (Somali immigrants, migrants and anthroposophic communities) and Bulgaria. In 2013, TIP is to be implemented in France and use in Romania and in Israel and Tajikistan is planned for2014. A tool assessment is planned in 2014 and expansion to other regions that have expressed interest. 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. |

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| General | SAGE requested to add strategies to reach older age groups and the issue of immune senescence on their list of agenda items for a future meeting. | Action | Apr 2013 | Done | These two agenda items have now been added on the list of topics on the horizon for SAGE. |
| General | SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage. | Action | Apr 2013 | Ongoing | Teleconference 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. |
| 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.<br>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 2013:<br>• investigation of measles outbreak in Jordan, that affected Syrian refugees<br>• Investigation of measles outbreak in Lebanon that affected the Syrian refugees<br>• implementation of multi antigen vaccination campaign in the 2 provinces hosting the refugees camps in Jordan<br>• resource mobilization and planning for the national MR/Polio synchronized campaigns in Syria and the surrounding countries (Syria, Jordan and Iraq)<br>• provided support to Tunisia for recruiting technical staff to support EPI<br>• Conducting comprehensive EPI review in Yemen, including DQS and PIE<br>• Conducting EVM in Yemen |
| 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 keys partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines. | Pending | Nov 2010 | Ongoing | Activities to lead to better vaccine price information and vaccine pricing transparency have being considered and under discussion for sufficient funding. Contribution of WHO to the DoV work stream on global access and vaccine price indicator and report. IVB staff are actively participating 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. Discussions have taken place with DCVMN as such and individual DCVMN members to consult on potential and actual role of emerging manufactuers in supplying affordable vaccines. This could be followed by offering the possibility for bilateral meetings with manufacturers to discuss this issue as well as exchange on strategic orientations as this is already being done with some members of The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster.<br><br>IVB has launched a new project on vaccine product, price and procurement V3P). The purpose of the project is to support GAVI graduating and middle income countries to accelerate the introduction of new vaccines through the provision of improved vaccine product and price information for decision-making. It is a 3-year project funded by the BMGF. Country needs assessments and review of experiences on price information sharing mechanisms have been conducted in 2012, a V3P database and capacity building activities are under development in close collaboration with partners to support countries and facilitate dialogue on price transparency and pricing policies. V3P is only one piece of work. Many other initiatives and activities are under way and others should be developed, in a coordinated manner, to make vaccines available and affordable to countries and to support emerging manufacturers to be competitive and innovative. |

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| Childhood mortality | SAGE noted the recommendation by QUIVER (now 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.<br>Specically, 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. |
| Cholera vaccines | Oral Cholera Vaccines(OCVs) - SAGE will further consider their use in endemic countries and whether a stockpile should be developed, particularly as current manufacturing capacity is limited. | Action | Apr 2011 | Completed | OCV stockpile: A meeting on use of oral cholera vaccines (OCVs) in complex emergencies was held in early May 2011, and also in May 2011 the WHA passed a resolution(64.15) calling for an integrated, comprehensive strategy of cholera prevention and control. In April 2012, a meeting of the WHO Technical Working Group on creation of an oral cholera vaccine stockpile was convened by the Pandemic and Epidemic Diseases Dept (WHO HQ) to develop SOPs for implementation of the OCV stockpile for outbreak response, including definition of specific criteria for deployment of vaccine from the stockpile. An agreement for procurement of 2 million OCV doses for the stockpile was issued in June 2013 (with financial support from EU-ECHO, USAID, USFDA and three private entities) and efforts are ongoing to make Regions and countries aware of the stockpile availability. A GAVI proposal is under consideration (subject to PPC and Board approval) to contribute to the global cholera stockpile for use in epidemic and endemic settings.<br>OCV use in endemic countries: A meeting was held in Feb 2012 to review the experiences of the Zanzibar study on pre-emptive use of OCV (2006-2012) and the Zanzibar Government developed a proposal for island-wide use of OCV in risk groups with the aim to eliminate cholera and to scale up WASH interventions. OCV campaigns for outbreak control were implemented in 2012 in Haiti and Guinea Conakry with positive results in both. |
| Decade of vaccines/GVAP | IVR was encouraged to contribute actively to the research component of the DoV. | Action | Apr 2011 | Ongoing | IVR participates in the Research and Development subgroup, and tracks research issues emerging from delivery group. R&D working group meeting was held on 29 September 2011. Tentative list of research priorities short, mid and long-term was developed.<br>IVR leads on coordinating R&D agenda with partners agencies. A formal memorandum was signed. Progress on establishing a vaccine research forum and implementation strategies in support of GVAP R&D related activities.<br>The Global Vaccines and Immunization Research Forum (GVIRF)to be held on 4-6 March 2014 in Bethesda, MD, will review and discuss progress in the field. |
| 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 | As part of GVAP resources invested in immunization will be tracked and monitored on a yearly basis throughout the decade, using the System of Health Accounts (SHA 2011) framework, the global standard to report spending in the health sector. The process to monitor resources invested in immunization will put emphasis on strengthening country capacity and creating a single platform for collecting, analyzing and reporting annually on all health expenditures, including those on priority diseases or programmes like immunization. This is intended to unify under a single platform other existing resource-tracking efforts, such as those being undertaken on national health accounts, and those for the Commission on Information and Accountability for Women's and Children's Health, and for the Global Fund to Fight AIDS, Tuberculosis and Malaria. This exercise will not only ensure regular and efficient reporting of good-quality data as part of the monitoring process, but also promote accountability and sustainability for immunization financing. |

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| Decade of vaccines/GVAP | SAGE requested consideration of the establishment of a SAGE standing working group to monitor GVAP implementation. | Action | Apr 2012 | Completed | A SAGE DoV-GVAP standing working group has been established. The group holds monthly teleconferences and met for their first face-to-face meeting from 9-11 September 2013 in Geneva. During this meeting the working group reviewed the indicators related to the GVAP strategic objectives. The group will present the first review of progress on the GVAP implementation at the November 2013 SAGE meeting. |
| Decade of vaccines/GVAP | The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data. | Action | Nov 2012 | Ongoing | The DoV SAGE Working Group reviewed the process to collection and reporting of data, the data quality and the formulation of the indicators and have made recommendations that will be presented in their report to SAGE in November 2013. The WG proposes to meet again in February 2014 where they may specifically address the formulation of indicators that they have found problematic in their review of progress and propose reformulation. |
| Dengue Vaccine | SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy. | Action | Apr 2012 | Ongoing | |
| Financing | SAGE identified the need to support countries that become ineligible and lower middle income countries through pooled procurement. | Action | Oct 2009 | Ongoing | Various activities are conducted at global and regional level to support non GAVI and Lower Middle Income Countries (LMICs) - At global level: a study to enhance global knowledge and understanding of the challenges that Lower Middle Income Countries face as they explore potential adoption of new vaccines. The study was completed in March 2011. Finding and preliminary conclusions and recommendations were presented to the SAGE in November 2010. At regional level: EMRO is working with MICs in the region to set up a pooled procurement system with the support of UNICEF SD, CDC and PAHO and other partners . Identification of graduating countries and their potential constraints and issues is ongoing with GAVI and UNICEF to define measures and activities to overcome the obstacles and develop transition plans. 2 regional and 6 country assessment were conducted in 2012 on GAVI graduating countries. 4 country assessments and transition plans were conducted in 2013. Despite some progress, the challenges are enormous not only on the financial aspects but also on ownership, decision making, capacity, pricing, regulation and procurement aspects. The establishment of a pooled procurement in EMRO has been decided by the Regional Committee in 2012 and is under development despite the unstable political situation in the region. In November 2012, SAGE reviewed the situation faced by middle income countries including countries graduating from GAVI support and made strong recommendation calling for a global and coordinated effort to support MIC and for the establishment of a task force on Middle Income countries to advocate and support the implementation of the platform discussed at the November 2012 session on MIC. Terms of Reference drafted, potential composition identified and contact with key partners done to set up the SAGE recommended task force and working group. First teleconference to be held by 31 October 2013. |

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| Financing | SAGE requests that WHO conduct further situation analysis of financial challenges for low or middle-income countries and consultation with countries concerned & partners to distil issues to more actionable activities. | Action | Apr 2008 | Ongoing | A Request for Proposal (RFP) has been drafted and submitted to the BMGF for funding. This was accepted, the RFP was issued in March 2009 and selection was made in June 2009. R4D was selected to conduct the study on LMIC to be launched early November 2009. Preliminary results were presented at the GIM and NUVI meeting in 2008 and 2010, findings and initial conclusions and recommendations will be presented to the SAGE in November 2010. Work is now underway to consider ways of addressing the potential obstacles and issues faced by the 20 graduating countries from GAVI support (as of Jan 2014). A Sharepoint on Middle-Income Countries and new vaccine introduction was created by IVB-WHO to facilitate data collection and exchange between the Middle-Income Country working group members. A Middle-Income Country presentation by EMRO during the 2009 WHA took place and was well received - the May 2008 WHA resolution on immunization referred explicitly to Middle-Income Countries. Sessions on Middle-Income Country was held during the NUVI meeting in June 2008 and 2010, an updated background document was discussed and an action plan for 2009-12 was approved with all concerned parties (vaccine industry, country and region representatives, WHO and UNICEF, Gates Foundation, ...). Ongoing discussions are taking place with UNICEF, BMGF and other entities to implement the R4D study recommendations. The GVAP has addressed some of the issues. A brainstorming meeting was organized on the lower-middle-income countries activity information and coordination on 12-13 March 2012 at HQ. On this occasion we discussed concepts, general approaches and specific plans for MIC with the ultimate objective of developing a platform and way forward for engagement and co-ordination with partners. The results of this and other consultations was presented at the November 2012 SAGE. A session was held on Middle-Income countries. The information provided in the paper was complemented by presentations from WHO, the former Yugoslav Republic of Macedonia, and UNICEF. Given the importance of the topic, SAGE requested that this issue and achievements be revisited in a subsequent meeting. A paper entitled "Global Support for New Vaccine Implementation in Middle-Income Countries" was published by Vaccine and shared with SAGE as a WHO contribution to define a common understanding and platform for action to be translated into actions by partners and donors. |
| 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 will host 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. |

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| 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 moderate 31.2% level of efficacy in preventing HIV infection and following SAGE recommendation on these aspects: WHO/IVR/HVI and UNAIDS implemented the following 2 activities:<br><br>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 held in June 2010 in Istanbul for the Eastern Europe region and Kuala Lumpur for the Asian region. This consultation allowed for the development of recommendations and drafting a new guidance point to be included in the new edition of the WHO/UNAIDS Ethics Guidelines.<br><br>2. In support of regulatory frameworks, WHO/IVR/HVI and UNAIDS have initiated a project on the development of policy/discussion paper to facilitate national decision making with regard to the novel strategies for testing HIV vaccines, namely, the recently proposed Adaptive Trail Design). A background working paper was developed and discussed at an expert group meeting co-organized in collaboration with WHO, UNAIDS, IAVI, NIH and the Global HIV Vaccine Enterprise. The expert group meeting took place on 10-11 February 2011 in New York. As an outcome of this meeting a technical discussion paper has been developed targeting the national regulatory authorities in countries where this type of trials are being planned in the coming years. This paper has been submitted to the journal Vaccine for review.<br><br>In October 2013 a written update was provided to SAGE on the progress of HIV-vaccine research. |
| 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 2012 epidemiological situation was provided to WHO. There is still no identified breakthrough case among vaccinated children since the introduction of hepatitis A in the national immunization program in 2005. A slight increase in the number of reported cases in 2012 mostly in those 45 years of age and over may in part be due to a surveillance artifact as surveillance keeps improving and the result of natural (or due to the impact of vaccination) evolution of the risk in those too old to have been vaccinated. These 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. Both health system and societal costs prevented totaled ~US$ 137 million with health systems cost ~US$ 44 million. Based on the Argentinian's experience, in 2012 both Colombia and Paraguay introduced a single dose national immunization schedule for 1 year old children.Yearly review of the Argentina surveillance data will continue. |

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| 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 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 and now steps are being taken to make HepB birth dose a WHO/UNICEF "best estimate" in line with previous SAGE recommendations. These WHO/UNICEF estimate process was piloted in 2012 in WPRO and will 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 GIVS goals. |
| 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 | WHO HQ has completed and disseminated a new global viral hepatitis strategy. EMRO is working with Member States to ensure achievement of the Regional Committee goal for HBsAg reduction in vaccinated children. In 2012, WPR TAG endorsed the region's Hepatitis B Expert Resource Panel (ERP) proposal to set 2017 as the target year to achieve the goal of reducing childhood hepatitis B prevalence to <1%, this is being considered as a resolution during the Oct 2013 RCM. SEARO has a draft regional strategy and AFRO has convened a regional hepatitis TAG. 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) has been published by the department of Immunization, Vaccines and Biologicals. |
| 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 | Ongoing | The SAGE Hepatitis E working group has been established. A first teleconference of the working group should take place prior to the SAGE Nov 2013 meeting. |
| HiB | Update SAGE HiB Vaccine position paper, including recommendations from the April 2013 SAGE meeting. | Action | Apr 2013 | Completed | The updated WHO Hib vaccines position paper was published in the 27 September 2013 issue of the WER. |
| Hib | SAGE recommended that a revised summary of the evidence, including a critical appraisal of the evidence with GRADE tables and justification for proposed recommendations, should be presented to SAGE in April 2013. | Action | Nov 2012 | Completed | A revised summary of evidence including all the aspects suggested by SAGE along with the GRADE tables were presented to SAGE in April 2013. SAGE recommended to include Hib vaccination into national immunization programmes using a 2p+1, 3p+0 or 3p+1 dose schedule. These recommendations were reflected in the WHO SAGE position paper which was published on 27 September 2013. |

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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 | - The WHO manual: Safe Management of Wastes from Health Care Activities second edition was published in 2013. http://apps.who.int/iris/bitstream/10665/85349/1/9789241548564_eng.pdf A series of 25 training modules for use in implementation of the manual and training health workers including waste handlers in the safe handling, treatment and disposal of health care waste has been completed. -Work is on-going through Project Optimize in collaboration with the Vaccine Packaging and Presentation Advisory Group to explore vaccine packaging that minimizes the impact on environment. VPPAG has 2 related streams of work 1) Working on recommendations to minimize primary, secondary, and tertiary container packaging. 2) Drafting a consensus statement with industry about use of materials for vaccine packaging that will minimize environmental impact. - A document on Environmental due diligence procedures has been developed and shared with GAVI. It expresses steps to be taken to minimize and manage waste from immunization activities in an environmentally friendly manner.The WHO reference document is: WHO policy paper on Health Care Waste Management(see http://www.who.int/water_sanitation_health/medicalwaste/hcwmpolicy/en/index.html)<br><br>- 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 (not recommends) the use of needle cutters but their introduction should come with training of HCWs on their use. An RCT on hub cutters has subsequently been completed in Ghana with WHO collaboration. |
| Immunization schedules | SAGE endorsed continuing work in the related research areas, with refinement of the research agenda undertaken by the research component of IVB, under the oversight of the research advisory bodies of WHO. SAGE asked to be kept informed of progress and results. | Information | Apr 2007 | Completed | Work in progress. Presentation of the PCV evidence was done at the SAGE November2011 meeting resulting in the updating of the pneumococcal conjugate vaccines position paper in April 2012. Evidence on rotavirus vaccines was presented at the April 2012 meeting and the updated rotavirus position paper will be published in January 2013. Evidence on Hib was presented at the November 2012 meeting. During the discussion, SAGE members noted that the evidence on the number of primary doses and the need for booster doses requires further evaluation before recommendations can be made on optimizing the current schedule. Hib was revised during the SAGE April 2013 meeting. Revision was completed for the vaccines listed above. Revised position papers were developed using this information. |

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| 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 | PCV: evidence was reviewed by SAGE on November 2011. New recommendation on schedules issued and data was used to update the position paper<br>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 will be published in February 2013.<br>Hib: No resources for model and/or ICEA. Evidence review is being completed; an ad hoc consultation will be held in September 2012 and outcomes were proposed for SAGE consideration at the November 2012 meeting. During the discussion, SAGE members noted that the evidence on the number of primary doses and the need for booster doses requires further evaluation before recommendations can be made on optimizing the current schedule. The issue will be revised during the April SAGE 2013 meeting.<br><br>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).<br>Completed for PCV, Rotavirus and Hib vaccines. Evidence on DTP, TT and Hep B will likely be presented to SAGE in April 2014 |
| 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. | 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 will be 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 2013. |
| Impact of the introduction of new vaccines on immunization and health systems | 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 | 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 to be published in 2013 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. |
| Influenza | SAGE recommends WHO continue urgent development of H5N1 stockpile. Further SAGE noted that WHO needs, concurrently with the acquisition of a stockpile, to develop the operational guidelines that would govern the management and release of the stockpiled H5N1 influenza vaccine, and to define appropriate methods for monitoring its use and evaluating outcomes. SAGE further recommended a feasibility study on the management and use of the stockpile. | Action | Nov 2010 | Ongoing | This project is being taken forward by the SAGE influenza working group for influenza vaccines and immunization. Discussions are ongoing and continued during the last 3 face to face meetings. During the 2nd meeting in February, 2011, the WG favored the option of keeping the stockpile mainly as a virtual stockpile with a small physical stockpile of filled and finished doses of H5N1 vaccine for rapid response and outbreak control in case of need. WHO should ensure that it has procedures in place to facilitate the deployment of pandemic vaccine to countries in need of support. Lessons learned from the deployment of the H1N1 pandemic vaccine in 2009 and 2010 are used to develop guidance and procedures for future vaccine deployment activities. Guidance document and associated work plans are available in all UN languages from: http://www.who.int/influenza_vaccines_plan/resources/deployment/en/index.html. WHO H5N1 stockpile is also being discussed in the Pandemic Influenza Preparedness (PIP) framework. Further discussion by the SAGE working group for influenza vaccine on the stock and the the PIP framework took place. The working group will report to SAGE at the November 2013 meeting. |

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| Influenza | SAGE recommended that the Influenza Vaccines and Immunization Working Group develop a research agenda. | Action | Nov 2010 | Ongoing | The Global Influenza Programme (GIP) presented their development of a WHO Public Health Research Agenda for Influenza (PHRAI) in the August 2011 SAGE WGIVI meeting. The WG acknowledged the extensive coverage of influenza research topics in the PHRAI and activities of the SAGE WGIVI can serve as one avenue to inform the RA. One area that may need further development is on vaccine communication and risk communication issues. It is recognized that communication is population-specific and how generalizable are the research work in this area would be an important topic to address. SAGE WGIVI also suggested that experiences from industry on the information gathered from countries on impact and lessons learned in view of research activities to inform the PHRAI. The importance of evidence-based recommendations was stressed and the PHRAI would be an important tool. There is also a need to identify more detailed research needs for influenza vaccines and the SAGE WGIVI encourages close collaboration with the PHRAI in addressing this need.<br><br>In January 2013 WHO held a consultation on influenza vaccines in clinical trials, and on the development of broad-spectrum influenza vaccines. A closed session was held to discuss a research agenda. The conclusions are currently under review and should be published in due course. |
| 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 | 1/10/2013-There is no sustained human to human transmission of H7N9 so far. It is still considered as a zoonotic disease.<br>The situation might change in Autumn whith colder weather conditions and more virus circulation in poultry and human populations.<br>The selection of the vaccine virus has been updated in September 2013. An update will be provided to SAGE at the November 2013 meeting as part of the pandemic influenza session. |
| Japanese encephalitis | Commercial kits for detection of JE-specific IgM should be compared and validated. Valuable experience had been gained from linking surveillance of encephalitis to detection of acute flaccid paralysis. | Action | Apr 2006 | Ongoing | Assessment using serum carried out by PATH, published Am J Trop Med Hyg July 07. Field validation of serum and CSF in India and Bangladesh assessed in a joint WHO/CDC meeting, SEARO, February 2008. Nepal and Cambodia field evaluation of JE assays is complete and paper 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 4ht quarter 2012. The three WPR JE regional reference labs (Japan, China and Republic of Korea) held their annual coordination meeting, Chengdu, China, 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 too 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.<br>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.<br>The currently used diagnostic assay produced by PanBio will cease production by 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. |

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| 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 | Some studies are being initiated by PATH, and planned by Governments considering introduction of the vaccine. Issue of interference with measles vaccination discussed at the December 2007 GACVS meeting. Measles co-administration (S Gatchalian, Vaccine 2008) had to be redone due to assay inconsistencies - results still pending. Number of doses required (one or two doses for primary immunization with live JE vaccine) has been assessed through case control studies in Nepal and India (the Nepal study is published and India study published as a note to the editor, 2 April 2009 in NEJM). A comprehensive review of the vaccine performance is planned in conjunction with an update of the JE position paper from 2006. |
| 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 | Planning and fundraising efforts are ongoing in the Regions. Control goals have currently not been formulated. A literature review on the JE burden of disease has been conducted, estimating the burden of JE to some 67,000 clinical cases and a CFR of above 20%. This was Published in the Bulletin of WHO, Bull World Health Organ 2011;89:766–774. Identification of target populations are being discussed in the context of country control strategies, and a review has been conducted at the 2011 biregional JE meeting. An update of the JE position paper (from 2006) is being initiated that will comprise a review of immunization strategies; a SAGE working group is being established. WHO also works with GAVI secretariat in preparing the opening of JE window, as a suitable JE vaccine has been WHO-prequalified. |

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| Lower middle-income countries: sustainable adoption and financing for new vaccines | SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines. | Action | Nov 2010 | Ongoing | Establishing a partnership among all relevant stakeholders to support middle income countries is our aim and has been clearly recommended by SAGE in 2011 and 2012. WHO has already started consulting with agencies, projects and initiative to explore what are the possibilities to collaborate and support middle income countries with procuring and financing vaccines and immunizations. This is the case with UNICEF, PAHO, SIVAC, OPTIMIZE, PROVAC and others. We have also consulted with the Bill and Melinda Gates Foundation (BMGF) on their concerns and plans. They showed a great interest and are trying. to identify the best approaches to support this objective. We have organized in January 2011 a successful brainstorming meeting on vaccine price and vaccine pricing focusing on issues faced by GAVI graduating and middle income countries. A proposal was submitted and is now funded by the BMGF on vaccine product, price and procurement (V3P project). This is a 3-year project aiming to identify, develop and establish the most appropriate and comprehensive method(s), mechanism(s) and/or tools to provide countries with accurate, reliable and useful data on vaccine product, price and procurement. This project has achieved its phase one (assessment if country needs and lessons learnt from other health sector) and is now starting its phase two (V3P tool development and roll out, testing with countries and capacity building activities). In parallel we have raised the LMIC issue within the Decade of Vaccines collaboration, it has been considered as one the priority of the decade of vaccines and is now reflected in the Global Vaccine Action Plan.(GVAP). Multiple consultations took place on GAVI graduating and middle-income countries activities and issues. The results of this consultative process were presented at the November 2012 SAGE. SAGE appreciated the efforts made by WHO, UNICEF and GAVI and other partners to extend discussions about vaccine supply and pricing to MICs where appropriate, and the adaptation of some activities to suit MIC-specific needs. However, 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 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. At regional level, EMRO is working to launch by the end of 2013 the EMR Initiative on pooled procurement and to contribute to the UNICEF SD initiative on MIC and new vaccines. The political and general situation in Middle-East might delay concrete actions in that domain. This question will be discussed during the 2013 EMRO regional Committee meeting. |
| Lower middle-income countries: sustainable adoption and financing for new vaccines | SAGE noted that the lack of access to life-saving vaccines in MICs has not significantly improved since this was first raised in 2008 and that rapid action is now required. SAGE requested that this issue and achievements be revisited in a subsequent meeting. | Action | Nov 2012 | Ongoing | Various initiatives are underway to facilitate access to new vaccines in middle income countries: UNICEF SD is consulting with Vaccine Industry and with countries to supply PCV, RV and HPV to middle income countries and to set up a ceiling price. The regional Committee of EMR has decided to establish a pooled vaccine procurement to support introduction of priority vaccines in middle income countries and to collaborate with UNICEF SD on its MIC initiative.<br>GAVI PPC requested in October 2013 the Secretariat “to conduct analyses and consultations to develop and propose instruments to support access to affordable prices for all Lower Middle Income Countries (LMICs), including graduated countries and non-GAVI LMICs. Options would be brought to the Board for consideration in 2014”<br>Concrete options, actions and results are still to be seen. Coordinated effort, consistent policy and financial support are needed to translate those initiatives into reality for middle income countries. |

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| Lower middle-income countries: sustainable adoption and financing for new vaccines | SAGE recommended, as a priority, the creation of a task force convened by WHO as a mechanism for inclusive stakeholder engagement and forum for harmonization and implementation of projects and activities. | Action | Nov 2012 | Ongoing | Terms of Reference drafted, potential composition identified and contact with key partners done to set up the SAGE recommended task force and working group. First teleconference to be held by 31 October. |
| 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 | Development of malaria vaccine PPCs is underway and scheduled for finalization by end 2014. |
| 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 | The timing for the "Decision" session depends on the outcome of the regulatory process. EMA is expected to make a regulatory decision in May 2015. If those timelines remain unchanged, a SAGE/MPAC (Malaria Policy Advisory Committee) joint session is expected in Oct 2015.<br><br>The third set of results from the Phase 3 trial of RTS,S/AS01 is to be made publicly available on 8 Oct 2013. These results include site-specific efficacy and 18 month follow-up in both the 5-17 month age group and 6-14 week age group.<br><br>SAGE members are to receive a 2 page briefing on 8 Oct 2013.<br><br>JTEG met to review the new results on 19-20 Sep. Their assessment is that the booster dose results, expected in 2014, are critical. Depending on these booster results, JTEG may propose recommendations for use in the 5-17 month age range. It is considered unlikely that JTEG will propose recommendations for use in the 6-14 week age range given the new results, unless booster dose results in this age group give higher efficacy than after the primary immunization series.<br><br>Any recommendation for use in the 5-17 month age range would require at least 2 new immunization visits. One possible schedule is 6 months (with vitamin A), 7-8 months (new visit) and 9 months (with measles first dose). JTEG considered that the data on co-administration with measles first dose is acceptable. Further exploration of possible schedules is underway.<br><br>The first regulatory submission will be to the European Medicines Agency under the article 58 procedure. The first wave of 5 national regulatory submissions will be to Kenya, Tanzania, Ghana, Senegal and Burkina Faso, where Phase 4 studies of safety and effectiveness are planned. |
| Measles and rubella | SAGE requested that the measles and rubella working groups should merge and monitor progress, oversee the research agenda required for eradication and report back to SAGE regularly. The working group should liaise with QUIVER and IPAC to address relevant quantitative issues as well as those related to immunization practices. This activity has been included in the draft terms of reference for the combined measles and rubella working group. | Action | Nov 2010 | Completed | The working group on measles and rubella was formed in late 2011. The terms of reference of the working group include overseeing the research agenda and liaising with other advisory groups. Peter Figueroa is the chair of the working group and as of 15 October 2013, the group has held conference calls approximately once a month as well as four face-to-face meetings. The working group will be providing an update to SAGE at its upcoming November 2013 meeting. |

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| Non-specific effects of vaccines | SAGE supported the two proposed literature reviews that include documentation of the current and proposed studies in the field. SAGE insisted that the reviewers should make efforted to include all available evidence and access all relevant data sets. | Action | Apr 2013 | Ongoing | Working group constituted and functional. The two reviews are ongoing. The results will likely be presented to SAGE in April 2014. |
| Optimizing immunization schedules | SAGE recommended that WHO provide support to country-level policy-makers on the rational use of analyses generated by the tool. | Action | Nov 2010 | Completed | We have approached SIVAC to collaborate in one African country as a case study (initially Cote d'Ivoire now considering Mozambique). After consulation with AFRO colleagues and, bearing in mind that the NITAGs have been only recently constituted, this activity has been postponed and no new date has been set yet.<br><br>DRAFT of website tool was presented to NUVI meeting participants in June 2013. It was well received and appreciated. |
| Pertussis control | SAGE endorsed the establishment of a pertussis-vaccine strain repository and a database on the genealogy and characteristics of different vaccine strains. A proposal should be presented to the Expert Committee on Biological Standardization. | Action | Apr 2010 | Ongoing | The initial offer of the pertussis strains made by Dr Nicole Guiso from the Institut Pasteur was not presented to the ECBS in 2010 due to the lack of information regarding the use of the strains and the related data. Discussions took place within the Institut Pasteur and their legal department advised that as strains had been received under specific contract from the vaccine manufacturers they could not be shared. They will however provide a list of strains received so that WHO can request permission directly from the vaccine manufacturers themselves for the strains to be used for research purpose in case of need and for the genetic filiation of the strains to be publicly released. |
| Polio | The documentation for 'legacy planning' should include contributions from communities<br>and front-line health workers on their experiences with the polio programme, what it has meant for them<br>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 is finalizing its workplan. One of the major activities within the workplan will be 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 will begin in early 2014 and continue 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. |
| 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 of OPV2 withdrawal and IPV introduction. The multi partner group has been operating wince mid-April in five areas of work : Regulatory, vaccine implementation, communication, financing and routine immunization strengthening. An update to SAGE will be provided at the next meeting. WHO/EPI is recruiting an additional 4 professional staff positions at HQ to contribute to this effort. Similar positions will also be supported at Regional levels, and at key partner organizations such as UNICEF and US-CDC. |
| Polio | SAGE recommended working closely with countries on activities towards OPV2 withdrawal. | Action | Apr 2013 | Ongoing | Regional offices are working with countries to develop timelines. Timelines vary by region, with WPR requesting all plans by end of 2013, and others to follow. In addition, now that regional consultation committees have given their approval, are in the process of developing a TA strategy for OPV2 cessation and IPV introduction. This work will be supported and coordinated through the IMG and directed by Regional Offices . |
| 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 | Ongoing | After the careful review of the a comprehensive plan for the implementation of IPV introduction, developed by<br>the collaboration between WHO, GAVI, and partners, the WG now encourages a WHA resolution in 2014 on accelerated IPV introduction due to the tight timelines for global IPV introduction |

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| Polio | SAGE will review suggested IPV schedules, a draft type 2 virus response protocol for the period after OPV2 cessation, and a draft IPV supply and financing strategy, at the next meeting in November 2013. SAGE requested to develop more detailed workplans for each of the main workstreams on critical OPV2 withdrawal pre-requisites, and the preparation of contingency plans for responding to possible delays or other problems. | Action | Apr 2013 | Ongoing | The WG has been closely following the progress made on the planning for IPV introduction into the routine immunization schedule and OPV2 cessation in detail, including two face to face meetings (June and October).<br><br>The WG will provide its key findings and recommendations at the next meeting in November 2013. |
| Polio eradication | SAGE requested that WHO/GPEI undertake further consultation with countries and regions to document the policy and programmatic implications of introducing an IPV dose (whether IM or ID) as part of the strategy to switch from tOPV to bOPV and to facilitate individual country decision-making. | Action | Apr 2012 | Completed | A review of operational differences between using IPV as a full dose (IM) vs. application as fractional dose (ID), comparing differences relating to service delivery, cold chain and logistics, management, training, supervision, and cost. The assessment included detailed interviews with EPI managers from Asia (India), and Africa (one West and one East African country). Results of this investigation were reported to the SAGE Polio Working Group, and at the October 2 meeting of the Immunization Practices Advisory Committee (IPAC).<br>Special sessions on the 'polio endgame', focusing in particular on the plans for OPV2 cessation (i.e. the switch from tOPV to bOPV for routine immunization) have been conducted at the EMRO EPI manager's meeting (September 2012) and are planned for the 4th quarter of 2012 at the regional EPI meetings in the South-East Asian and African Regions. During the November 2012 meeting, SAGE recommended that all countries should introduce at least 1 dose of IPV in their routine immunization programme to mitigate the risks associated with the withdrawal of OPV2.Over the next two years, the focus will be on introducing one IM IPV dose in addition to OPV. Many counties, and the African region as a whole, have indicated they will not consider an ID dose of IPV at this time. In addition, work will continue at the individual country level to support planning for IPV introduction and the switch to bOPV. |
| Polio eradication | SAGE recommended that WHO/GPEI work with vaccine manufacturers to develop both options and with regulatory authorities to initiate fast track review of ID IPV immediately, to ensure that a low-cost IPV option is available within a year. | Action | Apr 2012 | Ongoing | On 26 July 2013, WHO convened a meeting with representatives from National Regulatory Authorities from countries that are experienced in the regulation of polio vaccine products. The overall objective of the meeting was to seek guidance and input from these representatives regarding different products, including intradermally administrated IPV.<br><br>At the end of the consultation, the representatives from a few NRAs agreed on the design of the trial, which would meet the regulatory needs for a label change.The protocol was developed, and cleared by relevant NRAs and IPV suppliers. The study is expected to start early 2014. |
| 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 | Ongoing | WHO continues to assess the feasibility of using international mechanisms to implement such vaccination requirements and travel advisories. It is currently envisioned, that such measures (e.g. an IHR standing recommendation on vaccination of travelers) would be considered for any area with continuing poliovirus transmission at end-2014. Additionally, as in previous years, WHO has updated its International Travel and Health publication, providing vaccination recommendations to travellers based on the most up-to-date global polio epidemiology. |

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| Polio eradication | SAGE recommended that an IPV supply and funding strategy be established for timely introduction of IPV using existing whole dose products for a transition period if needed. For its next meeting SAGE requested additional details on the scientific evidence for, and programmatic implications of, targetng expanded age groups during polio campaigns in endemic areas. | Action | Nov 2012 | Ongoing | Work focusing on the establishment of the required IPV supply and funding strategy with stakeholders and with GAVI has continued to allow the introduction of whole-dose IPV in time before the planned cessation of OPV2. The polio session during the November 2013 SAGE meeting will also include an update on the global IPV supply, financing and introduction strategy by the GPEI Immunization Systems Management Group. |
| Polio eradication | SAGE strongly encouraged the Global polio Eradication Initiative (GPEI) to proceed with its full IPV research agenda, in particular to clarify the duration and quality of the priming immune response to inform the work of the SAGE IPV working group. | Action | Apr 2011 | Ongoing | The WHO polio eradication research team is coordinating additional research in this area, including further analysis of Cuba study data (e.g., titre of neutralizing Ab after one and two doses of IPV), and potential collaboration with the International Vaccine Institute (IVI), Korea, to measure mucosal and systemic antibody-secreting cell (ASC) responses against polio vaccines in young infants after one and two doses of IPV.<br>The data have been shared on multiple occasions both with the SAGE WG, and the full SAGE. In addition, a manuscript has been published that summarizes these data from Cuba. (Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. NEJM.2013;368:416-24). |
| Polio eradication | SAGE recommended that tight deadlines should be set for the completion of each step required to implement the switch from tOPV to bOPV. Similarly, urgent plans must be in place for the development of a low-cost IPV, and for its introduction by countries which choose to adopt this strategy. For countries planning to introduce IPV, including the low-cost IPV option, similar planning must take place. | Action | Apr 2012 | Completed | Discussions among the GPEI partners, and activities of the SAGE Polio Working Group have continued since the November 2012 SAGE meeting to further refine the definition and timeline for the programme of work on the six main pre-requisites that need to be in place before the withdrawal of OPV2 (i.e. replacement of tOPV by bOPV for routine immunization) can be considered. As requested by SAGE, the considerably expanded work-streams on the OPV2 withdrawal pre-requisites - including lab containment of polioviruses, introduction and uptake of affordable IPV, IPV and bOPV product development and licensing, and MOPV2 stockpile and outbreak response, and anticipated time-lines within the polio endgame - will be presented at the April 2013 SAGE meeting. |
| Polio eradication | SAGE requested that WHO/GPEI draft a 'GPEI Strategic Plan/Budget for 2013-2018' by November 2012 that incorporates OPV2 cessation and eventual bOPV cessation, with different scenarios for the timing of IPV introduction for the period of the tOPV/bOPV switch and longer term IPV uptake following complete OPV cessation. | Action | Apr 2012 | Completed | Following this request from SAGE and a similar recommendation from the GPEIs Independent Monitoring Board (IMB), a Strategic Plan for the Polio Endgame and Legacy Options 2014 to 2018 has been drafted. This document was developed in close consultation with GPEI spearheading partners and other initiatives (i.e. GAVI), as well as with WHO Regional Offices; the SAGE Polio Working Group also reviewed the draft and provided comments.<br><br>The document has three main sections: a) the endgame strategic plan, including the eradication of polio and management of associated risk, b) the financial requirements 2014 to 2018 (i.e. a 2014 to 2018 indicative budget), and c)the legacy, i.e. to define the broader global health benefits of the global polio programme. In November 2012, SAGE welcomed the long-term vision of the draft GPEI Polio Eradication and Endgame Plan, 2013-2018 and endorsed the 4 major components. |

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| Polio eradication | SAGE recommended that WHO/GPEI continue to work with GAVI to ensure financing is available within 18 months for any GAVI-eligible countries wanting to introduce a low-cost IPV option as part of the switch strategy. | Action | Apr 2012 | Ongoing | Since mid-April 2013, GAVI and GPEI have been working together through the Immunization Systems Management Group (IMG), utilizing their complementary strengths to ensure that the IPV introduction as well as existing vaccine introduction plans for other vaccines-- including those supported by GAVI-- can be achieved. The IMG's work has also focused on the broader objective 2 of the Endgame strategy and includes opportunities to strengthen routine immunisation services, through the use of polio human resources and through greater coordination between polio, GAVI and routine immunisation programmes. The IMG has created a financing sub-group to facilitate discussions on IPV financing across partners. The group has developed a joint budget for IPV introduction for 2014-2018; both GAVI and GPEI core partners are members of the group. In addition to developing the budget, the group has aligned costing and funding flow allocation mechansims to ensure the most efficient systems are used, and support is available to both GAVI and non-GAVI countries. GAVI has further been working on developing policies and processes around IPV introduction, with input from the IMG, to streamline and fast track the application and approval process for IPV funding in order to align with the endgame targets. |
| Reports from other advisory committees | SAGE recommended appointment of appropriate programmatic and implementation expertise to QUIVER's membership including representation of experts from low and middle-income countries. | Action | Nov 2011 | Ongoing | The new QUIVER AC called Immunization and Vaccines related Implementation Research (IVIR) advisory committee has been expanded to 15 members with programmatic and implementation research expertise. It remains a challenge to include representatives from low and middle-income countries. Four of the five new members nominated are from LMICs with expertise in vaccine implementation issues and vaccine trials.<br><br>Recruitment of new IVIR members is ongoing |
| Reports from other advisory committees on immunization | WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community. | 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.<br>This will be linked with an overriding review of Expert Committees by the department of Essential Medicines and Health Products. |
| 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 | Discussions with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Further work on the report is still pending.<br>Internal QSS-EPI discussions are in progress. |
| 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. |

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| 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 | Ongoing | A 3-year grant from the Bill and Melinda Gates to the Coalition against Typhoid (CaT) and Sabin Vaccine Institute ends in 2013 and an application has been initiated to seek a supplementary grant to 2016. CaT, WHO and other partners continue to implement and support typhoid control and prevention activities, including immunization as well as water, sanitation and hygiene (WASH) strategies. The International Conference on Typhoid Fever and Other Invasive Salmonelloses held 1-2 March 2013 in Dhaka served as testament to increased advocacy and prioritization efforts. As previously reported to SAGE, WHO pre-qualified the sanofi pasteur Vi polysaccharide vaccine in June 2011, the first typhoid vaccine to be WHO prequalified. However Vi polysaccharide vaccine uptake has remained low for multiple reasons including lack of funding. In November 2011 the GAVI Board re stated its 2008 commitment to typhoid conjugate vaccines in the GAVI Vaccine Investment Strategy; it is expected that a typhoid vaccine support window will be opened when a WHO prequalified conjugate typhoid vaccine is available. Currently it is not expected that the first WHO pre-qualification of a typhoid conjugate vaccine will be before 2015. WHO guidelines on the quality, safety and efficacy of typhoid conjugate vaccines are scheduled to be presented to the ECBS in Oct 2013 for approval. |
| Typhoid | Need for feedback from WHO's regional offices and countries to determine how countries could implement SAGE recommendations. | Action | Nov 2007 | Completed | A full report was presented to the November 2010 meeting of SAGE. SAGE reiterated that countries should consider introduction of existing typhoid vaccines and not necessarily wait for surveillance systems to be in place. Further, to take the typhoid agenda forward, the Bill and Melinda Gates Foundation awarded a three year grant to the Sabin Vaccine Institute, Washington DC,to coordinate the relevant stakeholders and to develop a global agenda for the control and prevention of typhoid fever. WHO is working closely with Sabin in this process.<br>Typhoid vaccine is one of the 7 vaccines listed by GAVI as priority vaccines for support and a case for typhoid vaccine support was presented to the GAVI Board at its November 2011 meeting. The Board issued a clear statement that GAVI will not support the Vi-polysaccharide vaccine and will wait for a conjugate vaccine to be available. Given this decision, there was no donor funding to support ViPS typhoid vaccine use. Since 2012, typhoid activities by WHO and key partners have focused on activities to support the development, licensure and introduction of conjugate vaccines and strengthening surveillance in countries to generate better data on typhoid burden. Preparations are under way to define the appropriate pathway for a future SAGE session to consider recommendations for the use of typhoid conjugate vaccines. |
| 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 http://www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf |
| Un/under-immunized children | SAGE recommended that WHO prioritize the ongoing work on the development of the framework to guide countries in identifying determinants of low immunization coverage and institute corresponding local solutions. | Action | Apr 2011 | Completed | A basic tool to identify the broad determinants of low immunization coverage has been developed. This tool then points to the use of one or more of 6 in-depth tools which will go into the depths of a particular issue flagged by the basic tool. The work has been prioritized. Parallel streams of work in EURO, AMRO, AFRO, UNICEF and other partners are going on to develop the in-depth tools to address different facets of the problem. The work on the TIP (tailoring immunization programmes) tool done by EURO is complete and the tool is available on the web at http://www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf |

| Topic | Recommendations/Action item | Category | Meeting Date | Status | Comments and Follow up |
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| Un/under-immunized children | SAGE recommended that the targeted approaches undertaken by Tanzania and Ethiopia to reduce to number of un/under-immunized children should be appropriately adapted for use in other countries. | Action | Apr 2011 | Ongoing | The targeted approaches undertaken by Tanzania and Ethiopia to reduce to number of un/under-immunized children were presented to SAGE in October 2009. The lessons that could be drawn from these two country examples were used to draft the basic tool to identify which of 6 problem areas applied to an area. The 6 problem areas will be tackled through 6 in-depth tools, each focusing on one problem area. The work on the TIP (tailoring immunization programmes) tool done by EURO is complete and the tool is available on the web at http://www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf |
| Vaccination in humanitarian emergencies | SAGE emphasized the value of piloting the framework in the setting of new emergencies if an opportunity is presented in the next 6 months, and retrospectively against recent emergencies including those described in the case studies. Ongoing collaboration with key stakeholders including regional offices and operational agencies should be arranged through the WHO Department of Emergency Risk Management and Humanitarian Response and the global health cluster. | Action | Apr 2012 | Completed | Pilot testing ongoing in the Horn of Africa (completed); Pakistan; and South Sudan |
| 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 | The Emergency Risk Management and Humanitarian Response (ERM) Department will be reviewing the framework approach for other health interventions in emergencies with Global Health Cluster partners and other WHO technical departments after relevant staff return after the summer break and a new Technical Officer joins the team in September. |
| 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 | Ongoing | The Working Group reworded the definition of vaccine hesitancy taking into account the proposed wording by SAGE:<br><br>"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." |
| 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 Groups monthly teleconferences partners are invited to present their work (eg UNICEF on their polio-related work) and link with the Working Group directly. |
| 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 20 Feb to solidify the workplan, and work started in 2012 to combine WHO and UNICEF databases on vaccine forecasting, supply and distribution in countries is ongoing. It was agreed to have a joint discussion on DTP, HepB mono and TT/Td supply in Q2 2013. Several monthly updating teleconferences have been held subsequently. WHO also took part in the global forecasting discussions on 28 September 2013. |

| Topic | Recommendations/Action item | Category | Meeting Date | Status | Comments and Follow up |
|---|---|---|---|---|---|
| Vaccine coverage | SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes. | Action | Nov 2011 | Ongoing | 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 will provide 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. A second meeting is scheduled for November 2013. |
| 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 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. |
| Vaccine coverage | WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. | Action | Nov 2011 | Ongoing | WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. A draft document which reviews, for a selected list of vaccine-preventable diseases, laboratory test available and associated requirements for specimen collection/transport, personal experience and training, and laboratory supplies and equipment has been prepared. The draft will be reviewed internally and following recommended changes will be submitted for review by external experts. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results was 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. |

| Topic | Recommendations/Action item | Category | Meeting Date | Status | Comments and Follow up |
|---|---|---|---|---|---|
| Vaccine preventable disease 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 also noted that country ownership should be enhanced and that Ministries of Health should be encouraged to increase their own funding for surveillance. SAGE appealed for sustained financial support to ensure quality for sentinel site surveillance. SAGE underscored the importance of ensuring the representativeness of sentinel sites. | Action | Nov 2011 | 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. SAGE's advice on the findings, results and conclusions from the strategic review will be sought during the November SAGE meeting. |
| 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 pregnacy was published and will be made available to SAGE ahead of the November 2013 meeting. A more systematic review has been piloted for Rubella and is expected to become available in summer 2014. |
| Vaccines during humanitarian emergencies will be discussed at a forthcoming SAGE meeting. | The use of vaccines during humanitarian emergencies will be discussed at a forthcoming SAGE meeting. | Action | Nov 2010 | Completed | A SAGE Working Group on vaccination in humanitarian emergencies was established in June 2011. Multiple teleconferences were held and two face-to-face meeting of the working group took place on 20-21 September 2011 and on 16-17 February 2012. The group reported to SAGE in April and November 2012. In November 2012, SAGE endorsed the complete framework for decision making on the use of vaccinations in humanitarian emergencies as a major step forward and considers that it fills an existing gap but acknowledged that the framework focuses on vaccination, which is only one priority consideration in humanitarian emergencies. SAGE strongly affirmed the potential utility of this framework and recommended pilot testing in the field. The working group was asked to adapt the document to take into consideration SAGE's comments and proceeds with its finalization, hopefully prior to the April 2013 SAGE meeting.Consideration was given to the potential inclusion of case studies in the documents but this was debated, as disasters are very diverse. It was left to the working group to decide whether these should be included. The working group has since then finalized the framework which following final editing has been published. |
| Yellow Fever | Update of the Yellow Fever Vaccine position paper, including recommendations from the April 2013 SAGE meeting. | Action | Apr 2013 | Completed | The updated Yellow Fever Vaccine position paper reflecting the new SAGE recommendations was published in the WER on 5 July 2013 |
| 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 | Guidance for States Parties on incorporating the SAGE conclusion into their practices regarding certificates for vaccination against YF is in preparation, as are different options for addressing related IHR processes. |

# TECHNICAL ADVISORY GROUP ON VACCINE-PREVENTABLE DISEASES
## XXI MEETING: "VACCINATION: A SHARED RESPONSIBILITY"
## QUITO ECUADOR, 3-5 JULY 2013

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## TAG MEMBERS 2013

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| **Dr. Ciro A. de Quadros**<br>Executive Vice President<br>Sabin Vaccine Institute<br>Washington, D.C., United States | President |
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| **Dr. Anne Schuchat**<br>Director<br>National Center for Immunization and Respiratory Diseases (NCIRD)<br>Centers for Disease Control and Prevention<br>Atlanta, GA, United States | Absent |
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| **Dr. Arlene King**<br>Chief Medical Officer<br>Ministry of Health and Long-term Care<br>Toronto, Ontario, Canada | |
| **Dr. Jeanette Vega**<br>Managing Director<br>Foundation Initiatives<br>The Rockefeller Foundation<br>New York, NY, United States | |
| **Dr. José Ignacio Santos Preciado**<br>General Director of Health Quality and Education<br>Ministry of Health<br>Mexico City, Mexico | Absent |
| **Dr. Peter Figueroa**<br>Chief Medical Officer<br>Ministry of Health<br>Kingston, Jamaica | |
| **Dr. Roger Glass**<br>Director<br>Fogarty International Center, NIH/JEFIC-National Institutes of Health<br>Bethesda, MD, United States | |
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## ACRONYMS

| | |
|---|---|
| AFP | Acute Flaccid Paralysis |
| BCG | Bacillus Calmette–Guérin – vaccine against severe forms of tuberculosis |
| CDC | Centers for Disease Control and Prevention of the United States |
| CRS | Congenital Rubella Syndrome |
| cVDPV | (circulating) Vaccine-derived Poliovirus |
| DPT | Diphtheria-Pertussis-Tetanus vaccine |
| DPT3 | Third dose of the Diphtheria-Pertussis-Tetanus vaccine |
| EPI | Expanded Program on Immunization |
| ESAVI | Event Supposedly Attributable to Vaccination or Immunization |
| EW | Epidemiological Week |
| GIVS | Global Immunization Vision and Strategy |
| GVAP | Global Vaccine Action Plan |
| JRF | Joint Reporting Form (PAHO-WHO/UNICEF) |
| HPV | Human Papilloma Virus |
| IBD | Invasive Bacterial Disease |
| IPD | Invasive Pneumococcal Disease |
| IEC | International Expert Committee (for the documentation and verification of measles, rubella, and CRS elimination in the Americas) |
| IPV | Inactivated Polio Vaccine |
| LAC | Latin America and the Caribbean |
| LAIV | Live Attenuated Influenza Vaccine |
| 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 |
| NIP | National Immunization Program |
| NITAG | National Immunization Technical Advisory Group |
| NNT | Neonatal Tetanus |
| OPV | Oral Polio Vaccine |
| bOPV | Bivalent Oral Polio Vaccine |
| mOPV | Monovalent Oral Polio Vaccine |
| tOPV | Trivalent Oral Polio Vaccine |
| PAHO | Pan American Health Organization |
| PCV | Pneumococcal Conjugate Vaccine |
| PoA | Plan of Action |
| 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 WHO |
| SIREVA | Regional Vaccine System – laboratory network for invasive bacterial pathogens |
| TAG | PAHO's Technical Advisory Group on Vaccine-preventable Diseases |
| TIV | Tetravalent Influenza Vaccine |
| UNICEF | United Nations Children's Fund |
| VWA | Vaccination Weeks in the Americas |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| WIW | World Immunization Week |

## PERTUSSIS (WHOOPING COUGH)

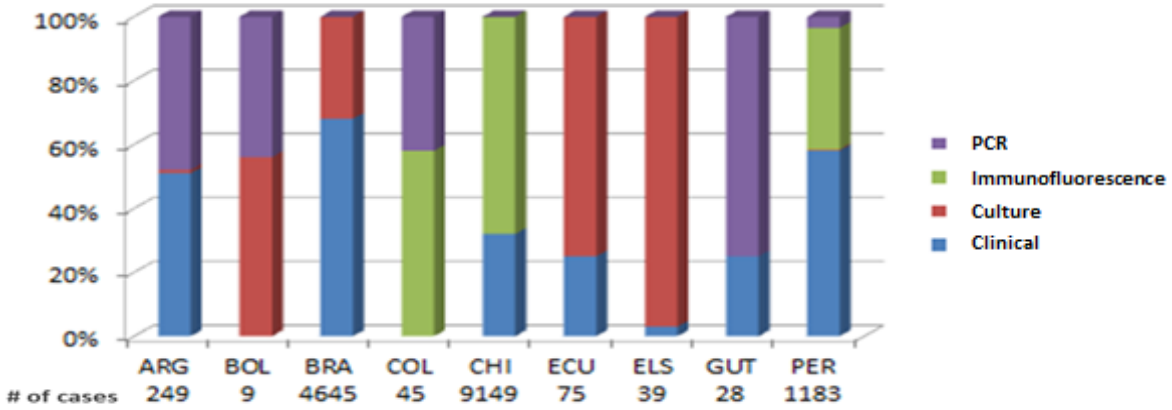
Pertussis is a significant cause of childhood mortality globally, and as such, it has been a topic for discussion in the last three TAG meetings. Recommendations made during these meetings include the need for strengthening of epidemiological surveillance; the administration of a 4th dose as part of the routine vaccination schedule; starting diphtheria-tetanus-pertussis (DTP) vaccination at 6 weeks of age and vaccinating pregnant women only during outbreaks; and carefully replacing the whole-cell pertussis vaccine with the acellular vaccine, while the duration of immunity conferred by acellular vaccines is still being evaluated.

Following previous recommendations, the regional pertussis epidemiological situation, the recommendations of the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE), evidence on the duration of the protection conferred by acellular vaccines, and the conclusions of the PAHO/WHO Pertussis Working Group were presented during this meeting.

**Figure1.** Countries that have had pertussis outbreaks over the last 3 years (2010 – 2013)

After holding two meetings and gathering information from Latin American and Caribbean countries (LAC), the Pertussis Working Group prepared a guidance document on Investigating and Reporting of Pertussis Outbreaks. In this document, the Group reported that: a) with the exception of Cuba, Costa Rica, Dominican Republic, Haiti, Honduras, Mexico, Nicaragua, and Venezuela, every Latin America country, as well as Canada and the United States, has reported pertussis outbreaks during the last 3 years; b) in 2012, the pertussis incidence rate (per 100,000 inhabitants) ranged from 0 (zero) in Cuba to 33.8 in Chile; c) the case-fatality rate varied widely, for example, in 2012 in the Dominican Republic it was 18%, in Paraguay 9%, in Honduras 6%, in Mexico 5%, in Brazil 1.5% and in Chile 0.2%; d) in countries that reported outbreaks, 42% of the cases involved infants under 6 months of age; e) eight countries use a general definition of pertussis cases, while nine have specific definitions by age group; f) some countries continue using immunofluorescence as a laboratory diagnostic method, despite the fact that its use is no longer recommended; and g) some countries reported numerous outbreaks, some with only two or three cases each.

Figure2. % of pertussis cases by confirmatory method by country. Selected Latin American countries, 2010-2012




The TAG appreciates and commends the efforts of countries in the Region, for preparing detailed information on the epidemiology of the outbreaks (case definitions used, sex and ages of cases, confirmation method, laboratory tests, signs and symptoms and relevant outcomes, such as hospitalization and death) for the first time. It should be noted that the high proportion of children under 6 months of age in the outbreaks could indicate an over diagnosis in that age group or an under identification of cases in other age groups. The great disparity in the incidence rates reported in the continent are difficult to explain between countries that have comparable vaccination schedules and coverage. The high proportion of deaths to the number of cases could only be due to an inadequate case management or the small number of cases captured by surveillance systems.

Information currently available on the duration of immunity conferred by acellular vaccines was presented during the meeting. This information continues to show that duration of immunity is

shorter than that of the whole-cell vaccine. Meanwhile, SAGE has asked its own Working Group to continue gathering epidemiological evidence to facilitate decision-making.

The recommendation of the October 2012 meeting of the United States Advisory Committee on Immunization Practices (ACIP) was also presented. In that meeting, ACIP recommended administering one dose of the Tdap vaccine during each pregnancy, regardless of the number of previous doses a patient has received. This dose should be administered between weeks 27 and 36 of pregnancy for the purpose of optimizing the transfer of antibodies to the newborn. If it is not administered during pregnancy, it should be administered in the immediate postpartum period. In order to estimate the potential impact of this strategy, a model showing that this strategy could prevent 9 deaths (ranging from 4-17) was used. The number of deaths recorded annually among children >12 months of age from 2000 to 2011 was 18 (ranging from 8-35).

The TAG reviewed the outputs of the Working Group, which include the guidelines and forms for outbreak monitoring and reporting, and expects them to serve as an input and stimulus for countries to gather epidemiological evidence for better decision-making.

## RECOMMENDATIONS

- Countries using current vaccination schedules with whole-cell pertussis vaccines should continue to do so. There is marginal and insufficient benefit to consider changing from whole-cell pertussis-containing vaccines to acellular pertussis-containing vaccines.

- Countries should continue striving to provide timely vaccination and achieve coverage levels $\geq$95% with pertussis-containing vaccines in all municipalities.

- All countries should strengthen pertussis surveillance to better monitor the epidemiology of the disease. Countries should continue assessing the quality of their 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.

- Countries should use the guidelines proposed for investigating all outbreaks, to allow national programs and TAG to continue evaluating the epidemiology of pertussis on an ongoing basis.

- TAG reiterates its previous recommendations related to outbreaks. These recommendations include lowering the age for initiating vaccination to 6 weeks and vaccinating pregnant women **only** in areas affected by the outbreak. Currently, there is no evidence for TAG to recommend routine vaccination of pregnant women.

## EVIDENCE BASED DECISION-MAKING FOR NEW VACCINE INTRODUCTION

New vaccines are considerably more expensive than traditional vaccines, and their introduction into national immunization programs in the Region imposes greater resource requirements. Given that national budgets for immunization are slow to expand relative to the needs of the programs, the scarce resources available must be used as efficiently as possible, and mechanisms should be sought to protect them. Arguments for increasing national immunization budgets must be strongly grounded in evidence given the many other existing public health priorities. The Global Vaccine Action Plan approved during the 2012 World Health Assembly, calls for the incorporation of evidence assessment into immunization policy-making with the aim of maximizing health impact and efficient resource use.

Recognizing this need, PAHO established the ProVac Initiative in 2004 with the goal of strengthening national capacities for evidence-based decision-making around new vaccine introduction, with a particular focus on the use of economic evaluations in the decision-making process. In 2006, the ProVac Initiative was officially endorsed by PAHO's Governing Bodies through resolution CD47.R10. Then, in 2009, the ProVac Initiative was awarded a five-year grant by the Bill & Melinda Gates Foundation to support country decision-making around new vaccine introduction. In 2010, the ProVac Network of Centers of Excellence was formed, including academic institutions in Latin America with expertise on economic evaluations to develop tools and guides for countries conducting economic studies with local and regional data. Thus far, over 25 economic evaluations and costing studies have been conducted by multidisciplinary national teams in 15 countries. The cornerstone of all technical assistance provided by the ProVac Initiative has been the bolstering of national capacities, South-South cooperation, and country ownership of the process of evidence generation.

Argentina is one of the countries in the Region that has achieved remarkable advances in the institutionalization of an evidence based decision-making process for new vaccine introduction with support from the ProVac Initiative. In addition to performing 3 nationally-based cost-effectiveness analyses on new vaccines over the last 5 years, they have also improved the operating procedures of the National Immunization Technical Advisory Group (NITAG) and added a full-time Ministry of Health professional solely devoted to generation and collection of evidence to aid immunization policy-making.

These efforts to strengthen national capacities in the Americas have gained global recognition and have led to repeated requests for support by other WHO Regions. Accordingly, in 2012 PAHO was awarded an additional grant to provide time-limited support for the use of economic evaluations in immunization decision-making in select countries of Africa, Europe, and the Eastern Mediterranean. This work is being carried out in collaboration with international partners: Agence de Médicine Préventive (AMP), PATH, CDC, Sabin Vaccine Institute and WHO headquarters, regional and country offices.

Despite these important steps that countries have taken thus far, much remains to be done to incorporate evidence into the immunization decision-making process. Countries must strive to create a broad, nationally based evidence framework for their decision-making, one that will consider not only technical criteria but also programmatic, financial, and social criteria. Countries

have successfully used cost-effectiveness analysis as an initial framework for generating information about new vaccine introduction related to the anticipated incremental program costs and projected cost savings from health service visits and hospitalizations averted. However, these data do not provide much guidance on logistical, financial, or social concerns, such as equity. While countries undoubtedly recognize the importance of incorporating these other criteria into national immunization decision-making, there is a need for additional tools and guidance on how to evaluate all these criteria—technical, programmatic, financial, and social.

The Region of the Americas has always been a pioneer and a global leader in immunization. These achievements are now potentially at risk due to the increased complexity of the decision-making and planning that must be undertaken by the national immunization programs (NIPs). New vaccine adoption without an adequate evidence base and careful planning could lead to an overall decrease in performance of the NIPs. The Programs could start facing problems of underfunding and inefficiencies, resulting in decreased public health benefits. This would also affect other health programs that benefit from the structure and reach of the national immunization programs to provide additional health services and interventions.

*Proposal to tackle these challenges*

To ensure that NIPs are equipped with the necessary capacities to meet decision-making challenges, a three-pronged approach is proposed.

I. *Expand the evidence base beyond cost-effectiveness:* The technical aspects of immunization policy-making should always be balanced with the programmatic and social aspects and should be considered in the context of the health system overall. In particular, the Region of the Americas is affected by the crippling effects of inequities within countries, in health and other areas of life, and immunization policy should aim to redress some of these inequities. Other dimensions that countries should include in their policy evaluations include assessing how the new vaccine could prevent high out-of-pocket health care expenditures and assessing subnational variations in the likely impact of the new vaccine.

II. *Institutionalize an evidence-based decision-making process for new vaccine introduction:* Institutionalization of NITAGs or similar technical advisory bodies, through ministerial decree or national law, is advisable to ensure continuity of policy recommendations and to establish explicit relationships between the advisory bodies and government agencies. These legal frameworks should also ensure financial support to carry out relevant research and operational studies to inform national immunization policies. Technical working groups should be formally established to expand the national evidence base, further cementing the infrastructure necessary to have a comprehensive, national, evidence-based decision-making process.

III. *Integrate policy-making and planning for NIPs:* Policy decisions followed by successful planning for adoption of new vaccines into national routine immunization schedules requires collaboration between several actors and harmonization of processes that have generally been treated separately. Integration of costing, budgeting, and planning processes and their accompanying tools will ensure that the incorporation of new vaccines in the routine program generates positive and sustainable results. The integration of these

processes can be supported by existing ProVac tools and methodologies and by technical cooperation from PAHO's regional immunization program.

This approach is proposed as the basis for the work plan of the ProVac Initiative in its second phase, which is planned for the period 2014 to 2019.

## RECOMMENDATIONS

- TAG recognizes the National Immunization Programs in the Region for their efforts in incorporating economic evidence into new vaccine policymaking processes.

- TAG commends the efforts and achievements of the ProVac Initiative in providing technical support to Member States for more informed decisions around new vaccine introduction.

- TAG recommends that PAHO Director and Member States provide their support for a future phase of the ProVac Initiative which will address issues related to equity and societal financial risks and the institutionalization of an evidence based decision-making process.

- TAG encourages the ProVac Initiative to continue sharing lessons learned around the evidence-based decision-making for new vaccine introduction with other WHO Regions.

## YELLOW FEVER

Yellow fever continues to be a significant public health problem for the 13 countries of the Americas with endemic areas. Over the last thirty years, yellow fever virus activity has been restricted to the enzootic area shared by Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Panama, Peru, Suriname, Trinidad and Tobago, and Venezuela. Since late 2007, the Region has experienced intense circulation of the yellow fever virus with extensive epizootics and outbreaks of human cases. The endemic area was extended to include Paraguay and northern Argentina, because of human cases and epizootics detected in 2008.

The main mode of transmission of yellow fever in the Americas is the sylvatic cycle. However, in 2008, cases of yellow fever were reported in the metropolitan area of Asuncion, Paraguay. Prior to this, the last confirmed urban outbreak of yellow fever in the Americas had occurred in 1942 in Brazil. This event, in addition to the proliferation of *Aedes aegypti* in the Region, shows the high risk of re-urbanization that still exists in the Americas.

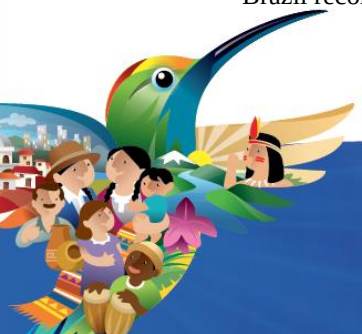
From 1985 through 2012, countries have reported 4066 cases and 2351 deaths from yellow fever in the Region, with a 58% fatality rate. During this period, 95% of the cases were reported by 4 countries: Peru with 54%, Bolivia with 18%, Brazil with 16% and Colombia with 7% of the cases, respectively. French Guyana, Guyana, Panama, Suriname and Trinidad and Tobago have not reported cases in more than two decades.

The yellow fever vaccination strategies used in the Region of the Americas include: 1) introduction of the yellow fever vaccine in national immunization programs for children 1 year of age[1] in every country with endemic areas; 2) vaccination campaigns during inter-epidemic periods; 3) vaccination campaigns in response to outbreaks or epizootics, and 4) administration of the vaccine to those traveling to areas where there is a risk of transmission of the yellow fever virus, except for those for whom vaccination is contraindicated.

As of 2012, every country in the Region with enzootic areas has added the yellow fever vaccine to their national immunization schedules. In Argentina, Brazil and Panama, the vaccine is only administered in areas with potential risk. Vaccination coverage of children 1 year of age in countries where yellow fever is endemic, which is approximately 70% for the period from 2007 to 2012, has been significantly affected by insufficient availability of the vaccine. This shortage of yellow fever vaccines places the achievements attained by the Region at risk, with regard to the strategy of vaccinating children one year of age, as well as the vaccination of susceptible individuals living in high-risk areas.

In 2013, the SAGE revised its 2003 position paper on the use of the yellow fever vaccine. This revision placed special emphasis on whether the need exists for a booster every 10 years and on vaccine safety in special populations such as the population ≥60 years of age, individuals infected with the human immunodeficiency virus (HIV), other immunosuppressed individuals, pregnant women and infants. SAGE's main recommendations are the following:

[1] Brazil recommends the administration of this vaccine at 9 months of age.



1. A single dose of the yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection against the disease. Therefore, no booster is required.

    a. However, surveillance should be intensified and clinical studies should be conducted to determine whether specific risk groups (for example, patients infected with HIV) require a second dose.

    b. The International Health Regulations need to be revised in order to make the necessary adjustments to the validity period required for international yellow fever vaccination certificates.

2. Regarding use of the vaccine for individuals ≥60 years of age, SAGE indicated that while the risk of vaccine-associated viscerotropic disease is greater than in younger groups that receive the vaccine, the overall risk is still low.

    a. Vaccination of individuals ≥60 years of age who have not been previously vaccinated and require it, should be recommended based on a risk-benefit evaluation in which the risk of contracting the disease is weighed against the risk of a potentially serious adverse event following vaccination.

3. The yellow fever vaccine is contraindicated in seriously immunosuppressed individuals (including those with conditions such as thymus disorders, symptomatic HIV, malignant neoplasms under treatment, treatments with immunosuppressants or immunomodulators, recent transplants, current or recent radiation therapy). The vaccine can be offered to individuals with asymptomatic HIV infection with CD4 counts + ≥ 200 cells/mm³ that require vaccination.

    a. It is recommended that the vaccine be administered to all clinically healthy children through routine vaccination programs, and that HIV tests not be a prerequisite for vaccination in this context.

    b. It is recommended that in situations in which the risk of yellow fever is high and large-scale vaccination campaigns are conducted, it is not necessary to determine HIV infection as a requirement for immunization.

4. Vaccination of pregnant and breastfeeding women

    a. Pregnant women that reside in enzootic areas: vaccination is only recommended in the case of outbreaks, as well as in any situation in which there is an apparent risk of yellow fever transmission (preventative campaigns), because the risk of transmitting the virus from the vaccine to the fetus is less than the benefits of vaccinating pregnant women.

    b. Breastfeeding women that reside in enzootic areas: vaccination is recommended because the risk of transmitting the virus from the vaccine to the infant is less than the benefits of vaccinating breastfeeding women.

c. Pregnant or breastfeeding women that travel to endemic areas: vaccination is recommended when the trip cannot be postponed or avoided. They should receive counseling on the benefits and potential risks of vaccination so that they can make an informed decision. The benefits of breastfeeding are far superior to those of other nutritional alternatives.

5. Simultaneous administration of yellow fever and measles vaccines. A number of studies have indicated that yellow fever and measles vaccines can be administered simultaneously without affecting the safety or immunogenicity of the yellow fever vaccine; however,

   a. A study showed that simultaneous administration of the yellow fever and measles, mumps and rubella (MMR) vaccines in children suggest that immunogenicity may be compromised for both the yellow fever vaccine and the rubella and mumps components of the MMR vaccine. However, to date, the evidence is insufficient to change current recommendations. Therefore, the simultaneous administration recommendation stands.

   b. SAGE recommended conducting additional studies on simultaneous administration of the yellow fever vaccine and others.

6. The strategy to control yellow fever should include surveillance and yellow fever vaccination through a combination of routine immunization strategies and large-scale disease-prevention campaigns. Campaigns in response to outbreaks should be conducted if vaccine coverage is inadequate in the population.

## RECOMMENDATIONS

- TAG endorses the recommendations issued by SAGE:
  - One yellow fever vaccine dose is sufficient to provide sustained immunity and life-long protection against the disease, therefore no booster is required.
  - In regards to special populations, immunocompromising conditions including symptomatic HIV or CD4+ counts < 200 cells/$mm^3$ are contraindications to vaccination while age ≥60 years, pregnancy, and breastfeeding are precautions to vaccination. A risk-benefit analysis is recommended for individuals with a precaution to vaccination.
  - The recommendation for the simultaneous administration of MMR and yellow fever is maintained, given that to date there is no sufficient evidence to change current recommendations.
- TAG calls for further studies to better understand the potential need for boosters in special groups, as well as the simultaneous administration of yellow fever and other live vaccines such as MMR in children. Also, additional studies are needed on the immunogenicity and safety of yellow fever vaccine in persons aged >60 years, HIV-infected adults and children, and pregnant and breastfeeding women.

- TAG reemphasizes the importance of yellow fever vaccination through the routine immunization program and of maintaining high coverage levels in order to prevent cases and outbreaks of the disease.

- PAHO should work towards addressing the long-standing issue of insufficient yellow fever vaccine supply in the Region through technology transfers and other mechanisms. Similarly, TAG strongly urges PAHO, WHO, partners, and vaccine manufacturers to develop a strategy to increase the global production capacity for yellow fever vaccine.

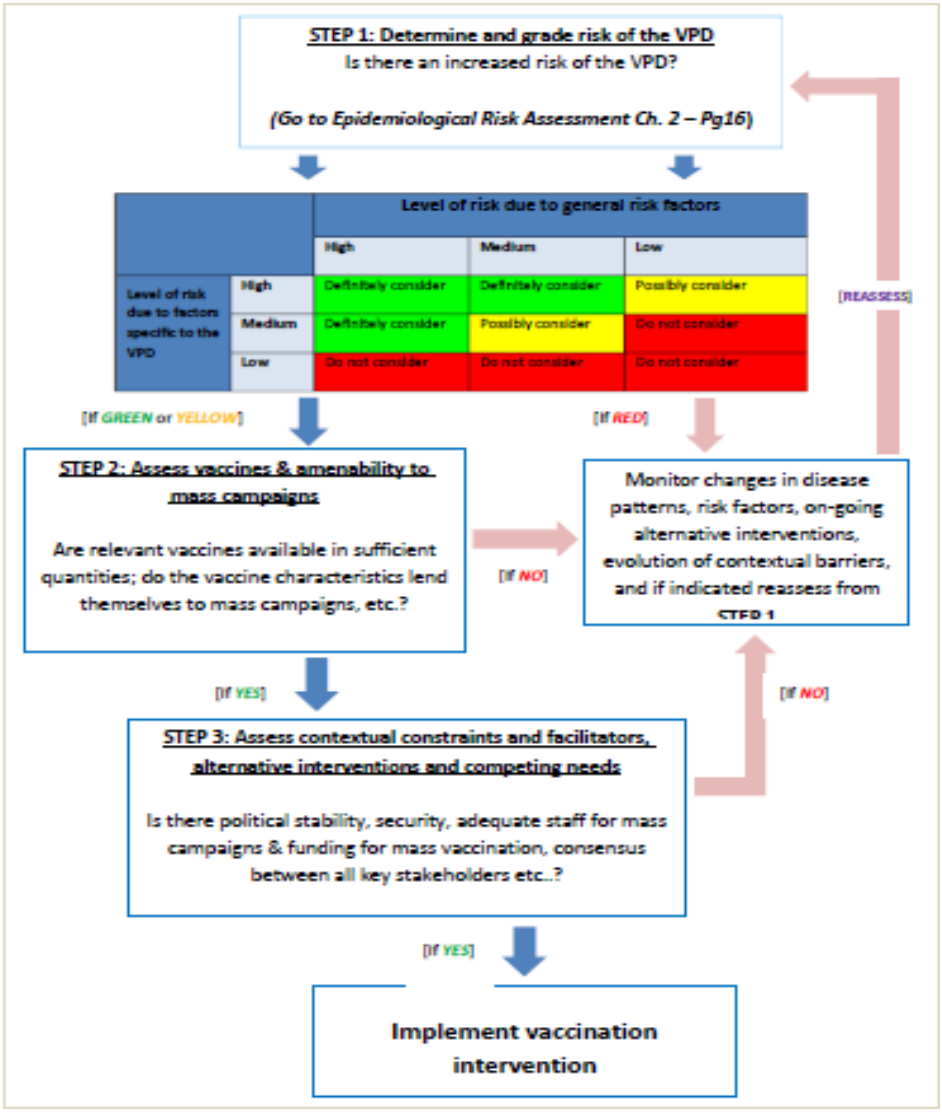
## VACCINATION DURING EMERGENCY SITUATIONS

Natural disasters and acute humanitarian emergencies are unforeseen events that can result in large movements of people, overcrowding, poor sanitation, disruptions in the supply of clean water, limited access to food, and damage to the health infrastructure. These conditions favor the emergence of communicable diseases like diarrheas and respiratory illness, including pneumonias, primarily affecting children and seniors. In some situations of natural disasters or mass violence, there can be a significant number of injured people. In situations like disasters, the question of whether to vaccinate, what vaccines to use, when and the scope of vaccination often emerge. For many years, PAHO's Immunization Program has issued recommendations regarding vaccination in disaster situations. The main objectives of these recommendations are to prevent outbreaks of vaccine preventable diseases (VPD), particularly of those with a high morbidity/mortality; to prevent tetanus cases in injured patients; and to reestablish routine immunization as soon as possible. The latest update to these recommendations was issued in 2010, following an earthquake that affected Haiti.

In 2011, the WHO's SAGE on Immunization of established a Working Group on Vaccination in Humanitarian Emergencies to review the available evidence on the current decision-making processes for vaccination in humanitarian emergencies. After conducting an exhaustive literature review and a review of current practical experiences with the decision-making processes for vaccination in these emergencies, the Working Group concluded that there was limited guidance for making decisions regarding vaccination in emergencies that was widely accepted or generally used. For example, the guidelines most widely used by humanitarian response agencies to respond to these emergencies are Sphere[2]. On vaccination, these guidelines used to only recommend measles vaccination among children between 6 months and 14 years of age, the provision of vitamin A supplements and the provision of critical vaccines and supplies, such as cold chain equipment, and experts on training and social mobilization. In an effort to fill this gap, the Working Group developed "Vaccination in Acute Humanitarian Emergencies: a Framework for Decision-Making". This framework was endorsed by the SAGE in 2012.

The framework for decision-making on vaccination in acute humanitarian emergencies was developed for national authorities and partner agencies to use, and it proposes a standardization of the decision-making process in 3 steps. These steps are shown in the following diagram:

[2] The Sphere Project is a voluntary initiative that brings a wide range of humanitarian agencies together around a common aim - to improve the quality of humanitarian assistance and the accountability of humanitarian actors to their constituents, donors and affected populations. The Sphere Handbook, Humanitarian Charter and Minimum Standards in Humanitarian Response, is one of the most widely known and internationally recognized sets of common principles and universal minimum standards in life-saving areas of humanitarian response. See more at: http://www.sphereproject.org/about/#sthash.KiyVzJ59.dpuf




In light of this new framework for decision-making on vaccination during acute humanitarian emergencies; of polio eradication being declared an operational emergency at the 2012 World Health Assembly; of the regional progress towards measles and rubella elimination and the emergency plan to maintain elimination of these diseases endorsed by the 2012 PAHO's Directing Council; and considering recent updates to WHO positions papers on some vaccines, notably cholera, yellow fever, hepatitis A, pneumococcal and meningococcal, PAHO has reviewed its recommendations and presented them to the TAG prior to dissemination. In these recommendations, countries are urged to adopt the decision-making framework for vaccination in acute humanitarian emergencies. PAHO's recommendations also summarize considerations on vaccines that could be used, highlighting polio and measles-rubella vaccination. Furthermore, they reiterate that mass vaccination is not always recommended in the wake of a disaster and that it could even be counterproductive. They cite which vaccines to be considered for disaster and

humanitarian emergency response teams, and emphasize the importance of reestablishing the routine immunization as soon as possible. These recommendations are included in Annex A.

## RECOMMENDATIONS

- The TAG adopts the SAGE Working Group's Framework for Decision-Making on Vaccination in Acute Humanitarian Emergencies and endorses the recommendations of PAHO's Immunization Program (Annex A).

## PROGRESS ON HUMAN PAPILLOMA VIRUS VACCINE INTRODUCTION & FRAMEWORK FOR IMPACT EVALUATION

Countries in Latin America and the Caribbean are increasingly introducing vaccines against human papillomavirus (HPV) in their national immunization schedules. In July 2011, four countries had included the HPV vaccine in their schedules and 2.6 million girls (34% of an adolescent female cohort typical for the Region) had access to HPV immunization. In July 2013, ten countries have included the HPV vaccine in their schedules and 4.5 million girls (58%) have access to HPV immunization.

While progress in HPV vaccine introduction over the past two years is notable, obstacles to a wider adoption by other countries of the Region persist. First, together with PCV, the HPV vaccine remains the most expensive EPI vaccine in the Revolving Fund intended for potential universal use. Vaccine cost is also perceived as unaffordable and sometimes as unfairly priced. Second, public health priorities in Latin America and the Caribbean often focus on childhood killers (pneumonia and diarrhea) and maternal mortality and, consequently, public investments are directed at their prevention. Finally, health professionals express uncertainty about safety and long-term efficacy of HPV vaccines, its delivery strategies, and the possible integration with cervical cancer screening.

The HPV vaccine is safe, but public and some health professionals continue to have concerns regarding HPV vaccine safety. In June 2013, WHO Global Advisory Committee on Vaccine Safety reviewed updated information about the safety of HPV vaccines. Based on that information and considering that more than 170 million doses have been distributed worldwide and more countries are offering the vaccine through national immunization programs, this Committee concluded that it continued to be reassured by the safety profile of the currently available HPV vaccines. The characteristics of today's HPV vaccines, the data generated in the large clinical trials and post-marketing surveillance (both with passive and active systems), and the efforts are all important considerations supporting such a conclusion.

Where the vaccine has been introduced, programmatic challenges remain in accurately measuring vaccination coverage and in integrating HPV immunization with other health programs for adolescents and cancer programs. HPV vaccination coverage data frequently show drop-out rates as high as 50%. It is currently difficult to determine whether those data reflect problems in HPV vaccine acceptance, in information systems, or both. As evidence accumulates on the effectiveness of HPV vaccines, the fulfillment of the potential of HPV immunization eventually rests in achieving and maintaining high vaccination coverage for all doses of the schedule.

The expectation that HPV immunization could lead to integration with, and consequently achieve greater access, to cancer programs, school health programs, and sexual health programs, has generally not happened. Integration is often reduced to joint communication campaigns that advocate for vaccination of adolescents and cervical cancer screening in adult women. However, Argentina started HPV DNA testing in the Province of Jujuy (with plans for a gradual nation-wide expansion) as part of a comprehensive cervical cancer prevention program and Uruguay is offering the HPV vaccine in health centers within the framework of sexual health programs. Both experiences are very promising.

Mexico and the two Canadian Provinces of British Columbia and Quebec have adopted immunization schedules that differ from the schedules licensed by regulatory agencies between 2008–2010. In these alternative immunization schedules, intervals between the administration of the first and subsequent doses are extended (second dose given at 6 months and the third dose given at 60 months after the first dose). As of July 2013, no cohort has reached an age when the administration of the third dose is expected and it is thus unknown whether vaccinated girls can be reached again five years after administration of the first dose. Colombia switched to an extended 3-dose schedule in the first semester of 2013 and the national TAG of Chile recommended the HPV vaccine introduction with similarly extended schedules. Immunological, programmatic and financial advantages are the rationale for alternative schedules. Clinical trials indicate that the immunogenicity of two HPV vaccine doses in adolescent girls is not inferior to the immunogenicity from three doses in young women through 36 months of follow-up. Post-hoc analysis of the data from a clinical trial conducted in Costa Rica suggests high efficacy for a less than 3-dose schedule. Additional evidence on alternative schedules can be expected over the next few years.

At its previous meeting, the TAG recommended that PAHO develop a framework to monitor HPV occurrence and to evaluate the impact of HPV immunization in the Region. The proposed framework outlines primary and complementary endpoints that can be monitored over three subsequent periods following a HPV vaccine introduction. On the short-term (5–10 years after vaccine introduction), prevalence of HPV genotypes in sexually-active adolescents is the primary monitoring endpoint, and, if the quadrivalent vaccine were introduced, prevalence of genital warts could be a complementary endpoint. On the medium-term (10–15 years after vaccine introduction), prevalence of precancerous lesions (with adjustment for screening coverage) and/or HPV genotype prevalence in invasive lesions are primary endpoints; cervical cancer screening coverage and positivity of screening tests could be complementary endpoints. On the long-term (≥20 years after vaccine introduction), cervical cancer incidence or mortality and HPV genotype prevalence in invasive cancer are primary endpoints; incidence of other HPV-related cancers, cervical cancer screening coverage, and follow-up of women with positive screening tests could be complementary endpoints. Rather than being prescriptive, this framework illustrates different options that Countries can adopt depending on the specific national and local conditions. Activities developed within the regional framework may have a positive influence on national programs for cervical cancer screening.

## RECOMMENDATIONS

- Countries which have introduced HPV vaccine should strengthen their efforts to characterize vaccination coverage at subnational and national levels.
- TAG also recommends that countries, which are considering an introduction, carefully plan information systems to collect and analyze coverage data at all levels.

- TAG endorses the June 2013 statement of WHO Global Advisory Committee on Vaccine Safety related to HPV vaccine and recommends that PAHO disseminate evidence of HPV vaccine safety in the Region.

- Countries should, depending on their capacities, adopt the activities laid out in the regional framework for impact evaluation of HPV vaccine. TAG recognizes that a regional network of HPV laboratories is an integral component of such a framework.

- TAG recommends 2- and 3-dose extended HPV immunization schedules for girls aged 9–13 years as they can offer immunological, programmatic and financial advantages. TAG also recognizes the need to gather data on a longer term for 2-dose schedules.

- PAHO should continue to explore mechanisms to make the HPV vaccine more affordable without compromising the principles of the Revolving Fund.

## LABORATORY MEETING REPORT

The Regional Laboratory Network of the of the Americas has been providing support for vaccine preventable disease (VPD) eradication, elimination, and control initiatives as soon as they have been approved by the Pan American Sanitary Bureau since 1986, when the US Centers for Disease Control and Prevention (CDC) and PAHO conducted the first training of country personnel and established the Polio Lab Network. The first training of measles-rubella laboratories in countries took place in 1995. This strategic alliance between the CDC and PAHO continues to this day and has enabled the strengthening of Regional Laboratories' responses to VPD surveillance, providing important and relevant information for decision-making and the steering of national immunization programs.

The aim of the Laboratory Network is to have national laboratories with sufficient response capacity available to support VPD surveillance, to confirm the presence or absence of pathogens and to generate high quality, timely and reliable results.

The Laboratory Network's role is based on: a) providing timely and precise information that allows for the confirmation or discarding of suspected/probable VPD cases; b) identifying the serotypes, serogroups, genotypes and patterns of transmission; c) providing reliable information that allows tailoring of resources towards control, elimination, and eradication of diseases, as well as, documenting the impact of new vaccine introductions; d) providing the capacity and ability to respond to unusual events; and e) advocating to national authorities on the need to continue strengthening laboratories and improving the services they provide.

Among the Laboratory Network's main accomplishments are: ≥98% of reported AFP cases had specimens analyzed by one of the network's laboratories; the timelines of laboratory results for polio has been reduced from 42 days to 28 days and currently to 21 days for viral isolation and intratypic differentiation; the Regional measles-rubella Laboratory Network has documented the Region's endemic genotypes and has confirmed the presence of imported cases in a timely fashion; the burden of rotavirus disease has been established and the circulating genotypes have been identified in various countries in the Region; surveillance of bacterial pneumonias and meningitis, through SIREVA and SIREVA II, has documented the main circulating serotypes/serogroups; recently, there has been an expanded participation of laboratories in Global External Evaluation Programs (3-polio, 2-measles-rubella, 1-rotavirus, 1-invasice bacterial vaccine preventable disease or IBVPD) that reveals the laboratories' technical capacity; and the building of capacities and training of lab personnel on new tests has been kept current.

The main challenges identified within the Regional Laboratory Network are related to: a) reaching and maintaining quality standards and surveillance indicators; b) guaranteeing national commitment, as sometimes laboratory surveillance is not considered a national priority; c) maintaining trained personnel as limited numbers of trained laboratory personnel and the permanent migration of personnel that exists; d) having adequate equipment given limited availability of equipment and reagents to implement new tests; e) providing timely response, noting that the usefulness of laboratory results is based on their reliability and on the timeliness in which they are communicated to the surveillance system; f) resource mobilization for all events under surveillance;

g) difficulties with customs/national authorities for specimen referrals and for receiving proficiency panels; and h) maintaining the support of groups from experts and strategic partners.

The need to consider the feasibility and relevance of establishing a Network of VPD Laboratories arises in response to the advent of new vaccine introductions that require the addition of new labs and new diagnostic methods. This Network would ideally guarantee that lab services necessary for the surveillance of these events are rendered; it would optimize management and communication of and with the different stakeholders in the system.

Lab participation in the Polio Eradication and Endgame Strategic Plan (2013-2018), recently defined by the WHO, is closely related to the plan's Objective 1: Detect and interrupt all poliovirus transmission. It requires a strong commitment, participation and compliance with performance indicators for polio labs to guide this final phase and consolidate the global eradication of poliomyelitis.

Moreover, at the Regional level, labs have had a strategic role during the verification of measles, rubella, and congenital rubella syndrome elimination phase. For this reason, the well-functioning of the Regional Laboratory Network should be kept current and its sustainability guaranteed.

TAG acknowledged the efforts and commitment of the Regional Laboratory Network in support of the eradication, elimination and control of vaccine preventable disease. Furthermore, it congratulated the national laboratories in the Region for their accomplishments and invites them to continue strengthening the essential role that labs play and to continue developing response capacities

## RECOMMENDATIONS

- Laboratories within the Network should harmonize the different procedures used to identify serotypes/serogroups/genotypes of the different VPD causing pathogens, in order to facilitate the comparability of lab results between countries and optimize the availability of data in all countries of the Region of the Americas.

- TAG reiterates that surveillance and labs are essential components of an effective immunization program and that they are required for strategic and evidence based decision-making. For these reasons, TAG urges countries to improve the integration of information generated by labs with those of the surveillance system.

- TAG recognizes that there is a need to establish a Regional Network of Vaccine Preventable Disease Laboratories that would generate reliable results, under the implementation of standardized tests and quality assurance programs, to facilitate decision-making in health and support impact evaluations of new vaccine introductions.

- PAHO should analyze the possibility of procuring reagents and diagnostic kits for vaccine-preventable disease surveillance through the Revolving Fund.

- TAG endorses the recommendations issued during the meeting of the Regional Vaccine Preventable Disease Laboratory Network held in Quito, Ecuador on 2 July 2013 (Annex B).

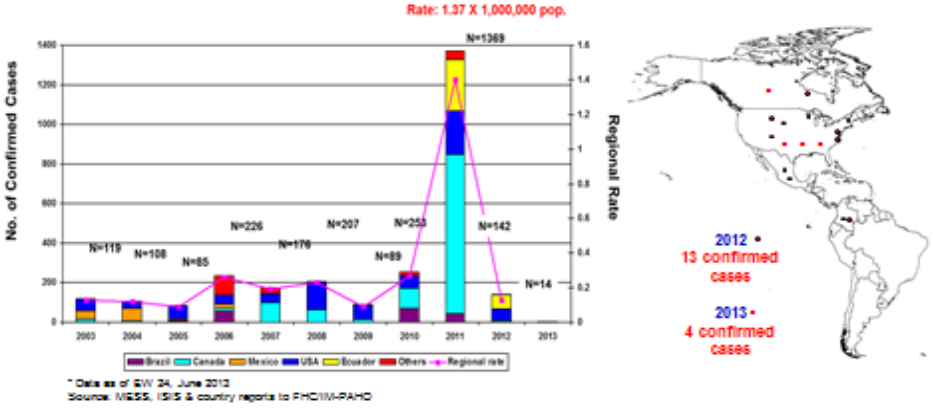
## MEASLES, RUBELLA & CONGENITAL RUBELLA SYNDROME

The countries of the Americas have demonstrated indisputable progress on the interruption of the endemic transmission of the measles and rubella viruses. Since 2002, the Region of the Americas has achieved and maintained elimination of measles and the last case of endemic transmission of rubella was reported in 2009. Continued circulation of the measles virus in other regions of the world has had an impact on the epidemiology of measles in the Americas. Following the annual occurrence of 89 to 249 imported cases and cases secondary to importation since 2003 and a large increase in cases reaching 1369 in 2011, the number of confirmed cases decreased to 142 cases in 2012 (Figure 1). All of the measles cases in 2012 were linked to importations and were reported by the following seven countries: Argentina, 1; Brazil, 2; Canada, 10; Colombia, 1; Ecuador, 72; United States of America, 55; and Venezuela, 1. Most outbreaks in the Region have been linked to the genotypes of imported viruses D8, D4 and B3; the most common is B3, mainly due to several secondary cases reported in Ecuador.

Starting in 2009, there have been imported cases of rubella. During 2012, 13 cases were reported (Figure 1), 5 were associated with importation and 8 had an unknown source of infection. Canada, Colombia and Mexico reported 2 cases each, and the United States reported the remaining 7 cases. In the cases in the United States and Mexico, the genotypes detected were 1E and 2B.

In 2012, 831 suspected cases of congenital rubella syndrome (CRS) were reported, 3 imported cases were confirmed. These cases were detected in the United States in infants whose mothers came from Africa, where the rubella virus is endemic.

**Figure 1. Distribution of confirmed cases of measles 2003-2013*and rubella 2012-2013* in the Americas**




Integrated epidemiological surveillance of measles/rubella met nearly all of the performance indicators for 2012, over 80%, with the exception of adequate investigation. However, the quality of active epidemiological surveillance is not homogenous at the sub-national and local levels. Nonetheless, countries have responded well to reported cases of measles and rubella, carrying out additional activities such as searching for cases, locating contacts, and evaluating risk.

There are some gaps in the surveillance of CRS; where they exist, countries use alternative and complementary lines of evidence.

This year and in the coming years, the Region of the Americas is the venue of a number of large-scale events at the national and international levels, including the 28th World Youth Day 2013 in Rio de Janeiro, Brazil, the 9th World Games 2013 in Cali, Colombia, and the 2014 FIFA World Cup and the 31st Summer Olympic Games in 2016, both in Brazil. This raises the possibility of the importation of the measles and rubella viruses from other regions of the world, which could lead to outbreaks, and at a high cost in terms of health, placing the maintenance of the elimination of these diseases at risk.

***Regional progress on the verification of the elimination of measles, rubella and CRS***

At the 28th PAHO/WHO Pan American Sanitary Conference, held in September 2012 in Washington, D.C., the International Expert Committee (IEC) presented progress made in the documentation and verification process to the Member States. In its regional report, it concluded that "it appears that the interruption of endemic measles and rubella virus transmission has been achieved." However, the report establishes that "as part of the documentation and verification process, several Member States have identified challenges they need to overcome for maintaining elimination of measles, rubella and CRS. In addition, some countries have reported weakness and failures in their national surveillance systems and routine immunization programs, which must be dealt with."

In light of the Region's vulnerability and risk, at the Pan American Sanitary Conference, the IEC presented a plan of action for maintaining the elimination of measles, rubella and CRS in the Region of the Americas, which was approved by the Member States by means of resolution CSP28.R14. In this resolution, countries are called upon to strengthen active surveillance of measles, rubella and CRS; to ensure measures for responding in a timely manner to viruses and imported outbreaks; and to maintain 95% or more immunization coverage at the national level and in every municipality.

In order to achieve 95% or higher coverage with two doses of the MMR or measles-rubella (MR) vaccine, many countries offer a second dose of the vaccine (MMR2) in follow-up campaigns. In order to determine the timing of these campaigns, the accumulation of susceptible individuals is monitored. When the number of susceptible individuals is nearly equivalent to a cohort of newborns, which generally occurs every 4 or 5 years, a follow-up campaign is conducted.

A second opportunity to vaccinate against measles and rubella prevents the accumulation of susceptible children to dangerous levels, as some older children may not have been vaccinated or developed the disease and remain susceptible. There are a growing number of countries that have introduced MMR2 to their national routine immunization schedule, but many of them are not reaching 95% coverage. Countries have recommended different ages for administering MMR2. In 2012, 42/47 countries and territories in the Americas reported that they are administering the MMR2 in their routine program. In 32 countries (76%), it is administered to children from 3 to 6 years of age, in 5 countries (12%) from 15 to 18 months of age of age, in 2 countries (5%) at 2 years of age, in 2 other territories (5%) at 9-12 years of age and in 1 country (2.4%) at 6-7 years of age. During 2011, these countries and territories reported higher coverage for the first dose (MMR1)

(94%), recommended at one year of age, than for MMR2 (83%). Bolivia, Guatemala, Haiti, Honduras and Nicaragua reported that they had not introduced MMR2 in their routine schedule.

In order to maintain the elimination of measles and rubella, coverage >95% with two doses of MMR or MR is required. In light of this situation, countries should review and take advantage of programmatic considerations that make it possible to achieve high coverage and the highest immunity of the population with the MMR2. They should take advantage of every opportunity when children receive treatment, other child health interventions and simultaneous administration with other vaccines. For example, administration of the MMR2 at the age of 15-18 months of age ensures early protection of the individual and slows the accumulation of susceptible children. Therefore, it lengthens the period between one campaign and another. The MMR vaccine can be administered simultaneously with other vaccines in the routine program (for example, the DTP booster). Currently, coverage rates for DPT4 tend to be higher than those for MMR2. It should be noted that if school enrollment is high (> 95%), reviewing completion of the schedule at school entry can be an effective strategy for achieving high coverage and prevention of outbreaks in the schools. Diversity in MMR2 schedules in the Region limits monitoring of susceptible individuals and the addition of data for determining regional coverage with the same precision as the MMR1.

In May 2013, the fourth meeting of the IEC was held jointly with the 23 national commissions and a sub-regional commission from the British Caribbean in order to:

1) follow-up on progress made on the documentation and verification of elimination,

2) know the results of IEC members' country visits and the status of the national documents presented by the countries,

3) identify obstacles and challenges to maintaining the elimination of measles, rubella and CRS in the Region, and

4) discuss the implementation of the Regional Plan of Action for maintaining the elimination of measles, rubella and CRS and the work plan for 2013-2014.

The report on the meeting, which was presented to the TAG, includes general recommendations, with specific recommendations for some countries and the PAHO Secretariat. IEC members will continue making visits to countries where maintaining elimination remains a major challenge.

*Laboratory network*

For the purpose of analyzing the performance and challenges of the Measles and Rubella Laboratory Network, a meeting was held in May 2013 with the participation of experts from regional reference laboratories for measles and rubella for the Region of the Americas, including Fiocruz (Brazil), the National Microbiology Laboratory (Canada), the CDC and the Caribbean Public Health Agency (Trinidad and Tobago), as well as PAHO immunization professionals. Representatives of national laboratories and the WHO global laboratory coordinator participated virtually. Recommendations made during the meeting were presented to the TAG.

In view of the efforts made to verify and maintain the elimination of measles, rubella and CRS, the TAG wishes to congratulate the members of the IEC, the countries and their national commissions. Likewise, it congratulates and thanks the members for helping the Region of the Americas demonstrate that measles and rubella can be eliminated and sustained over time.

It also commends Ecuador and its healthcare workers for the efforts made to control the outbreak of measles, to demonstrate the interruption of the virus transmission and to maintain the elimination of measles in the Region of the Americas.

**RECOMMENDATIONS:**

- The TAG commends countries for their efforts in maintaining measles and rubella elimination and encourages countries to continue implementing its previous recommendations in order to maintain the elimination of measles, rubella and CRS.

- TAG endorses the IEC recommendations, made at the fourth joint meeting with representatives of the national commissions, and urges countries to implement them and to submit their final verification reports by 01 December 2013.

- With the goal of achieving the highest MMR2 coverage possible, administration of the MMR2 vaccine is recommended at 15-18 months, and can be given simultaneously with other vaccines, such as the first DPT booster.

- Countries should continue to verify vaccination status at school entry and immunize children who have not been vaccinated with MMR2.

- Countries should continue with high-quality follow-up vaccination campaigns in order to guarantee a high level of immunity, while the Region continues with the verification process and vaccination coverage $\geq$95% has been achieved with two doses of MMR or MR in the routine program.

- PAHO Governing Bodies and Member States should continue advocating for measles and rubella elimination in global forums such as the World Health Assembly considering that importations of the virus pose a challenge for maintaining elimination in the Americas.

- PAHO should support country efforts to systematize the lessons learned from the recent measles outbreaks and to share them with other countries of the Americas as well as with the rest of the world.

## VACCINES UNDER DEVELOPMENT: UPDATE ON DENGUE, TUBERCULOSIS AND MALARIA VACCINES

Dengue occurrence remains at historic highs. In 2012, 1,120,902 dengue cases were reported in 43 countries and territories of the Americas. Of those cases, 32,748 cases (2.9%) were severe and 784 (0.07%) case-patients died. Reported cases only represent a fraction of dengue virus infections. A comprehensive modeling effort estimated 13.3 million apparent infections (confidence interval: 9.5–18.5 millions) and 40.5 million unapparent infections (30.5–53.3 millions) for 2010. Since 2004, an increasing number of countries have adopted a PAHO-recommended prevention and control strategy that integrates case management, vector control and social communication. No antiviral drugs or vaccines are available to treat or prevent dengue.

While research on dengue vaccines has faced unique challenges, two dozen vaccine candidates are currently in preclinical development and five in clinical development. The latter are designed to protect against infections from all four dengue viruses (tetravalent vaccines); three candidates are chimeric live-attenuated vaccines and two are inactivated or subunit vaccines. In October 2012, preliminary results of the phase IIb trial of the lead vaccine candidate (CYD-TDV, a chimeric live-attenuated tetravalent vaccine) were published. This trial is being conducted in a Thai district among 4,000 children aged 4–11 years and is meant to provide the first results on efficacy. The results show safety and immunogenicity against all four dengue viruses. However, efficacy was statistically not significant (30.2%; 95% confidence interval [CI]: -13.4%–56.6%) and differed by serotype. Phase III trials for the CYD-TDV candidate are ongoing (including in Brazil, Colombia, Honduras, Mexico and Puerto Rico) and their results will eventually be critical for a CYD-TDV licensure.

In anticipation of the potential licensure of a dengue vaccine, PAHO initiated a project to strengthen national dengue surveillance systems so that they can generate the information necessary to define vaccination strategies and to evaluate their impact in November 2012. The project's specific objectives are to create a regional working group that provides input to Technical Advisory Groups on Immunization on dengue prevention and control and on vaccine-preventable diseases, to harmonize case and diagnostic definitions used in national surveillance systems, to propose a regional surveillance model, and to strengthen the regional laboratory network. HIV/AIDS, tuberculosis (TB), and malaria also cause a considerable health burden in the Americas. For our region, 170,000 new HIV infections and 96,000 AIDS-related deaths were estimated for 2010. Likewise, 260,000 incident tuberculosis cases were estimated for 2011, and 490,000 malarias cases were confirmed in 2011.

Significant research efforts have been dedicated over the past decades toward finding vaccines against these diseases, but at the present time no vaccine is available except for the 90-year-old BCG vaccine (which offers an unreliable protection against pulmonary TB). Similar challenges are faced in the development of vaccines against HIV, TB and malaria. These challenges include the need to target various components of the immune system, attempts to induce humoral and cell-mediated immune responses, and knowledge gaps in the correlation between immunogenicity and protection. Multiple HIV vaccine models are being researched concurrently. Since 1987, more than 30 vaccine HIV candidates have been tested in >80 phase I/II clinical trials; two phase III trials have been carried to completion and a third one is in progress. The RV144 HIV vaccine trial was the first and still only study to demonstrate efficacy for an HIV vaccine. This trial

included 16,395 participants from rural areas in Thailand and used a combination of two vaccines with one vaccine given in four doses and then "boosted" by two further doses containing both vaccines. Results presented in 2010 showed a 31.2% vaccine efficacy (p = 0.039). Although this efficacy was insufficient to pursue licensure of the vaccination approach, several trials are incorporating lessons from the RV 144 trial and, if the adequate efficacy can be shown in the ongoing trials, an HIV/AIDS vaccine could become available from 2020.

A tremendous progress in TB vaccine development happened over the past decade and a rich pipeline of vaccine candidates is researched today. Twelve candidates are currently evaluated in clinical trials, of which two preventative vaccines—the MVA85A vaccine and M72/AS01 vaccine—are in phase IIb clinical trials. The MVA85A vaccine is designed to boost the immune responses that have been primed by the BCG vaccine. Results at two-year follow-up carried out in South Africa among 2,797 children aged 4–6 months were published in February 2013. Efficacy against tuberculosis was 17.3% (95% CI: -31.9%–48.2%) and against *M. tuberculosis* infection was -3.8% (95% CI: -28.1%–15.9%). Several reasons may explain the lack of protection in young children and it is still hoped that protection may result in older children, adolescents and adults. Phase IIb trial results for the vaccine M72/AS01 are not available yet. International partners devised a strategic blueprint to introduce the safest and most effective vaccines worldwide over the decade. Assuming that one of the most advanced vaccine candidates shows sufficient efficacy, the first new TB vaccine since the 1920s could become available by 2020.

While only one candidate for *Plasmodium vivax* malaria vaccine is in clinical development, several *P. falciparum* vaccines are tested in clinical trials. Among the latter candidates, the lead candidate RTS, S/AS01 is being studied in a phase III trial conducted in seven African countries. At one-year follow-up, the estimated vaccine efficacy against all clinical malaria episodes was 33.0% (95% CI: 26.4%–38.9%) in children vaccinated at ages 6–12 weeks and 55.1% (95% CI: 50.5%–59.2%) in children vaccinated at ages 5–17 months. An expert committee, which reports jointly to WHO's SAGE and Malaria Policy Advisory Committee (MPAC), reviewed these phase III trial results and considers that several questions remain unanswered, such as how efficacy changes over time after immunization, by transmission intensity, and seasonally. As long as further data and analyses become available, a joint session of SAGE and MPAC may make malaria vaccine policy recommendations in the last quarter of 2015.

## RECOMMENDATIONS

- TAG recognizes PAHO's work toward the harmonization of dengue surveillance systems across countries in the Americas and recommends that all countries contribute and participate in this effort.

- PAHO should support national regulatory authorities in defining harmonized regulatory pathways for the licensure of dengue vaccines.

- TAG considers important that, once licensed, dengue vaccine is not only made available to larger countries in the Region but also to smaller countries, if they so choose.

- TAG recognizes that several institutions in countries of the Americas, beyond Canada and the United States, have made great contributions to the development of new vaccines but

still represent largely untapped potential. International efforts should be undertaken to strengthen and coordinate research in vaccine development across the Americas.

## PNEUMOCOCCAL VACCINATION IN ADULTS

Pneumococcal pneumonia and other diseases caused by *Streptococcus pneumoniae* 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. In addition, the burden of pneumococcal disease has increased due to the number of individuals with chronic diseases or infected with HIV, as well as the aging 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.

Currently, there are two vaccines available in the market for use in adults: the 23-valent pneumococcal polysaccharide vaccine (PPV23), (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F), licensed since the 1980s for the population > 2 years of age, and the 13-valent (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A,19F and 23 F) pneumococcal conjugate vaccine (PCV), licensed in 2013 for use in adults over 50 years of age. Both vaccines are considered safe and well tolerated.

Many studies have been conducted on the effectiveness of the PPV23 in healthy adults and adults with risk conditions since this vaccine was licensed. The results of these studies are not consistent and there is considerable controversy regarding the efficacy in the different population groups against different outcomes studied (invasive pneumococcal disease – IPD, pneumonia, mortality, etc.), in the context of childhood PCV vaccination.

The 2012 WHO position paper mentions the meta-analyses performed on the studies on efficacy and effectiveness of the PPV23, among them a meta-analysis and review of the randomized controlled clinical trials (RCTs) conducted by Cochrane Database Systemic Reviews and published by Huss A et al. in the Canadian Medical Association Journal. These meta-analyses demonstrate that the results of the RCT on the PPV23 are compatible with a protective effect against IPD and all-cause pneumonia in young adults with overall good health and, to a lesser extent, protection against IPD in the elderly population in general. These RCTs have not demonstrated that the PPV23 is effective against IPD or all-cause pneumonia in populations with greater risk, such as adults and children with underlying conditions that increase the risk of contracting pneumococcal disease or highly immunosuppressed individuals of any age.

Many studies underscore the possibility that IPD rates will remain high among people for whom the PPV23 is recommended, partially due to low coverage with this vaccine, because of its limited effectiveness in populations with risk conditions and the potentially short duration of immunity.

More recently, immunogenicity studies have been conducted for the 13-valent PCV in adults. These studies have shown good immunogenicity, especially for the serogroups included in the vaccine.

In many industrialized countries, the incidence of adult IBD has decreased sharply with the introduction of childhood pneumococcal conjugate vaccines, including age groups that are not the primary vaccination target group, due to the herd immunity effect these vaccines provide.

## RECOMMENDATIONS

- PCV should be introduced in the routine vaccination schedule for children and high coverage should be maintained. PCV not only protects vaccinated children, but also protects other age groups as a result of herd immunity.

- Countries should establish high quality epidemiological surveillance of pneumonia and invasive bacterial diseases in adults and the elderly, at sentinel sites, to better understand the epidemiological profile of the disease in these age groups and to measure the herd effect of the conjugate vaccines used.

- The available evidence does not support the use of PPV23 in adults with risk factors due to the questionable effectiveness of the vaccine in preventing pneumococcal disease in this risk group.

- Countries currently using PPV23 in adult populations should consider conducting strategic research to contribute to the understanding around the value this vaccine.

- At this time, TAG does not recommend the use of conjugate pneumococcal vaccines for all adults. Introduction of PCV in adults should be grounded in evidence and decisions should not be based on the availability of donations or other factors.

## SEASONAL INFLUENZA VACCINATION

The Region of the Americas has made considerable strides in the introduction of the seasonal influenza vaccine. Among the main criteria used by the countries are TAG and WHO recommendations, and cost/effectiveness studies in countries such as Colombia and Costa Rica, among others.

By 2012, 41 of the 46 countries and territories were using the seasonal influenza vaccine in the public sector to protect one or more risk group. This includes 39 countries and territories that vaccinate the elderly; 37 have vaccinated healthcare workers, 30 vaccinate children, and 34 that vaccinate individuals with chronic diseases. It is important to note the progress made in the vaccination of pregnant women. As of 2008, only seven countries were vaccinating pregnant women against seasonal influenza. Following the H1N1 pandemic, there has been a rapid increase in the number of countries vaccinating this group, which grew from 7 to 22 countries in the last two years.

Although significant progress has been made in the introduction of the influenza vaccine in the majority of countries, there are still challenges such as a few effectiveness studies on the vaccine in 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.

During 2012, a pilot phase was carried out in four Central American countries in order to evaluate the effectiveness of the influenza vaccine in a collaborative project between the CDC, TEPHINET and PAHO. In a technical meeting on influenza held in the city of Antigua, Guatemala on February 25-27, 2013, in which representatives of 12 LAC countries and technical cooperation research centers and agencies participated, a network (REVELAC-i) was established to evaluate the effectiveness of the influenza vaccine in Latin America and the Caribbean. For 2013, in addition to the Central American countries, the participation of countries such as Argentina, Brazil, Colombia and Paraguay, among others, is expected.

Despite generalized use of the vaccine, other significant challenges such as the following remain:

- Quality and completeness of coverage data – lack of trustworthy denominators and variability in definitions of risk groups.
- Low level of acceptance of the vaccine by healthcare personnel.
- Operational challenges to complete two-dose schedules for children <9 years of age vaccinated for the first time.
- Seasonality in tropical countries.
- Coordination between vaccination, epidemiology and laboratory programs.

- Purchase of seasonal influenza vaccines, outlook, formulation and timely delivery of the vaccine due to production processes.

- Inserts for vaccines contain precautions or contraindications for vaccination of pregnant women, which presents an obstacle to vaccination of this priority group.

***SAGE Recommendations***

During the SAGE meeting held in November 2012, it was recommended that countries using or considering the introduction of the seasonal influenza prioritize 5 groups, with pregnant women as the group with top priority. In addition, the vaccination of 4 other groups was recommended in no particular order: children under five (particularly ages 6-23 months), healthcare workers, the elderly and individuals with chronic diseases. SAGE also placed special emphasis on the fact that countries should individually take into account the burden of disease and cost-effectiveness, feasibility and seasonality studies, in order to make evidence-based decisions on groups to prioritize and when to vaccinate.

*Pregnant women* have a high risk of severe complications and death. This risk is exacerbated by the presence of co-morbidities. Infection in pregnant women causes complications in the fetus, including low birth weight, fetal death or child mortality. The effectiveness and safety of the TIV has been demonstrated for the mother and the child. (Children under 6 months of age have high rates of hospitalization associated with influenza.)

*Children under five*, especially children 6-23 months of age, experience a high burden of disease due to influenza. Protection of this immunologically naive group requires two doses of the vaccine, and its effectiveness particularly depends on a match between vaccine strains and circulating viruses. Children from 2–5 years of age also have a high burden of disease, although lower than the under 2 years of age group, and may respond better to influenza vaccines.

*Healthcare workers* are at greater risk of contracting influenza than the population at large. In this group, the vaccine not only protects the individual, but also vulnerable patients, and may reduce absenteeism from work. Immunization of healthcare workers should be considered as part of a broad hospital infection control program.

*Seniors (or older adults)* have a greater risk of serious disease and mortality associated with influenza, due to which they continue to have high priority for vaccination. Although evidence shows that the vaccines are less effective, they continue to be a very important measure, due to the high vulnerability of this group.

*People with chronic diseases* include groups at high risk for influenza as well as those with HIV, asthma, and cardiac and lung diseases.

The current influenza vaccines are trivalent inactivated influenza vaccines (TIV) or live attenuated influenza vaccines (LAIV). They include two A strains and a B strain. Inactivated vaccines are the only ones licensed for children from 6 to 24 months of age, people over 50 years of age, and pregnant women. There are also quadrivalent vaccines (2 A strains and 2 B strains) that have been licensed or will be soon (LAIV, IIV).

The TAG commends the countries for efforts made in the Region in relation with vaccination against seasonal influenza, especially the vaccination of high risk groups such as pregnant women, among others. In addition, it applauds the formation of the first network of developing countries for the purpose of evaluating the effectiveness of the influenza vaccine, which is a multicentric, collaborative effort with support from PAHO, CDC and TEPHINET.

## RECOMMENDATIONS

- TAG reiterates its and SAGE's previous recommendations on the vaccination of high risk groups against seasonal influenza, with special emphasis on pregnant women. Due to the vulnerability of pregnant women to complications from influenza infection, countries should strengthen vaccination of pregnant women.

- Countries should increase vaccination coverage in healthcare workers and identify the reasons for non-vaccination in this group in order to try to reduce these obstacles.

- Countries should improve the quality of coverage data on the influenza vaccine in high-risk populations, including the standardization of denominators.

- TAG encourages countries to continue evaluating the effectiveness and impact of the vaccine, which entails an effort to strengthen epidemiological surveillance, as well as immunization and laboratory programs.

## PROGRESS AND CHALLENGES ON NATIONAL VACCINATION REGISTRIES

Countries in the Americas continue making progress towards the development and implementation of immunization registries. Mexico, Panama (though not throughout its entire territory), Uruguay, and some Caribbean islands are using national immunization registries. Belize, Brazil, Chile, Colombia, Costa Rica and Guatemala are undergoing a gradual implementation process and facing diverse challenges. Argentina, the Dominican Republic, Honduras and Paraguay are in development and piloting phases; while El Salvador and Venezuela have recently begun advancing towards an immunization registry. In the case of Canada and the United States, existing immunization registries are kept by province, state or jurisdiction. This list does not include immunization registries used by sub-national levels in Latin American countries, or registries used by other entities such as non-governmental organizations, social security systems, among others.

The immunization registries have followed a variety of approaches in terms of their development and maintenance, financing, data entry model (vaccinator vs. data entry clerk) and online and offline versions. Similarly, some registries are independent, while others are part of larger health information systems. Some registries are related with other immunization information systems, such as vaccine and supply logistics management systems or tools for epidemiological surveillance of vaccine preventable diseases and events supposedly attributable to vaccines and immunization (ESAVIs). However, as is no data that would enable the comparison of the advantages and disadvantages of the different approaches used, it is currently impossible to determine which is the most effective and efficient model.

There is evidence indicating that measuring vaccination coverage better, results in improved coverage levels. National immunization registries facilitate monitoring coverage by cohort and geographical area, allowing for the individualized follow-up on increasingly complex schedules and identification of individuals with delayed or incomplete schedules, and facilitate sending automated recall/reminders. If an immunization registry is complete, its data could be used as denominators to calculate coverage. Registry data can be triangulated with census projections. Furthermore, the rosters can be contrasted periodically, using capture-recapture techniques, with birth rosters or other data sources. This is already being done by some immunization programs using a registry. Nominal immunization registries are a key tool for monitoring vaccination coverage in each community, which is a goal established in the Global Vaccine Action Plan approved by the World Health Assembly in 2012. The implementation of these registries is facilitated by the increasing availability of new information and communication technologies (ICTs), as well as the rapid increase in availability of computers and connectivity.

As more countries develop and implement this type of registries, lessons learned continue to emerge. Highlighted among these is the fact that the implementation of an immunization registry cannot be seen as a project, but rather should be considered a process that will take time and will need to be monitored and accompanied. Furthermore, the registry will require continuous human and financial resources for its maintenance and proper use. Similarly, it has become evident that in order for a system to be accepted and the data entered be of good quality an immunization registry should not only obtain vaccination coverage rates for managerial use, it should be useful to vaccinators and facilitate work at the operational and local levels. Finally, there is a need to evaluate existing national immunization registries and the experiences of their development and

implementation – in terms of effectiveness, costs, and impact on the efficiency of workflows – in order to distil and standardize best practices and lessons learned.

Other challenges for developing and using national immunization registries include: a) costs, not only those incurred during the development phase but those incurred for maintenance and for continuous updates and improvements; b) issues related to policies for data security and privacy of personal information; c) the need for registries to be flexible enough to accommodate new vaccines, new schedules and special situations; d) the need for training, which in some cases goes as far as to teaching how to use a computer; e) its acceptability at the various levels, but primarily at the operational level; and f) practical issues such as the best forms for capturing data, how to manage duplicate records and correct and timely synchronization of databases for offline registries. The Region of the Americas is at a crucial point with regard to the use of immunization registries. It will be important to disseminate and share experiences and lessons learned on this topic in order to pave the way for countries that are developing an immunization registry or considering one.

## RECOMMENDATIONS

- Recognizing the progress made on the development and implementation of computerized nominal immunization registries in the Region, TAG reemphasizes its previous recommendations on the topic.

- Countries should monitor the implementation of an immunization registries to ensure that they perform properly and, if necessary, implement timely corrective actions.

- Vaccination registries should always meet the needs of vaccinators at the local level.

- PAHO should assess country experiences on immunization registries and continue fostering the exchange of country experiences, lessons learned and good practices at the regional and global level.

- PAHO and countries should explore the use of innovative mobile technologies linked to immunization registries, where applicable.

## PROGRESS OF HAITI'S IMMUNIZATION PROGRAM

The Expanded Program on Immunization (EPI) is a priority of the Haitian Ministry of Public Health and Population (MSPP). The EPI is focused on reducing morbidity and mortality due to vaccine-preventable diseases, as well as maintaining the elimination of polio, measles, rubella and congenital rubella syndrome (CRS). Despite commendable progress made recently (such as the implementation of intensive child health activities), the EPI still faces significant challenges in some of its components.

In this regard, the MSPP, with on-going support from strategic immunization partners and based upon the multi-annual plan for 2011-2015, developed a 2013 work plan for the purpose of strengthening regular immunization services in the country. PAHO is supporting this work plan by providing technical and financial support to strengthen management and coordination of the EPI, the organization of regular vaccination services, the logistics system, the cold chain, communication, social mobilization, the introduction of new vaccines and epidemiological surveillance.

***Progress to date***

*Vaccination coverage*

Historically, vaccination coverage for the different antigens has been low, without surpassing the 80% mark. However, starting in 2011, vaccination coverage began to improve progressively, particularly with BCG (82%) and the third dose of DTP3 (85%), which indicates improvement in access to vaccination services at the local level. Sustaining this progress is the greatest challenge facing the EPI in Haiti. In 2012, coverage levels fell to 69 and 80% respectively (see Table 1). Furthermore, the following five departments are below the national average with DTP3: Artibonite (64.8%), North (68%), South (74%), Northwest (65.3%) and Southwest (70.8%).

**Table 1**: Vaccine coverage in children < 1 year, Haiti 2008-2012

| Year | BCG | Measles Rubella | DTP3 | Polio3 |
|---|---|---|---|---|
| 2008 | 61 | 54 (a) | 53 | 52 |
| 2009 | 66 | 60 | 68 | 65 |
| 2010 | 64 | 45 | 69 | 62 |
| 2011 | 82 | 58 | 85 | 79 |
| 2012 | 69 | 66 (b) | 80 | 76 |

Source: Country report to PAHO (JRF)

(a) 2007 figure for the measles vaccine

(b) The country conducted a follow-up on children < 9 years of age, achieving >95% national coverage.

In this regard, the EPI has proposed 4 strategic lines of action for the purpose of improving access to vaccination services at the local level, achieving timely vaccination of the target population; these lines of action are the following:

- Reorganization of the network of vaccination services.

- Organization of vaccination services through the implementation of model immunization clinics. To date, 22 immunization clinics have been installed in each of the country's departments, including the Metropolitan Area, and the installation of at least 2 more per department is expected by the end of 2013.

- Definition of the best tactics for capturing the target population, according to the area of influence, demographics, population density and sociocultural characteristics.

- Integration of vaccination with other health interventions (such as vitamin A and deworming drugs).

As part of the improved access to vaccination services, the EPI has prioritized training on micro-planning at the local level, which includes the communication and social mobilization component. Likewise, in light of the weaknesses of the National Vaccination Program, training workshops have been held at the departmental level to improve the gathering and analysis of vaccination data. Timely supervision by department carried out by local professionals trained by PAHO will facilitate regular submission of high-quality data from the departmental level to the national level, achieving the indicators. Lastly, the EPI has obtained strategic partners' commitment to improve vaccine storage capacity immediately at the departmental level and in outlying areas. This is critical for timely introduction of the rotavirus vaccine (scheduled for the second semester) and the pneumococcal vaccine (2014).

*Epidemiological surveillance*

As part of the process for documenting and verifying the elimination of measles and rubella, the country demonstrated the absence of circulation of these viruses through the implementation of active searches in healthcare and community services during 2012. Similarly, the country carried out a retrospective search for congenital rubella syndrome (CRS) in selected institutions for the period 2007-2012, the results of which were zero cases of CRS detected.

Achievement of the indicators of the measles/rubella surveillance system has improved substantially since 2012. By epidemiological week (EW) 22/2013, the country had reported 124 suspected cases of measles and rubella, and had complied satisfactorily (>80%) with every surveillance indicator.

Surveillance of acute flaccid paralysis (AFP)/polio, tetanus and neonatal tetanus (NNT) continues to present significant challenges with regard to both periodic reporting of cases and compliance with indicators. In the case of polio, by EW 23, the notification rate for AFP was 0-17% per 100,000 <15 years of age and the percentage of adequate samples was 66%. Between 2009 and 2012, the country was in epidemiological silence for reporting cases of NNT. However, as part of the plan to eliminate neonatal tetanus, 65 at-risk municipalities were identified. In 2013, with support from Brazilian epidemiologists in each department, 2 cases of NNT were confirmed and investigated.

## RECOMMENDATIONS

- The TAG congratulates Haiti on the commendable progress made, and urges the national authorities to maintain their strong commitment to the regular immunization program.

- The country should, based on the strategic lines of action, prepare a road map to strengthen the regular immunization program. The implementation of this road map implies the development of a single plan of action agreed upon with the strategic partners, in order to guarantee timely mobilization of resources.

- The country should continue building national vaccination capacity, giving local professionals greater stability, for which the strategic partners should maintain ongoing support on the training and supervision of these professionals.

- The TAG endorses the ICE's specific recommendations for Haiti on the verification of the elimination of measles, rubella and CRS.

- The TAG urges Haiti to maintain its momentum in completing the agenda and facing new challenges in vaccination, such as the introduction of new vaccines.

- The country should formulate a communication and social mobilization plan aimed at generating a higher demand for vaccination.

## UPDATE ON THE STATUS OF PAHO'S REVOLVING FUND FOR VACCINE PROCUREMENT AND PROGRESS REPORT ON REGIONAL DEVELOPMENT OF VACCINES AND HEMODERIVATIVES

***Status of the Revolving Fund***

For over 32 years, PAHO's Revolving Fund for vaccine procurement (RF) has been the strategic tool of countries in the Region, in order to gain access to a continuous, timely supply of good-quality vaccines at the lowest available price. During the meeting, key figures regarding the operation of the RF were presented and the context in which the RF operates and the importance of the countries' participation were explained.

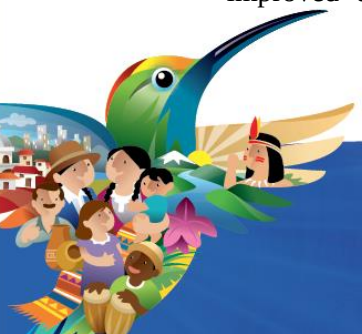
In 2012, the RF purchased 60 products including 28 different biologicals on behalf of 34 countries and 7 territories. A total of 180 million doses were procured for a total purchase value of US$512 million. The RF coordinated and monitored a total of 1200 shipments, arranging for their timely arrival. In that same year, the capital fund, which allows countries to reimburse PAHO for the purchase cost 60 days after the arrival of their orders, amounted to US$102 million dollars. This is the result of the solidarity contribution of 3% over the countries' purchase value. More than 80% of the purchases were made using the line of credit, which to date amounts to US$9 million for each country.

Its mission has not only contributed to the elimination of vaccine-preventable diseases, but also to quick and sustained introduction of new vaccines, as well as the financial self-sustainability of immunization programs in the Region. The continuous success of its mission mainly depends on three factors: the context of the global vaccine market, PAHO´s role in the management of the mechanism, and countries' active, committed participation.

Currently, the global vaccine market poses challenges with regard to covering the Region's total demand and obtaining lower prices. There is a limited supply of vaccines, such as yellow fever, oral polio and acellular pertussis containing vaccines, to meet the global demand. In addition, limited competition in the supply of new vaccines (i.e. pneumococcal conjugate, rotavirus, human papillomavirus), plus the existence of other actors in the market, make providing access at even lower prices a challenge. The RF constantly seeks ways to meet the challenges found in the global vaccine context, while preserving its principles of Pan-Americanism, equity, universal access and quality.

Another challenge the RF has faced is related to the seasonal influenza vaccine. The RF has facilitated countries' access to it; however, the content of the inserts of some of the producers does not clearly indicate the use of the vaccine in recommended populations, such as pregnant women. In addition, given that, in the case of some producers, the same vaccine does not cover all of a country's target populations, from children to adults, awarding the bids according to countries' programmatic needs, ensuring competition among producers, has been a challenge.

With regard to the management of the RF, its Working Group, composed of representatives of PAHO technical and management areas, analyzes, recommends and implements policies, processes and tools for continuous improvement of the RF's performance. A planning tool for improved demand and the implementation of management monitoring systems that facilitate



monitoring the timely arrival of orders and the use of the capital fund, for example, are some of the improvements. In order to meet the challenges of the global vaccine market, long-term purchase agreements have been established and communication with the producers has been increased. In addition, coordination with other partners, such as the GAVI Alliance and UNICEF, is being improved in situations where the global supply is limited.

Once more, emphasis is placed on the fact that in order to maintain and strengthen the economy of scale and benefits of the RF, active and committed participation of countries and territories is important. Their commitment to oversee increasingly precise forecasts of demand, as well as timely payment of obligations, contributes to producers' trust in the RF. Changes in demand or cancellations on the part of countries mean that the producers assume opportunity costs, which affects the credibility of the RF with them and the supply in terms of quantity and price for everyone. In addition, requirements that were not planned originally are lost opportunities with regard to obtaining lower prices and are a challenge to the timely deliveries, as producers may not have the stock readily available.

***Progress Report: Developing regional vaccine and hemoderivative manufacturing capacity***

Some Latin America and the Caribbean countries have an important manufacturing capacity for vaccines and blood derived products. This capacity could potentially lead to the further development of a regional capacity. Following TAG recommendation of October 2012, PAHO held a workshop bringing together regionally-based vaccine manufacturers, national authorities from the ministries of health and the national regulatory authorities and other relevant stakeholders with the aim of strengthening this Regional capacity.

*The objectives of this workshop were:*

- establish a network to facilitate information sharing and actively cooperate in strengthening initiatives;
- identify political, financial, expertise and regulatory hurdles, and
- explore suitable mechanisms to determine medium and long-term vaccine demand.

*Meeting participants agreed on the following list of recommendations:*

- strengthen regional capacity to forecast and quantify future demands to better inform manufacturing decisions;
- facilitate and maintain an ongoing dialogue with other similar initiatives at the global and regional level, and, taking advantage of PAHO's leadership, enable discussions between different actors to meet any challenges that may emerge;
- PAHO, manufacturers and national authorities should map the current needs for production and innovation on vaccine and blood derivative to better inform the manufacturing decisions and to develop regional RD&I agendas for these products;

- ensure that technology transfer agreements respond to regional needs and have don't negative effects on the overall access to health technologies due to market segmentation; and

- taking into account the capacity of regulatory agencies in the Region, PAHO should explore viable alternatives to expand eligibility of vaccines to expand the supply of and access to additional vaccines and hemoderivatives, while ensuring quality requirements.

The development of a regional network that can share knowledge, information and other resources and advocate for necessary changes was identified as the foundation for the overall program of work. Regional National Regulatory Authorities (NRAs) play a fundamental role in ensuring the safety and quality of the products and facilitate their introduction into the health systems. Thus, the proposed regional network and eventual work plan should include a strong regulatory component and close coordination with Regional NRAs.

*Based on these general recommendations, participants agreed on the following next steps:*

- develop a Community of Practice within PRAIS to bring together regional manufacturers, national health and regulatory authorities and other relevant stakeholders, under PAHO's supervision, to improve coordination and communication towards improving access of vaccines and blood derivatives in the Region;

- map the current strengths, opportunity and needs on the supply of vaccines and blood derivatives. PAHO will circulate a survey among regional manufacturers to collect the necessary information;

- coordinate and link with other relevant initiatives and networks and look for synergies at the regional and global levels; and

- develop network bylaws, once the survey information is systematized, functionally and structure and work plan that can guide the activities of the network. The proposal should be holistic and encompass technical, political and financial components. The initiative needs to ensure funds to implement any work plan.

## RECOMMENDATIONS

➢ TAG reiterates its recognition of the RF as a key pillar of immunization programs and reconfirms its recommendations[3] made in October 2012 on the importance of countries' ongoing participation, and that PAHO maintain communication and coordination with the main partners in the global field of immunization, in order to take advantage of opportunities and meet the challenges of the global vaccine market.

[3] TAG Report, October 2012, page 19
http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=19264&Itemid=270&lang=es

- TAG recommends that countries ensure more accurate demand forecasts. The Revolving Fund should provide the countries with support on the planning and follow-up process.

- PAHO should continue with its commitment to strengthen operating and financial management of the Revolving Fund in order to provide increasingly better service and greater capacity to extend credit to participating countries and territories.

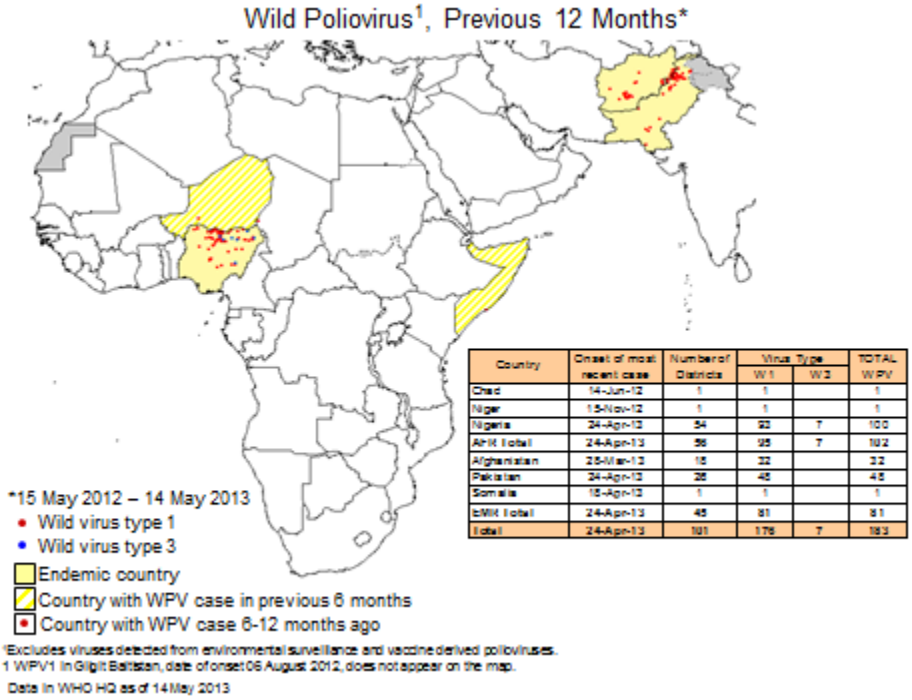
- The TAG ratifies the importance of developing regional vaccine production capacity as a strategy to strengthen implementation of immunization and health programs in the region. PAHO should continue to lead the network and its work program. It also calls for the producers, regulatory agencies, health authorities and actors maintain an active interest in the work program as soon as it is established.

## POLIO

The last endemic wild poliovirus was detected in the Region of the Americas in 1991, and in 1994 the International Commission for the Certification of Poliomyelitis Eradication (ICCPE), established by PAHO's director, certified the Region of the Americas to be polio-free. Since its elimination in 1991, the Region has not have outbreak due to importations of wild polio viruses, and the only cVDPV outbreak occurred in 2000-2001 in the Dominican Republic and Haiti, and was caused by a type 1 polio-derived virus. The elimination was achieved using tOPV and the TAG recommended the OPV as the vaccine of choice for the American Region as long as wild poliovirus continues to circulate in the world.

The progress towards global polio eradication continues, and by the end of 2012, the total number of polio cases worldwide decreased 66% over the previous year to 223.

**Figure1.**




| Country | Onset of most recent case | Number of Districts | Virus Type | | TOTAL WPV |
|---|---|---|---|---|---|
| | | | WT1 | WT3 | |
| Chad | 14-Jun-12 | 1 | 1 | | 1 |
| Niger | 15-Nov-12 | 1 | 1 | | 1 |
| Nigeria | 24-Apr-13 | 54 | 93 | 7 | 100 |
| AFR total | 24-Apr-13 | 56 | 95 | 7 | 102 |
| Afghanistan | 25-Mar-13 | 18 | 22 | | 22 |
| Pakistan | 24-Apr-13 | 26 | 45 | | 45 |
| Somalia | 18-Apr-13 | 1 | 1 | | 1 |
| EMR total | 24-Apr-13 | 45 | 81 | | 81 |
| Total | 24-Apr-13 | 101 | 176 | 7 | 183 |

Wild poliovirus (WPV) was endemic only in Afghanistan, Nigeria and Pakistan, and three of the four countries that had re-established WPV transmission following importations (Angola, the Democratic Republic of the Congo and Sudan) did not have a single case in 2012. The fourth, Chad, has not reported a case since June 2012.

On May 2012, the World Health Assembly declared ending polio a "programmatic emergency for global public health" and called on the WHO's Director-General to develop and finalize a comprehensive polio endgame strategy. The Polio Eradication and Endgame Strategic

Plan 2013-2018 was developed to capitalize on this new opportunity to end all polio disease. It accounts for the parallel pursuit or wild poliovirus eradication and circulating vaccine-derived poliovirus (cVDPV) elimination, while planning for the backbone of the polio effort to be used for delivering other health services to the world´s most vulnerable children.

The Plan has four major objectives. The first one is to stop all wild poliovirus transmission by the end of 2014 and any new outbreaks due to cVDPV within 120 days of confirmation of the index case. The second objective is Immunization system strengthening and OPV withdrawal. This objective engages all 144 countries that currently use OPV and calls for the withdrawal of the type 2 component from the trivalent OPV and the introduction of at least one dose of affordable IPV (inactivated polio vaccine). Objective number three is to certify all of the regions of the world as polio free and ensure that all poliovirus reserves are safely confined. Finally, objective number four is Legacy Planning.

In 2012, the SAGE, the world's chief policy guidance body for immunization, recommended the withdrawal of the type 2 component of oral polio vaccine (OPV) as soon as possible from routine immunization programmes1 in all countries, facilitated by the introduction of at least one dose of IPV. In April 2013, the Scientific Community endorsed the Plan. The SAGE recommendation is based on the fact that "poliovirus type 2 was eliminated in 1999 and that the continued use of trivalent Oral Polio Vaccine (tOPV), in areas where coverage is not adequate, contributes to ongoing type 2 vaccine-associated paralytic poliomyelitis and vaccine-derived virus outbreaks (cVDPV)" The SAGE working group emphasized that before interrupting the use of the type 2 vaccine, the following conditions should be met: the current outbreak of cVDPV2 in Nigeria must be interrupted; absence of outbreaks caused by cVDPV2 for at least one year; adequate epidemiological surveillance that makes it possible to detect and control any cVDPV2outbreak; adequate quantities of bOPV available; an inactivated polio vaccine (IPV) at an affordable price, a global reserve of type 2 monovalent vaccine (mOPV); and an international agreement to discontinue the global use of tOPV.

In April 2013, the by members of the scientific community signed the Scientific Declaration on Polio Eradication, which endorses the Eradication and Endgame Strategic Plan and called on actors in the global community to do their part to ensure the full implementation of the plan.

During this meeting the TAG received a report on the global eradication situation, the scenarios for polio vaccine supply, the status of the epidemiological surveillance in the Americas and on the Polio Eradication and Endgame Strategic Plan 2013-2018. The TAG discussed the implication of a potential change in vaccination recommendations and noted that the Region eliminated polio and has remained polio-free using the tOPV.

## RECOMMENDATIONS

- Countries of the Americas must wait for the fulfillment of the conditions stated by SAGE for the cessation of the use of Sabin type 2 containing vaccines; these conditions must be met before making any change in vaccination policy. As long as there are outbreaks caused by cVDPV type 2 and the wild poliovirus continues to circulate in the world, the trivalent oral polio vaccine (tOPV) remains the vaccine of choice for the Americas.

- PAHO should convene a Working Group to develop a strategic plan describing current options and scenarios, as well as the timelines for the implementation of the polio endgame in the Americas. This plan should discuss the feasibility of using different OPV/IPV schedules; the availability of combination vaccines containing IPV, where the ideal situation would be having an hexavalent DTwP-Hib-IPV-HepB vaccine, among other issues.

- All countries must reinforce the activities aimed to achieve or maintain vaccination coverage >95% in every district or municipality. If countries do not achieve that coverage they must evaluate the accumulation of non-immunized and conduct vaccination campaigns.

- All countries must continue to maintain adequate acute flaccid paralysis (AFP) surveillance in order to timely detect any importation or emergence of VDPVs, and must report to PAHO on a timely fashion to allow the proper monitoring of the Regional situation.

- TAG reinforces its previous recommendations (Argentina 2011) for countries considering the introduction of inactivated polio vaccine (IPV): compliance with sanitary conditions and vaccination coverage guaranteeing an adequate protection to their communities.

- PAHO must continue to maintain a dialogue with vaccine suppliers in order to guarantee the provision of polio vaccines for the Americas.

## MONITORING AND REPORTING OF GVAP INDICATORS

The Global Vaccine Action Plan (GVAP) is an effort to strengthen the achievements of immunization and continue urging governments to continue with their commitment to protect their populations from vaccine-preventable diseases. The GVAP builds on the Global Immunization Vision and Strategy (GIVS), which was launched in 2005 and was the first 10-year strategic framework to maximize the potential of immunization. The GVAP reiterates the existing global goals and proposes new goals for this Decade of Vaccines (2010-2020). On May 25, 2012, in its 65th meeting, the World Health Assembly backed the GVAP and passed Resolution 65.17 on behalf of this plan. A year later, WHO and its partners have made progress on the definition of a Monitoring and Accountability Framework for the purpose of documenting the GVAP's impact. This monitoring framework will be adapted to the needs of the programs in the 6 different regions and 194 member countries of the WHO.

In the Americas, the GVAP will complement the Regional Immunization Vision and Strategy, a document that was developed to adapt the GIVS to regional priorities in 2007. The monitoring and reporting mechanisms for measuring the Region's progress regarding the GIVS will be used to monitor the implementation of the GVAP.

The GVAP has indicators, with targets for 2015 and 2020, to track progress on the 5 goals of the plan (Table 1) and 16 indicators to track progress on the plan's 6 strategic lines of action (Table 2). The Monitoring and Accountability Framework establishes data gathering for these indicators as a shared responsibility of the different levels of the immunization community: the global, regional and national levels. The majority of these monitoring indicators are based on information that is gathered routinely in this Region, with the exception of vaccination coverage reported by income level (Table 2) and the evaluation of the degree of confidence in vaccines among the population. Special studies should complement the WHO/UNICEF Joint Reporting Form (JRF), which will be the primary reporting mechanism for GVAP monitoring.

The reporting of these indicators will be a shared responsibility between the national, regional and global levels. All proposed indicators with the exception of those related to strategic objective 6, which monitors progress in research and development of new vaccines, require information from the national level. WHO will gather data and monitor progress on strategic objective 6 at the global level. Through the JRF, Member States will continue reporting to PAHO on the technical and programmatic performance of the national immunization programs (NIP) in March of each year. In preparation for submission of the JRF, the NIP should begin the process of analyzing data at the beginning of each year, reviewing national data with the partners of the NIP (interagency committees) and with national immunization technical advisory groups (NITAGs) where they exist. This review will serve to adapt GVAP monitoring at the national level and disseminate progress regarding the goals with the actors involved in the NIP. After finalizing the national process of gathering, synthesizing and disseminating the annual EPI progress, PAHO will consolidate this information and share it with the Regional Technical Advisory Group (Regional TAG), the PAHO Directing Council and WHO.

## RECOMMENDATIONS

- TAG applauds the Member States for joining global efforts to extend the benefits of immunization to all individuals during this Decade of Vaccines (2010-2020) through the GVAP.

- TAG recognizes the efforts of the Member States in monitoring progress towards achieving the national and regional immunization goals and encourages the NIPs to continue to provide timely reporting of progress to PAHO through the WHO-UNICEF JRF.

- PAHO should, in the context of GVAP, report annual progress to the organization's Governing Bodies, the TAG and WHO.

**Table 1: Indicators for global level goals**

| Goal | **Target by 2015** | **Target by 2020** |
|---|---|---|
| 1) Achieve a world free of poliomyelitis | **1) Interrupt wild poliovirus transmission globally (by 2014)** | **1) Certification of poliomyelitis eradication (by 2018)** |
| 2) Meet global and regional elimination targets | **2a)** Neonatal tetanus eliminated in all WHO regions<br>2b) Measles eliminated in at least four WHO regions<br>2c) Rubella/congenital rubella syndrome eliminated in at least two WHO regions | **2)** Measles and rubella eliminated in at least five WHO regions |
| 2) Meet vaccination coverage targets in every region, country and community | **3)** Reach 90% national coverage and 80% in every district or equivalent administrative unit with vaccines containing diphtheria-tetanus pertussis | **3)** Reach 90% national coverage and 80% in every district or equivalent administrative unit with all vaccines in national programmes, unless otherwise recommended |
| 4) Develop and introduce new and improved vaccines and technologies | **4)** At least 90 low- and middle-income countries have introduced one or more new or underutilized vaccines | **4a)** All low- and middle-income countries have introduced one or more new or underutilized vaccines<br>4b) Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases<br>4c) Licensure and launch of at least one platform delivery technology |
| 5) Exceed the Millennium Development Goal 4 target for reducing child mortality | **5a)** Reduce by two thirds, between 1990 and 2015, the under-five mortality rate (Target 4.A) | **5a)** Exceed the Millennium Development Goal 4 Target 4.A for reducing child mortality |

*Indicators in bold fall under the responsibility of the national/regional level.

**Table 2: Indicators for strategic objectives**

| Objetivo estratégico | Indicadores |
|---|---|
| 1) All countries commit themselves to immunization as a priority | • Domestic expenditures per person targeted<br>• Presence of an independent technical advisory group that meets defined criteria |
| 2) Individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility | • Percentage of countries that have assessed (or measured) confidence in vaccination at subnational level1<br>• Percentage of unvaccinated and under-vaccinated people in whom lack of confidence was a factor that influenced their decision |
| 3) The benefits of immunization are equitably extended to all people | • Percentage of districts with 80% or greater coverage with three doses of diphtheria-tetanus-pertussis-containing vaccine<br>• Reduction in coverage gaps between lowest and highest wealth quintile and another appropriate equity indicator |
| 4) Strong immunization systems are an integral part of a well-functioning health system | • Dropout rate between first dose and third dose of diphtheria-tetanus-pertussis-containing vaccines<br>• Sustained coverage with diphtheria-tetanus-pertussis containing vaccines of 90% for three or more years<br>• Immunization coverage data assessed as high quality by WHO and UNICEF<br>• Number of countries with case-based surveillance for vaccine-preventable diseases that meets quality standards |
| 5) Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies2 | • Percentage of doses of vaccine used worldwide that are of assured quality |
| 6) Country, regional and global research and development innovations maximize the benefits of immunization . | • Progress towards development of vaccines against HIV infection, tuberculosis and malaria<br>• Progress towards a universal influenza vaccine (protecting against drift and shift variants)<br>• Progress towards institutional and technical capacity for conducting vaccine clinical trials<br>• Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8 ºC range<br>• Number of vaccine-delivery technologies (devices and equipment) that have received WHO prequalification compared to 2010 |

*Indicators in bold fall under the responsibility of the national/regional level.

## MENINGOCOCCAL DISEASE AND VACCINES CURRENTLY AVAILABLE

Meningococcal disease (MD) refers to the spectrum of infections caused by *Neisseria meningitides* including meningitis, bacteremia and bacteremic pneumonia. In the majority of countries, *Neisseria meningitides* is recognized as the leading cause of fulminant meningitis and *septicaemia*. Therefore, it is considered to be a significant public health problem. MD is associated with high mortality (10-20%), and approximately 20% of survivors develop sequelae, such as deafness, neurological deficit or amputation of a limb.

MD affects every age group, but the highest incidences are found in children under five, especially those under one year of age. In some populations, peaks of incidence may also occur in adolescents or young adults and adults over 65 years of age. During outbreaks and epidemics, changes tend to occur where the highest incidence rates are in adolescents and young adults. The majority of MD cases are sporadic. The disease presents seasonal variations, especially in the winter, and outbreaks occur at irregular intervals. Invasive meningococcal infections are mainly caused by serogroups A, B, C, X, W135 or Y capsular polysaccharides, but is important to note that this disease is marked by great variation in relation with the distribution of serogroups by region and over time.

*Neisseria meningitides* has become the leading cause of bacterial meningitis in children in Latin America and the Caribbean, especially, following the introduction of the *Haemophilus influenzae* type b vaccine in routine vaccination schedules. In Latin America and the Caribbean, the incidence of MD varies widely, with rates ranging from <0.1 cases per 100,000 inhabitants in countries such as Mexico, to 2 cases per 100,000 inhabitants in Brazil.

Although MD is a notifiable disease, its incidence in the majority of countries in the Region is likely underestimated, since in many countries the epidemiological surveillance systems for this disease are weak and the information available is of poor quality. When data from the different countries are analyzed, problems detected include considerable heterogeneity in the quality of the information; significant variability in morbidity and mortality records; very low rates of incidence as a consequence of under-registration; and a large proportion of meningitis cases without an identified etiological agent, due to limitations in obtaining adequate specimens for culture and prior use of antibiotics.

In Latin America, available data indicate that serogroups B and C are still responsible for the majority of cases. Serogroups W135 and Y are emerging and have been reported in some countries, while serogroup A has virtually disappeared in the Region. Although the proportion of isolated serotypes in the Region is known, the burden of disease cannot be inferred from these serotypes due to the aforementioned weaknesses in epidemiological surveillance.

There are single meningococcal polysaccharide vaccines or vaccines conjugated with a carrier protein. Although polysaccharide vaccines produce an antibody response, conjugate vaccines are more immunogenic and also induce immunological memory. Polysaccharide and conjugate vaccines against meningococcal groups A, C, W135 and Y are available in the market. Both vaccines are safe and effective. The polysaccharide vaccine does not provide adequate immunity in children aged <2 years of age and in children over 2 years of age, it offers limited-duration

immunity because it does not induce immunological memory. Recently, in January 2013, the first recombinant meningococcal serogroup B vaccine was licensed by the European Commission.

## RECOMMENDATIONS

- It is imperative that the countries implement systems for epidemiological surveillance of meningococcal disease in order to know its real magnitude and epidemiological profile. PAHO should continue providing guidance for the standardization of lab diagnostic methods and for the reporting of the disease.

- Countries that already have sentinel epidemiological surveillance for bacterial meningitis and pneumonia in children under five should establish a plan of action to improve the quality of information, including improvement in and standardization of diagnostic laboratory techniques.

- Countries should establish sentinel sites for other age groups for bacterial meningitis and pneumonia, using standard laboratory techniques and case definitions.

- Countries should analyze their epidemiology, during outbreaks and epidemics, before making decisions regarding control measures, including the identification of groups to vaccinate and the vaccine to be used.

- Countries with high burden of disease in young children that decide to introduce meningococcal conjugate vaccine as part of the routine immunization program targeting children aged <1 or <2 years should ideally include catch-up vaccination of children and adolescents, or at least of adolescents, given that this is the age-group with the highest carriage levels.

## PROGRESS IN THE INTEGRATION OF EPI COSTING AND PLANNING

If we compare the situation of the Expanded Program on Immunization (EPI) in the year in which it was created (1974) with the current situation, we find that:

- Early on, the EPI had vaccines against 6 diseases (tuberculosis, polio, diphtheria, pertussis, tetanus and measles) available. It currently protects against 14 diseases (including hepatitis b, *Haemophilus influenzae* type b, rubella, mumps, pneumococcal disease, rotavirus, yellow fever, influenza and human papilloma virus).

- The EPI used to administer a total of 10 doses per child, while currently it delivers up to 20 doses per child.

- The EPI used to vaccinate children exclusively, while it now vaccinates entire families. Today, adolescents, pregnant women, occupational risk groups and the elderly receive vaccines.

- The annual cohort to vaccinate in the Region in 1975 was approximately five million children under 1 year of age, while for 2011 the cohort comprised nearly 15 million children less than one year of age.

- The cost per child vaccinated was less than five dollars then, while it is currently approximately 70 dollars per child immunized, taking into account only the cost of the vaccines.

Given the above considerations, planning and costing for the EPI requires careful work based on data for adequate decision-making and to ensure the program's sustainability.

In 1974, with the creation of the EPI, an annual planning tool was generated that included nine areas of action or components of the plan of action (Biologicals and supplies, Cold chain, Training, Social mobilization, Operating expenses, Supervision, Epidemiological surveillance, Research and Evaluation). Due to the rapid development of the program, countries independently introduced other required components according to their scope of work (i.e. management, coordination, logistics, new vaccines, etc.). Thus, countries currently send PAHO their plans of action with a variable number of EPI components, and they include different activities in one component or another according to their own criteria. At the same time, PAHP requests that countries submit separate plans for certain activities (such as campaigns) that are not included in the master plan of action. This makes it difficult to compare across different country plans or to adequate interpret each plan, since it is not clear which activities have been included in each component. For all of these reasons, PAHO has proposed the standardization of all of the existing tools (Plan of Action form, WHO-UNICEF Joint Reporting Form, multi-year immunization plans and the GAVI report, among others) through the creation of a standard definition of the 12 components of the EPI and their content.

Countries in the Region consistently carry out a planning process based on: 1) national government and, specifically, health sector planning, 2) the reality in the country 3) the teams' technical capacity 4) the team's participation, as well as that of other actors involved in the process, 5) monitoring and evaluation allows for the adaptation of activities, and 6) a defined budget framework. This systematic process has contributed to strengthening EPI management and the mobilization of resources for the EPI. However, greater integration is still required in order to avoid duplicative efforts and to facilitate the management and monitoring of the plan's execution.

In addition, it is important to perform adequate costing of past activities periodically, in order to provide greater clarity on details of budget execution. This facilitates better understanding of the components and activities that consume the greatest amount of resources, as well as the identification of inefficiencies and opportunities for improvement in the operational and logistic aspects of the EPI.

Currently, the majority of countries do not routinely perform costing studies at every level of the EPI; nor do they have a methodology or tool to perform these studies adequately, which requires gathering information on costs and resource use through adequate sampling of healthcare facilities throughout the country. The ProVac initiative has developed a tool and methodology called CostVac, which is a package of materials designed so that EPI coordinators can select an adequate sample of vaccination centers, adapt surveys to the national situation and analyze the information gathered within a standard, consistent framework. In 2012 and 2013, a pilot study was conducted on EPI costing in Honduras using the CostVac tool and methodology. For the first time, the Honduran EPI gathered information on costs and the use of resources at the local level at 71 health facilities in 8 of the country's regions. The information gathered from the healthcare facilities and regional offices showed that over 50 percent of the economic costs of the EPI are incurred at the healthcare facility level. These costs are generally underestimated at the central level, and taking them into account can help in distributing limited resources more efficiently. In addition, a more precise estimate of the real cost of the EPI will serve as an important input for management of the EPI and mobilization of resources.

PAHO has proposed a tool for integrating planning and costing of the program that countries can use to produce simpler costing information annually, which will be useful for the planning and budgeting of the following year. They will also be able to do more thorough five-year costing (accompanied by an international evaluation of the EPI or independently) for the purpose of performing closer analysis of the efficiency of the program and identifying challenges and opportunities for improvement. The information on cost of immunization should be complemented with information regarding the benefit provided by the program, such as prevention of disease and therefore reduction of costs regarding hospitalization, treatment, rehabilitation services, days-off and immeasurable suffer and sorrow. The cost of immunization should always be compared with its absence. Therefore, it should be considered a sound investment and not costs because health is essential for economic development.

## RECOMMENDATIONS

- Recognizing that costing of the EPI is of great value for making informed decisions when planning immunization activities and negotiating the budget; countries should test and adopt the tools proposed by PAHO.

## VACCINATION WEEK IN THE AMERICAS

In April 2013, Vaccination Week in the Americas (VWA) was celebrated for the eleventh time. Over its tenure in the Region, more than 450 million individuals have been vaccinated under the framework of the initiative. VWA has also become a key annual opportunity to promote equity and access to vaccination services and to highlight the work of national programs through the media. The regional slogan for VWA 2013 was "Vaccination: a shared responsibility," which was chosen to highlight the importance of governments, health care workers, parents and children each doing their part to support national immunization programs and maintain high coverage. VWA 2013 was covered by press outlets in more than 29 countries in the Region, in addition to information disseminated by other agencies and partners (such as UNICEF, United Nations Information Centre, GAVI and the Bill and Melinda Gates Foundation).

Dozens of national and international launching events were carried out to celebrate VWA 2013. Two regional launches were held with the participation of PAHO's Director, Dr. Carissa F. Etienne. The first regional launch took place on 24 April in the adjacency zone between Benque Viejo, Belize, and Melchor de Mencos, Guatemala and served as a bridge to peace, reinforcing diplomacy and confidence between both nations, a process supported by the Organization of American States. The second regional launch was held on 27 April in Carrefour, Haiti, outside of Port-au-Prince. These events counted on the participation of high level authorities including Ministers of Health, partner organizations such as GAVI and the United States Centers for Disease Control and Prevention (CDC), and other United Nations Agencies (UN), such as UNICEF, UNAIDS and UNOPS, and the UN Resident Coordinators of Belize and Haiti, who participated on behalf of the Secretary- General.

Based on country VWA plans and reports submitted to PAHO headquarters, to date, 44 countries and territories participated in VWA 2013, targeting approximately 44 million people for vaccination against diseases including poliomyelitis, measles, mumps, rubella, and congenital rubella syndrome, diphtheria, whooping cough, tetanus, hepatitis B, seasonal influenza, yellow fever, diarrhea caused by rotavirus and bacterial pneumonia, in a wide variety of campaigns. Of note, several countries carried out immunization or promotional campaigns focused on the human papillomavirus (HPV) vaccine this year. Eighteen countries and territories also integrated other preventative interventions with vaccination, including deworming, vitamin A supplementation, growth monitoring, cancer detection and health screenings, among others.

This year also marked the second celebration of World Immunization Week (WIW), which was endorsed by the World Health Assembly in 2012 following a global movement of sister initiatives being established in all other regions of the WHO and advocacy efforts on the part of Member States. The slogan for WIW was "Protect your world, get vaccinated" and overarching activities were coordinated by the WHO headquarters office. In 2013, the themes for vaccination week initiatives around the world included:

- 8th European Immunization Week-“Prevent. Protect. Immunize.”
- 4th Vaccination Week in the Eastern Mediterranean-“Stop Measles Now!”
- 3rd African Vaccination Week-“Prevent disabilities, vaccinate!”
- 3rd Vaccination Week in the Western Pacific-“Finish the job-No more measles for anyone”
- 2nd Vaccination Week in South-East Asia focused on the intensification of routine immunization

## RECOMMENDATIONS

- TAG congratulates all countries and territories in the Region for their exemplary achievements over the history of VWA and for the establishment of World Immunization Week.

- VWA should continue to be supported as an initiative that strengthens routine vaccination programs in the Region and helps to ensure political commitment to them.

- The use of VWA as a platform for the integration of other preventative interventions should be continued in countries where it is applicable, and countries should also continue to explore methodologies to evaluate VWA’s impact on the routine program.

# Conclusions and recommendations of the 12th meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE)

Copenhagen, Denmark
9–11 October 2013

The European Technical Advisory Group of Experts on Immunization (ETAGE) met on 9–11 October 2013 to review and discuss immunization activities and developments in the WHO European Region and provide advice to the WHO Regional Office on appropriate activities.

The main topics for discussion included operationalization of the monitoring, evaluation and accountability framework for the Global Vaccine Action Plan (GVAP); planning for inactivated polio vaccine (IPV) introduction; progress toward measles and rubella elimination in the Region; implementation of the *Package of accelerated action for measles and rubella elimination*; development of strategies for adult immunization practices; sustaining immunization investments in countries graduating from GAVI support; and development of a Regional Vaccine Action Plan (RVAP).

## Conclusions

- ETAGE acknowledges the important role played by National Immunization Technical Advisory Groups (NITAGs) and welcomes participation in the meeting by NITAG representatives from Armenia, Azerbaijan, Belarus, Denmark, Republic of Moldova, Kazakhstan, Kyrgyzstan, Ukraine and Uzbekistan.

Operationalization of the monitoring, evaluation and accountability framework for the Global Vaccine Action Plan (GVAP)

- ETAGE notes that the GVAP timeframe for operationalization of the framework appears to be feasible for most countries. However, the information needed to complete the joint reporting form (JRF) and other reports comes from multiple sources; and there is concern about the quality of the data produced. Strengthening reporting to meet the requirements as well as avoiding parallel reporting activities will require greater organization in Members States and will be a collaborative effort at various levels.
- Indicators need to be well defined, and standardized if possible. ETAGE recognizes that the first year of reporting within the GVAP framework will involve a learning curve and lessons learnt will contribute to improvements in subsequent years.
- ETAGE notes that NITAGs can play an important role in implementation of the GVAP framework: not to supervise activities but to profit as the end user of the data, which will allow them to define policy and advise decision-making authorities.
- ETAGE notes that the whole GVAP process should create added value for the beneficiaries of the immunization programme – this message needs to be understood by all and thus better communicated.

Planning for inactivated polio vaccine (IPV) introduction (to mitigate risks associated with withdrawal of type 2 component of OPV)

- ETAGE notes that there is great need to clarify to national authorities, health providers and parents the purpose of IPV introduction as envisioned in the Endgame Strategy, why it is expected to work, and why this approach is different from historical combinations of IPV/OPV. If people do not understand the principles involved, implementation will not achieve what is being sought.
- For the IPV introduction process, each country might be starting from a different point based on the historical context. Member States are accordingly requesting tailored support from the Regional Office. WHO, UNICEF and others are working to produce Frequently Asked Questions (FAQs) and other documents, but additional resources will need to be invested in communication on all topics related to introduction.
- ETAGE notes that the challenges for IPV introduction also include licensing of vaccine products and mobilization of sufficient resources. The long-term involvement of GAVI will be decided by the GAVI Board in November. This decision will be instrumental to achieving the Endgame Strategy for polio eradication.

Progress toward measles and rubella elimination in the Region and implementation of the *Package of accelerated action for measles and rubella elimination*

- ETAGE is concerned about persistent immunization gaps, the lack of case-based surveillance, continuing outbreaks of measles and rubella and the lack of an adequate response to these outbreaks in the European Region. Moreover, ETAGE notes that these factors threaten the 2015 measles and rubella elimination target for the Region. To reduce complacency and mobilize the necessary resources to address gaps (also in middle-income and high-income Member States), measles and rubella elimination will need to become a high priority for decision-makers. It is necessary to look at what ETAGE and the Regional Office can do to put pressure on the ministries of health to make elimination a priority.
- ETAGE is enthusiastic about the efforts initiated by WHO/Europe's Vaccine-preventable Diseases and Immunization unit (VPI) under the framework of the *Package of accelerated action for measles and rubella elimination*. The Package encompasses many activities and tools which can be used at country level to enhance elimination efforts, such as the *Guide to tailoring immunization programmes* and *Guidelines for measles and rubella outbreak investigation and response*. At the same time, ETAGE recognizes that ownership in each country is also needed.
- ETAGE recognizes that this effort will also include strengthening relations between organizations, services that provide immunization and educational institutions.

Development of strategies for adult immunization practices

- ETAGE recognizes that adult immunization is an emerging area. Immunization does not end after childhood: it is necessary to extend the concept to one of lifelong immunization. If adult immunization is recommended, a tailored infrastructure needs to be in place for delivery. Topics to be considered are how to reach adult populations, cold chain issues, how to document their immunization status, who in each country is responsible for the adult immunization, the role of health insurance, etc. A set of standards (that tailors immunization practices) to be developed by WHO/Europe would provide a checklist that countries could review and that would assist them in the implementation of an adult immunization programme.
- ETAGE recognizes that there is scope for targeting schools, universities and employers with information on the cost–effectiveness of increasing immunization uptake among young adults.

## Graduation challenges – sustaining immunization investments in countries graduating from GAVI support

- ETAGE notes that GAVI has been a catalytic platform for introducing new antigens in immunization programmes and for strengthening immunization programmes in eligible countries.

- ETAGE is concerned that countries identified as graduating from GAVI support face challenges in maintaining the sustainability and quality of their immunization programmes. More clarity is needed regarding post-process, and graduating countries (as well as middle-income countries) need assistance and guidance in areas such as understanding vaccine market dynamics, impact of national procurement systems and regulations on vaccine supply, in order to access quality-assured vaccines at an affordable and optimum price after graduation. ETAGE is accordingly concerned about the lack of transparency regarding vaccine prices and appreciates the work initiated by WHO in this area.
- ETAGE appreciates VPI's ongoing work together with partners and Member States to identify graduation challenges, facilitate inter-country collaboration, and facilitate the development, monitoring and review of transition (graduation) plans.
- ETAGE acknowledges the important role NITAGs will play in mobilizing the financial resources required and in strengthing the programme functions in addressing the graduation challenges. Collecting country-specific data on the burden of vaccine-preventable diseases and the impact of the immunization programme in reducing this burden is needed to demonstrate the importance of the programme. This evidence is the driving force for convincing policy-makers and ministers of health and other ministries to allocate more of their countries' own resources to immunization programmes. WHO/Europe is already assisting countries in using costing and cost–effectiveness data to understand where they are now, where they are heading and what to expect in future.
- With 6 of 17 globally graduating countries located in the European Region, ETAGE notes that experiences gained here will be watched by, and provide valuable lessons for, other regions.

Development of a Regional Vaccination Action Plan (RVAP)

- ETAGE supports development of the RVAP, which will set out the Regional Office's vision and strategies for the coming seven years in line with the applicable goals and objectives of the GVAP. The RVAP will be a policy document intended to be operationalized at the country level. ETAGE is pleased to offer assistance and to be actively involved in the development process at all stages, through regular consultations with VPI and participation in country-level consultations.

## Recommendations

1. ETAGE advises the Vaccine-preventable Diseases and Immunization unit of the WHO Regional Office for Europe (VPI) to provide technical assistance to national and supranational regulation authorities in licensing products pertinent to the polio Endgame Strategy.

2. Due to the threat to the 2015 measles and rubella elimination goal for the WHO European Region, ETAGE encourages Member States to formulate or revisit their current action plans for measles and rubella elimination and to urgently address immunity gaps in their populations.

3. Recognizing that most Member States have not developed a framework to provide immunization services to adolescents and adults, ETAGE encourages Member States to include adequate practices and facilities for adult immunization in their health care systems.

4. ETAGE urges VPI to assist GAVI-graduating and lower middle-income Member States in ensuring access to quality-assured vaccines at an affordable and optimal price.

5. ETAGE recommends that WHO support the development of generic training materials on immunization for schools, as school populations are highly receptive to the immunization topic.

6. ETAGE recommends that WHO support the development of training materials on immunization for continuous medical education schemes. Accreditation of this material could take place through national or international medical professional organizations or national licensing schemes.

# Fourth Meeting of the South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG)

*A Report*
*New Delhi, India, 2–3 April 2013*

# Contents

# Acronyms

| | |
|---|---|
| AES | acute encephalitis syndrome |
| AFP | acute flaccid paralysis |
| AEFI | adverse events following immunization |
| AI | Appreciative Inquiry |
| ASHA | Accredited Social Health Activist |
| AVD | alternative vaccine delivery |
| bOPV | bivalent oral polio vaccine |
| CMYP | comprehensive multi-year plans |
| CRS | congenital rubella syndrome |
| cVDPV | circulating vaccine-derived polio virus |
| DoV | Decade of Vaccines |
| EPI | expanded programme on immunization |
| EVM | effective vaccine management |
| EVSM | effective vaccine store management |
| GAVI | Global Alliance for Vaccines and Immunization |
| GIVS | Global Immunization Vision and Strategy |
| GMP | good manufacturing practices |
| GVAP | Global Vaccine Action Plan |
| HIV | human immunodeficiency virus |
| HPV | human papillomavirus |
| IMB | Independent Monitoring Board for Polio Eradication |
| IMCI | integrated management of childhood illness |
| IPV | inactivated polio virus |
| IRI | intensification of routine immunization |
| ITAG | Immunization Technical Advisory Group |
| ITSU | Immunization Technical Support Unit |
| LJEV | live japanese encephalitis vaccine |
| MCV | measles-containing vaccine |
| MCV1 | first-dose measles vaccine |
| MNT | Maternal and Neonatal Tetanus |
| mOPV | monovalent oral polio vaccine |
| MR | measles and rubella vaccine |
| MRI | Measles Rubella Initiative |

| | |
|---|---|
| NCC | National Certification Committee |
| NCL | National Chemical Laboratory |
| NIDs | national immunization days |
| NRA | national regulatory assessments |
| NTAGI | National Technical Advisory Group on Immunization |
| NUVI | new and underutilized vaccine introduction |
| OPV | oral polio vaccine |
| PATH | Program for Appropriate Technology in Health |
| PMS | post-marketing surveillance |
| RI | routine immunization |
| RC | Regional Committee |
| RCCPE | Regional Commission for Certification for Polio Eradication |
| SIA | supplementary immunization activity |
| SEAR | South-East Asia Region |
| TCG | Technical Consultative Group |
| tOPV | trivalent oral polio vaccine |
| UNICEF | United Nations Children's Fund |
| VDPV | vaccine-derived polio virus |
| VDC | Village Development Committee |
| VMA | vaccine management assessment |
| VPD | vaccine-preventable diseases |
| WHO | World Health Organization |
| WPV | wild poliovirus |

# 1. Introduction

The fourth meeting of the World Health Organization's South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) was held from 2–3 April 2013 in New Delhi, India.

The SEAR-ITAG is composed of technical experts who provide Member States with technical and policy guidance on immunization, vaccines and related technology to reduce vaccine-preventable diseases in the Region. The terms of reference are:

(1) To review regional and Member States policies, strategies and plans for control, elimination and eradication of vaccine-preventable diseases, especially for polio eradication, measles control and maternal and neonatal tetanus (MNT) elimination, including the setting of regional immunization priorities;

(2) To guide Member States in strengthening routine immunization programmes;

(3) To make recommendations on a framework for national immunization policies as well as operational aspects of the immunization strategies; guide Member States on the incorporation of new scientific knowledge and technology on vaccines, vaccine delivery and immunization practices;

(4) To advise Member States on the appropriate choices of new vaccines, guide optimal strategies for their introduction, and provide technical guidance on monitoring the impact of new vaccines once introduced into national immunization programmes;

(5) To promote and provide technical guidance for the implementation of high-quality vaccine-preventable disease surveillance, including laboratory networks for surveillance;

(6) To advise Member States on regulatory requirements to ensure quality and safety of vaccines used in national immunization programmes;

(7) To identify and advise on appropriate subject areas for operational research in the fields of immunization and vaccines and review the conduct and results of the research projects; and

(8) To advocate and promote linkages and liaise with global policy-making bodies such as the Strategic Advisory Group of Experts (SAGE), and national committees for immunization practices at the country level.

In addition to SEAR-ITAG members, other participants included members of national committees for immunization practices of Member States, SAGE members representing the Region, WHO headquarters, Regional Office for South-East Asia and country office, Expanded Programme on Immunization (EPI) focal points.

Dr Sangay Thinley, Director, Department of Family Health and Research, opened the meeting on behalf of the Regional Director, Dr Samlee Plianbangchang. Professor Lalitha Mendis chaired the meeting with Dr Supamit Chunsuttiwat as rapporteur and Dr Patrick O'Connor as co-rapporteur.

## 2. Objectives

The objectives of the fourth SEAR ITAG meeting were as follows:

(1) To assess the progress made on intensification of routine immunization in the Region and assess a tool developed for monitoring progress of the intensification efforts;

(2) To review the progress of polio eradication, and management of the remaining issues and challenges towards polio-free certification in February 2014 and the polio endgame;

(3) To review and endorse the regional strategic plans for elimination of measles and control of rubella and congenital rubella syndrome;

(4) To review SAGE recommendation for intussusception surveillance and to review evidence that supports a favourable risk–benefit for the relaxation of rotavirus vaccine age restrictions;

(5) To review the current status and process of effective vaccine management (EVM) assessments of the SEA Region;

(6) To review and discuss a newly developed decision-making algorithm for new and underutilized vaccine introduction into the Region;

(7) To review adverse events following immunization (AEFI) monitoring, preparedness and response plans in the Region;

## 3. Background

During the third meeting of the SEAR-ITAG in 2012, there was an extensive discussion on efforts for intensification of routine immunization coverage, measles elimination, introduction of rubella vaccine and strategies for prevention and control of Japanese encephalitis. In addition, achievement of regional polio eradication, acute flaccid paralysis (AFP) surveillance and integrated vaccine-preventable diseases (VPD) surveillance were discussed. The progress in achieving MNT elimination, status of implementation of vaccine post-marketing surveillance, seasonal influenza vaccine introduction in the South-East Asia Region, and the need for pooled procurement of vaccines in the Region were reviewed.

## 4. Implementation of recommendations from the third meeting

The implementation status of the recommendations from the third meeting of the SEAR ITAG, 2012 are listed below:

| Recommendations | Status |
|---|---|
| **Global progress on immunization: Decade of Vaccines and Global Vaccine Action Plan** | |
| Validate administrative coverage by using biomarkers, more accurate denominators and linking immunization registries with birth registries. | 1. Myanmar – measles and polio sero-survey, coverage evaluation surveys and a post-introductory evaluation of pentavalent vaccine introduction are planned;<br>2. Bangladesh – Hepatitis B impact sero-survey completed; implementing EPI and surveillance review recommendations; examining denominator issue in Dhaka;<br>3. Nepal – attempting to validate routine immunization (RI) coverage through "Appreciative Inquiry";<br>4. Indonesia – to validate RI coverage during EPI and surveillance review in June 2013. |
| **Intensification of routine immunization (IRI) in 2012: progress of implementation** | |
| 1. Existing immunization initiatives should be streamlined to financially support IRI.<br>2. Establish realistic IRI targets.<br>3. Provide plans to highlight main barriers and strategies.<br>4. Conduct regular performance measurements; guidelines for EPI and surveillance reviews. | 1. Overall, implementation of IRI has been slow, but there have been positive effects on the national level immunization coverage (i.e. high priority countries India, Indonesia and Timor-Leste);<br>2. In India, an Immunization Technical Support Unit (ITSU) was established to support programme operations, supply chain, demand generation, AEFI surveillance and VPD surveillance; India is reaching the unreached through immunization weeks, resulting in coverage of ~5 million children. |

| Recommendations | Status |
|---|---|
| **Measles elimination in the Region** | |
| 1. Focus on integrating measles case-based surveillance/outbreak investigation/immunity gaps/sero-surveys into IRI.<br>2. Review progress in 2013. | 1. Regional consultation conducted in Kathmandu, 19–22 February 2013;<br>2. Measles elimination and rubella/ congenital rubella syndrome (CRS) control on RC66 agenda in September 2013;<br>3. Nepal – measles and rubella vaccine (MR) campaign completed;<br>4. India – third phase measles catch-up campaign almost completed (Bhopal and Indore cities are expected to complete by July 2013);<br>5. Bangladesh – MR campaign planned in quarter 4 of 2013;<br>6. Immunization and Vaccine Development (IVD) plans to conduct a surveillance standardization workshop, 23–27 September 2013. |
| **Introducing rubella vaccine (RV) into national immunization programmes** | |
| Provide technical assistance for translating global recommendations, documenting regional experience; facilitating introduction of RV into remaining five countries. | 1. Regional strategic plan has been drafted for measles elimination and for accelerating rubella/CRS control;<br>2. India is considering RV introduction – National Technical Advisory Group on Immunization (NTAGI) sub-group to review the current situation and potential future strategies for roll-out;<br>3. Regional consensus on 2020 rubella/CRS control goal. |
| **Progress of introduction of new vaccines** | |
| Facilitate and share experience of new vaccines introduction and learn best practices. | 1. New vaccine introduction meeting held in December 2012; experience shared and a draft algorithm was developed;<br>2. Post-introductory evaluation conducted in Bangladesh, and Kerala and Tamil Nadu in India. |

| Recommendations | Status |
|---|---|
| **Strategies for prevention and control of Japanese encephalitis** | |
| Support acute encephalitis syndrome (AES) surveillance and conduct research on:<br>1. Adequate number of doses to achieve high immunity for SA 14-14-2 live japanese encephalitis vaccine (LJEV).<br>2. Optimal age for immunization.<br>3. Need for vaccinating adults.<br>4. Aetiology of AES. | 1. Supporting AES surveillance; exploring expansion;<br>2. A situational analysis will be carried out in six Program for Appropriate Technology in Health (PATH) supported countries;<br>3. Bi-regional meeting will be held in April/May 2014 for sharing experience;<br>4. Research activities to better understand immunization gaps and aetiology of AES – India and Nepal. |
| **Progress of polio eradication: regional certification commission recommendations** | |
| 1. National polio commissions for polio eradication (NCCPE) submit updates yearly to Regional Commission for Certification for Polio Eradication (RCCPE) for certification in February 2014.<br>2. Countries with high risk of importation and immunity gaps continuing supplementary immunization activities (SIAs) until the Region is polio-free.<br>3. Convening a consultation to review endgame strategies. | 1. Regional consultation on polio endgame strategy conducted in December 2012;<br>2. Bangladesh, India and Nepal – national immunization days (NIDs) in 2012 and 2013;<br>3. Regional polio certification commission meetings in August and December 2012 and March 2013;<br>4. India phase-1 laboratory containment started. |
| **AFP surveillance and integrated VPD surveillance** | |
| 1. Document current practices; move towards integrating VPD surveillance with surveillance of other communicable diseases.<br>2. Translate AFP surveillance to include other VPD surveillance and retain skilled personnel and well-functioning infrastructure. | 1. Work in progress;<br>2. EPI and surveillance reviews conducted;<br>3. Integration is on the agenda. |

| Recommendations | Status |
|---|---|
| **Immunization research priorities: implementation research** | |
| Develop a process for identifying immunization research priorities. | Research in the IVD area:<br>1. Hepatitis B impact evaluation studies in Bangladesh and Nepal completed;<br>2. Burden and economic impact of varicella infections in Sri Lanka (ongoing);<br>3. Human papillomavirus (HPV) demonstration project in Bangladesh (planned). |
| **Progress in achieving MNT elimination** | |
| Develop timelines for completing validation and plan for sustaining elimination standards. | 1. Timor-Leste validated MNT elimination in 2012;<br>2. Four states in India (Delhi, Mizoram Orissa, and Uttarakhand) are in the process of MNT elimination validation in April 2013;<br>3. Validation to be completed in Indonesia in 2013. All other provinces except two (Maluku and Papua) have already validated MNT elimination. |
| **Capacity building of national regulatory authority (NRA) and status of implementation of vaccine post-marketing surveillance (PMS)** | |
| 1. Continue improving capacity of NRAs.<br>2. Establish functional AEFI committees with expertise in causality assessments; develop a pool of experts in the Region for assisting countries in managing AEFI issues.<br>3. Rename AEFI committees as national vaccine safety committees.<br>4. Invite select AEFI committees to present vaccine safety workplans. | 1. NRA assessments conducted in Indonesia (June); Thailand (July); India (Dec). All three functional;<br>2. Implementing NRA institutional development plan in progress:<br>a. Bangladesh: National Control Laboratory (NCL) upgrade<br>b. India: NRA good manufacturing practices (GMP) training, AEFI Secretariat<br>c. Indonesia: PMS pilot project<br>3. AEFI training: Myanmar in April 2013, Nepal in October 2013;<br>4. Regional consultation on AEFI April–May 2013. |

| Recommendations | Status |
|---|---|
| **Seasonal influenza vaccine introduction in the South-East Asia Region: needs and feasibility** | |
| 1. Continue updating pandemic vaccine deployment plans.<br>2. Conduct burden studies.<br>3. Enhance surveillance.<br>4. Assess the feasibility of vaccine introduction in high-risk groups. | 1. Work in progress;<br>2. Regional consultation held in 2012. |
| **Explore the need for pooled procurement of vaccines in the Region** | |
| Initiate a consultative process to outline the steps/requirements for pooled procurement of vaccines. | 1. The WHO South-East Asia Regional Office internal consultation convened by Regional Director in late 2012;<br>2. A similar mechanism is being offered by UNICEF with GAVI Alliance support and Sri Lanka has shown interest. |

# 5. Global progress on immunization: Decade of Vaccines and Global Vaccine Action Plan

In May 2011, at the Sixty-fourth World Health Assembly, the vision for the Decade of Vaccines 2011–2020 (DoV) and development of a Global Vaccine Action Plan (GVAP) were discussed. At its 130th Session in January 2012, the Executive Board considered the GVAP and provided guidance. The final GVAP was endorsed at the Sixty-fifth World Health Assembly in May 2012. The Health Assembly urged Member States to apply the GVAP principles to their own national plans, commit resources and report annually to regional and global governing bodies.

***Goals for the Decade of Vaccines***

(1) Achieve a world free from poliomyelitis;

(2) Meet vaccination coverage targets in every region, country and community;

(3) Exceed the Millennium Development Goal 4 target for reducing child mortality;

(4) Meet global and regional elimination targets;

(5) Develop and introduce new and improved vaccines and technologies.

***Guiding principles of the Global Vaccine Action Plan***

(1) **Country ownership:** Countries have primary ownership and responsibility for establishing good governance and for providing effective and quality immunization services for all.

(2) **Shared responsibility and partnership:** Immunization is an individual, a community and a governmental responsibility that transcends borders and sectors.

(3) **Equitable access:** Providing equitable access to immunization is a core component of the right to health.

(4) **Integration:** Strong immunization systems that are a part of the broader health systems and closely coordinated with other primary health care delivery programmes are required.

(5) **Sustainability:** Informed decisions and implementation strategies, appropriate levels of financial investments, and improved financial management and oversight are required.

(6) **Innovation:** The full potential of immunization is realized only through learning, continuous improvement, and innovation across all aspects of immunization.

***Discussion and recommendations:***

- New guidelines are under development for updating comprehensive multi-year plans (cMYPs) so that they are in alignment with GVAP strategies. Updated cMYPs will be field tested by regional offices.
- IVD has plans to review the regional strategy for immunization and vaccine development in order to align it with GVAP.
- Immunization systems need further strengthening and national authorities should take ownership and be accountable.
- Issues related to vaccine shortages need to be addressed.
- The Global Vaccine Research Forum is revamped to include more operational research.

***A tool for monitoring IRI***

A draft tool for monitoring IRI progress and performance was presented to the ITAG. The purpose of the tool is to enable both the programme manager at the country level and the regional focal point to track the progress of IRI activities in carrying out the routine immunization intensification efforts by countries. The tool assumes that the country has a written and approved plan of action for the intensification efforts. The tool was also proposed to be used at least on a quarterly basis.

In the discussions, it was clear that the Members of the ITAG had different expectations of such a tool. While the tool was developed with the objective to track progress of IRI, the ITAG members felt that it should be capable of being used to capture a snapshot of the situation when a visit is made to the peripheral level, for example, a district. However, the ITAG noted that the tool as it is, still might have some use.

***Discussions and recommendations:***

- The ITAG recommended development of a tool that can be used to assess immunization performance at the lowest level.
- The IRI monitoring tool should check policy and governance level changes.

# 6. Implementation of "2012-Year of Intensification of Routine Immunization"

The goal of the "2012-Year of Intensification of Routine Immunization" was for all Member States in South-East Asia Region to achieve at least 90% national immunization coverage and at least 80% district level coverage (subnational level) for the six basic antigens as measured by the coverage of third dose of DTP/pentavalent vaccine by 2013. Overall, implementation of IRI has been slow, but there have been positive effects on the national level immunization coverage (in high priority countries including India, Indonesia and Timor-Leste.

In India, an Immunization Technical Support Unit (ITSU) was established to support programme operations, supply chain, demand generation, AEFI surveillance and VPD surveillance. Through immunization weeks resulting in coverage of ~5 million children, India had been able to reach the previously unreached. India also has worked to modernize alternative vaccine delivery (AVD) mechanisms and enhance human resources to improve access to immunization services. India's key strategies included: (1) demanding generation for routine immunization services; (2) regular programme reviews and monitoring; (3) a web-enabled mother and child tracking system; (4) strengthening of AEFI and VPD surveillance; (5) utilizing lessons learnt from the polio eradication initiative for RI to strengthen micro-planning, monitoring and accountability mechanisms at all levels; and (6) adding additional incentives for Accredited Social Health Activist (ASHA) workers for ensuring full immunization of children.

The slow progress for IRI can be attributed to many reasons. IRI was launched at a very high level that caused delay due to the non-availability of funds until the financial year began. The same team was assigned to IRI activities amidst other immunization priorities. The approach was broad-based, lost focus on subnational areas and included a large number of subnational areas without first considering resource requirements. Activities were also weakly monitored.

Countries could improve IRI efforts by focusing more on areas where coverage is comparatively low, reaching children unreached by routine services. Staff should be oriented to focus on poor performing areas. Resource requirements need to be assessed and allocated. Internal reviews should take place with monitoring of conducting immunization sessions and vaccine distribution. Immunization coverage should be evaluated at regular intervals.

***Discussion and recommendations:***

- The ITAG endorsed the recommendation from the EPI-Managers' meeting in October 2012 that the IRI 2012 components should be included in multi-year immunization plans that capture GVAP strategies.
- There is a need for community-level evaluation of immunization coverage and for validating the existing immunization coverage survey methodologies.
- There should be a mechanism to externally evaluate immunization coverage.
- There should be a plan to improve data quality and to strengthen VPD and AEFI surveillance.

# 7. Progress of polio eradication: Recommendations of the Regional Certification Commission

## Status of global polio eradication

Notable gains in interrupting wild poliovirus (WPV) transmission have occurred since the Sixty-fifth World Health Assembly declared that polio eradication was an emergency for global public health on 25 May 2012. The Health Assembly also requested the Director-General to rapidly finalize a comprehensive polio endgame plan. The number of countries with WPV transmission decreased from 16 in 2011 to 5 in 2012 and by 31 December 2012, there were 223 total cases of WPV compared to 642 cases in 2011, representing a 65% decrease.

## Status of regional polio eradication

India was removed from the list of polio-endemic countries on 25 February 2012. India (last case 13 January 2011) and Nepal (last case 30 August 2010) have been polio-free for over two years. The remaining nine countries in the Region have been polio-free for more than five years. All countries in the Region remain susceptible to importation while there is wild poliovirus circulating anywhere in the world. With the current progress in India, the Region is on-track to be certified polio-free in February 2014.

## Polio-Free Certification, 2013–2014

WHO regions are certified polio-free by the Regional Certification Commission and certification is based on convincing evidence presented by National Certification Committees (NCC). The Region can be certified polio-free three years after the last reported indigenous WPV is found in any country in the Region in the presence of high quality AFP surveillance. Completion, documentation and verification of phase-1 laboratory containment is a certification requirement.

The South-East Asian Regional Certification Commission on Polio Eradication (SEA-RCCPE) during its most recent meeting held from 5–7 March 2013 in Malé, Maldives, made two recommendations for maintaining the Region's polio-free status:

(1) All NCCs should review with their respective national health authorities the current WHO recommendations for polio vaccination requirement for travellers. Regardless of age, all travellers to countries or areas with current or recent poliovirus transmission, or who plan to attend mass gatherings with the risk of exposure to infected persons should be fully vaccinated (per International Health Regulations)[*] against polio before departure;

(2) All NCCs should advocate with their respective governments to support the Independent Monitoring Board for Polio Eradication (IMB) recommendation to use the International Health Regulations to introduce pre-travel vaccination or vaccination checks for all travellers from the last three endemic countries (Afghanistan, Pakistan and Nigeria) until national transmission is stopped. No country should allow a citizen from any polio-endemic country to cross their borders without a valid vaccination

[*] International Travel and Health, 2012 Edition, World Health Organization http://www.who.int/ith/en/

certificate. The World Health Assembly should request the Director-General to move forward with the implementation of this recommendation prior to the Sixty-sixth World Health Assembly in May 2013.

## Polio endgame strategy

The post-eradication timeline requires vaccine-derived polio virus (VDPV) elimination and validation. From 2000 to 2011, an overwhelming majority of VDPV cases have been type-2 (type-1, 79 cases; type-2, 478 cases; type-3, 9 cases). This has driven discussions of making the switch from trivalent oral polio vaccine (tOPV) to bivalent OPV vaccine (removing the type-2 component) and eventually making the switch to inactivated polio vaccine (IPV) alone or in combination with OPV. At the South-East Asian Regional polio endgame meeting in Bangkok, Thailand on 14 December 2012, the six global prerequisites for cessation of the type-2 component of the oral polio vaccine were discussed. The regional status of the prerequisites were reviewed:

| Prerequisites | Status |
|---|---|
| (1) Validation of circulating vaccine derived polio virus (cVDPV) type-2 outbreaks for at least six months | Achieved; there have not been any cVDPV type-2 in the Region since 2009 |
| (2) Stockpile of mOPV2 and response capacity | Achieved; mOPV2 stockpiles will be maintained at the global level; and there is sufficient capacity in the Region for outbreak response |
| (3) Surveillance and international notification of Sabin, Sabin-like and cVDPV2 | Achieved; the AFP and environmental surveillance systems in the Region are well functioning and capable of detection of the polio viruses |
| (4) Licensed bivalent oral polio vaccine (bOPV) must be available | Not achieved; bOPV is not licensed in all countries |
| (5) Affordable IPV options must be available for all OPV-using countries | Not achieved; affordable IPV is not available |
| (6) Completion of phase II laboratory containment for cVDPV/WPV2 and phase I for type-2 Sabin virus | Not achieved; phase-1 laboratory containment is not completed |

All countries in the Region agreed to the technical feasibility of the tOPV to bOPV switch and use of IPV. However, countries and experts expressed their concerns about the polio endgame including the cost per dose and how doses will be financed (national versus external), the supply, how dose will be scheduled, the mode of administration, licensure, communication strategy and the degree of high-level advocacy. Additional consultation at the country level might be required to operationalize the evolving polio endgame strategy.

***Discussions and recommendations:***

- The ITAG endorses the SEA-RCCPE's recommendations for pre-departure polio vaccination for travellers to endemic countries and mass gatherings (endemic country

participants) and the implementation of an IHR requirement for polio vaccination for travellers from the three endemic countries as means to protect the South-East Asia Region's polio-free status.

- The ITAG endorses the SEA-RCCPE's programme of work including the implementation of the recommendation to the NCCPE on a regional polio-free certification goal by February 2014.
- The ITAG recommends that the WHO Regional Office for South-East Asia support country level consultations to implement the evolving polio endgame activities.
- In shifting to IPV, there is a need to look at individual country situations.
- Introduction of IPV may not give desired results without appropriate plans for sustainable coverage.
- The vaccine manufacturers need a lead time for manufacturing vaccines.

# 8. Measles elimination and rubella/congenital rubella syndrome control in the South-East Asia Region

From 19–22 February 2013, the South-East Asia Region convened a consultation on the elimination of measles and control of rubella/congenital rubella syndrome (CRS) in Kathmandu, Nepal. The consultation discussed the global and regional measles and rubella situations, the technical and programmatic feasibility of measles elimination and rubella/CRS control, issues and challenges, and the target year for measles elimination and rubella/CRS control.

Globally, significant achievements have been made in measles mortality reduction. The estimated global measles mortality decreased 74% from 535 300 deaths in 2000 to 139 300 in 2010. Prior to the consultation, all WHO regions except for the South-East Asia Region had measles elimination goals with established target dates between 2002 and 2020. The Region of Americas already eliminated measles in 2002 and rubella in 2010.

From 2000 to 2011, first-dose measles vaccine (MCV1) coverage increased from 61% to 79% in the South-East Asia Region. Four of the eleven countries in the Region have surpassed the ≥95% World Health Assembly MCV1 coverage target and nine countries introduced a second dose of measles vaccine (MCV2). Annual measles incidence decreased by 29% to 36 cases per million compared to 51 per million and estimated measles mortality decreased by 48% from 137 000 to 71 000 during this period. India has accelerated its measles efforts with SIAs in 14 states followed by inclusion of MCV2 in routine immunization. In South-East Asia Region, Bhutan, Democratic People's Republic of Korea, Maldives and Sri Lanka may have already eliminated measles.

At the consultation, the biological, technical and programmatic feasibility of measles elimination were affirmed. Programmatically, all countries in the Region have strong national EPI programmes as the foundation for measles elimination. Four countries (Bhutan, Democratic People's Republic of Korea, Maldives and Sri Lanka) are close to measles elimination. National laboratories are capable of diagnosing and genotyping measles at fully accredited laboratories. All countries in the Region (except India) already implemented case-based measles surveillance. A major portion of measles vaccines are produced in this Region. There is strong partner support

from the GAVI Alliance, Measles and Rubella Initiative (MRI) and others. The strong polio infrastructure can serve as an asset for measles elimination in the Region.

At the conclusion of the consultation, all countries of the Region came to the consensus that the target year for the Region for achieving measles elimination and rubella CRS control should be set at 2020. This proposal will be submitted to the Sixty-sixth Regional Committee in September 2013 for consideration.

***Discussion and recommendations:***

- The ITAG endorsed The Kathmandu consultation recommendation for a regional measles elimination and rubella/CRS control goal of 2020.
- It was recognized that measles elimination activities provide an opportunity for rubella/CRS elimination with the recognition that there are country-level operational issues to be addressed.
- Measles surveillance should be streamlined and there is a need to ensure that India is taking up case-based surveillance as per the international guidelines.
- The five countries not using rubella-containing vaccine should develop plans for introduction and all countries should establish CRS surveillance.
- An update of the country-level measles elimination and rubella/CRS control plans should be provided at the next meeting of the SEAR ITAG.
- SIAs will help reach targeted age groups but there is a need to identify strategies for reaching other age groups as well.
- The existing regional experience on CRS surveillance (such as in Sri Lanka) needs to be documented to share with countries that do not have CRS surveillance.
- There is a need for an integrated VPD control and prevention plan including CRS.

# 9. SAGE recommendation for intussusception surveillance and relaxation of rotavirus vaccine age restrictions

In its April 2012 meeting, the WHO Strategic Advisory Group of Experts (SAGE) recommended removal of the age restriction for rotavirus vaccines. Based on the recommendations of that SAGE meeting, WHO published a revised rotavirus vaccines position paper in January 2013 stating that immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccine by allowing infants to receive rotavirus vaccine together with DTP regardless of the time of vaccination.

The SAGE recommendation was largely based on a modelling exercise that explored the risk–benefit of removing the age restriction in the belief that more children can be vaccinated. The modelling output showed that if the rotavirus vaccine were administered without age restrictions in low- and middle-income countries, 203 000 rotavirus deaths would be prevented (range 10 000–281 500) while 547 intussusception deaths (range 237–1160) potentially would have occurred. Therefore, removing age restriction would prevent an additional 47 200 rotavirus deaths (18 700–63 700), but cause an additional 294 intussusception deaths (range 161 471), for an incremental benefit–risk ratio of 154 deaths averted for every death caused by the vaccine.

The ITAG reviewed the available information and after extensive discussions it was felt that careful communication around this issue is needed for those countries that intend to introduce rotavirus vaccines in future.

***Discussion and recommendations:***

- It was noted that removing age restrictions can increase the number of children vaccinated against rotavirus, but also has the potential risk of increasing intussusception deaths and therefore, recommended that countries carefully examine the implications of this recommendation.
- Each country should measure its baseline level of intussusception before vaccine introduction.
- Countries should establish sentinel surveillance sites to establish background rates of intussusception and also to enable monitoring intussusception trends after rotavirus vaccine introduction.
- If AEFI occurs, parents should be advised to bring back their children either to the health facility or to the health worker for further management.

## 10. Effective vaccine management assessments in the South-East Asia Region

A high-quality vaccine supply chain is one of the most crucial elements for a successful immunization programme. New lifesaving vaccines are readily available and most of these new vaccines are much more expensive and bulkier than traditional vaccines. The supply chain will need to handle increased volumes.

The effective vaccine management (EVM) assessment tool was introduced in 2010 and combines the strengths of two previously introduced tools, the vaccine management assessment (VMA) tool and the effective vaccine store management (EVSM) tool. Ministries of health are encouraged to carry out an assessment every three years with technical support from a consultant. The key outcome of an assessment is a list of recommendations to address weaknesses and reinforce strengths. An improvement plan is prepared and implemented by the national EPI team with financial and technical support of partners. There are nine key criteria for a satisfactory vaccine supply chain and at each level of the supply chain, each of the nine criteria is assigned a score out of 100% (target 80%). Assessment is done at national, subnational, district or lowest distribution and service delivery points.

Most countries struggle with the implementation of improvement of vaccine management. EVM assessments show where the problems are, but solutions are often complex. EVM improvement plans represent a strategic opportunity to bring about positive changes to public health logistics. Successful implementation requires strong country leadership, including strong project management, effective communication between various government agencies and commitment to change at all levels of the government structure, from health logisticians to directors. The schedule of EVM assessments is given in the following Table.

***Table:*** *Schedule of EVM assessments in the South-East Region*

| Country | Last EVM | Next EVM 2014 | Next EVM 2015 | Lead agency (2011–2012) |
|---|---|---|---|---|
| Democractic People's Republic of Korea | 2011 | x | | UNICEF |
| Indonesia | 2011 and 2012 | x | | UNICEF |
| Myanmar | 2011 | x | | UNICEF |
| Timor-Leste | 2011 | x | | UNICEF |
| Bangladesh | 2011 | x | | WHO |
| Bhutan | 2012 | | x | UNICEF |
| India[1] | 2011, 2012 and 2013 | | | UNICEF |
| Nepal | 2011 | x | | UNICEF |
| Sri Lanka | 2012 | | x | UNICEF |
| [1]India nationwide EVM assessment conducted March–April 2013 | | | | |

***Recommendations/comments:***

- UNICEF should be requested to work with countries and partners so that countries could conduct a self-assessment prior to the EVM exercise.
- Countries should ensure implementation of the EVM assessments recommendations.
- There should be a plan to carry out EVM assessments in non-GAVI-eligible countries, not just in GAVI-eligible countries.
- NTAGI should include EVM and related issues on their agendas.

# 11. Decision-making algorithm for new and underutilized vaccine introduction (NUVI)

At the new vaccine introduction meeting held in Bangkok in December 2012, the country participants reviewed existing criteria for introducing a new vaccine in the South-East Asia Region, added new criteria to the existing set and drafted an algorithm for NUVI in the Region. Subsequently the draft was updated and presented to the SEAR-ITAG for review during the current session. The draft algorithm takes into consideration whether the disease is of public health concern, the quantum of mortality or morbidity, the attributable risk without the vaccine, and vaccine availability, evidence for its use, safety, efficacy, acceptability, affordability and programme capacity.

***Discussion and recommendations:***

- It was recognized that the NUVI algorithm was a work in progress.

- Adding strategies that may be complementary to immunization should not be considered only as alternatives to vaccination.
- Adding quantification of vaccine efficacy, safety and acceptability should be considered.
- Adding cost-effectiveness analyses at the family and national levels should be considered.
- Adding an assessment of return on investment (e.g. productivity gained) should be considered.

## 12. AEFI monitoring, preparedness and response plans

National Regulatory Assessments (NRAs) provide insights into the level of enforcement of regulatory functions including vaccine safety PMS and AEFI. These are mostly conducted at the central level and provide limited information on the AEFI system at the subnational level. In the vaccine producing countries of the Region, AEFI monitoring systems are in place; there are national AEFI committees and guidelines for reporting AEFI and taking regulatory actions. However, AEFI detection capacity is a limitation. In countries procuring vaccines directly, strong AEFI committees have been established and good AEFI detection capacity exists. Countries procuring vaccine through UNICEF have AEFI committees that lack expertise to be able to establish national surveillance systems and have a limited AEFI detection capacity.

Training programmes are not enough to increase AEFI detection capacity or to strengthen capacity to manage and analyse AEFI data. Constraints and barriers to AEFI reporting need to be identified to include all vaccine safety shareholders at each level to update national AEFI guidelines and standard operating procedures. Gaps need to be identified and prioritization of activities should be evidence-based. Institutional capacity building should proceed with clear roadmaps, responsibility and deadlines for completion. To these ends, national AEFI guidelines are being updated in line with new vaccines introduction. Thirteen training workshops on AEFI were conducted in seven countries of the Region and support was provided to the national AEFI Secretariat to establish pilot projects. Technical support was provided to develop operational studies to identify factors affecting AEFI reporting. An intercountry workshop on causality assessment of AEFI will be held during 28 April–2 May 2013 in Bangkok, Thailand.

At the global level, new training materials and tools for causality assessment have been updated or developed. These include an update of training materials for a five-day course with new Council for International Organizations of Medical Sciences case definitions. The WHO basic course on AEFI monitoring went online in 2012 (http://www.who.int/vaccine_safety/initiative/tech_support/ebasic/en/index.html). In addition, the WHO updates and maintains information sheets on observed rates of vaccine reactions which are useful to compare AEFI rates collected at the country level with what has been observed globally (http://www.who.int/vaccine_safety/initiative/ tools/vaccinfosheets/en/index.html).

***Discussion and recommendations:***

- While appreciating the efforts of the WHO Regional Office for South-East Asia towards establishing a pool of regional experts, it was recommended that WHO should accelerate building capacity at the regional and national levels.

# 13. Strengthening of maternal health and immunization through mobilization of local community resources and increased ownership using Appreciative Inquiry approach

One of the ways of intensifying and sustaining routine immunization is through creation of community demand, community participation, building ownership and mobilization of local resources. A new approach/tool known as Appreciative Inquiry (AI) was used in Nepal for mobilization of local resources, community participation and building ownership.

AI is about the co-evolutionary search for the best in people and their organizations. In its broadest focus, it involves systematic discovery of what gives "life" to a living system when it is most alive, most effective in that socioeconomic setting. AI involves, in a central way, the art and practice of asking questions that strengthen a system's capacity to apprehend, anticipate, and heighten positive potential. In AI, the arduous task of intervention gives way to the speed of imagination and innovation. Instead of negation, criticism, and spiralling diagnosis, there is a discovery, dream, and design.

In Nepal, the AI approach was piloted initially in two districts (Achham and Rukum) bringing together Village Development Committee (VDC) secretaries, health staff, journalists, local leaders, government officers, nongovernmental organizations and supporting partners together in a three-day workshop combining both immunization and maternal health. The outcome was impressive. Several participants made the commitment to ensure all children in their villages are fully immunized and no pregnant women should die because of pregnancy-related complications. Pregnant women should have service at their level and receive timely referral. However, AI alone is not enough. There should be a strong health leadership in the district to convert commitment into action and implementation should be followed up.

The outcome of the AI workshop after six months in the areas of immunization and maternal health was impressive. Several villages are waiting for declaration as fully immunized VDCs; vaccinators have been recruited; emergency funds have been established and funds have been allocated for establishment of birth centres, all by using local resources and community participation.

***Discussion and recommendations:***

- The potential of community mobilization to improve maternal health and immunization through innovative approaches such as AI is recognized and its utility should be further explored.

22ND WESTERN PACIFIC REGION TAG MEETING
25-27 JUNE 2013, MANILA

CONCLUSIONS AND RECOMMENDATIONS

## 3.1 Polio Endgame Strategy

*Conclusions*

1. The TAG welcomes the RCC conclusion that Western Pacific Region maintains its polio-free status, and commends China for the highly successful 2011 outbreak response they have conducted.

2. The TAG acknowledges the Polio Eradication and Endgame Strategic Plan 2013–2018 that was noted by the World Health Assembly in May 2013.

3. The Western Pacific Region has been certified polio-free since 2000; however, many countries are still facing immunity and AFP surveillance gaps, as identified and discussed during previous RCC meetings. Risk assessments demonstrate that the Philippines and Papua New Guinea are at highest risk for poliovirus importation and spread. The current international spread of poliovirus of Nigerian origin to Somalia and Kenya is increasing this risk to these and other countries in the Region.

4. The TAG acknowledges the special efforts made to increase surveillance sensitivity in Papua New Guinea as well as activities in the Lao People's Democratic Republic and China and planned in Cambodia and the Philippines to increase immunity protection by adding OPV delivery to other interventions. Other countries facing similar challenges could consider similar good practices. Regular data analysis should be used to identify areas that need to be addressed.

5. To operationalize the Endgame Strategic Plan at the national level, a multisectoral sequenced and coordinated effort will be required to get political and other key stakeholders' endorsement and commitment. Therefore, coordinated partnership support will be critical to successfully implement endgame strategies on the very tight timeline required (coordinated introduction of IPV by October 2015; replace tOPV with bOPV by April 2016). Some countries may wish to convene a task force to coordinate this effort.

6. Timely and close follow-up through the polio endgame reporting system is crucial to ensure coordination of activities at all levels in order to meet the regional and global targets, especially for OPV-using countries.

*Recommendations*

WHO Western Pacific Region countries and areas

The TAG recommends that countries and areas:

1. Ensure that any wild or vaccine-derived polioviruses are detected in a timely fashion and appropriate control measures are initiated (country outbreak response plans should be updated).

2. Improve AFP surveillance sensitivity by:

a. Providing special support to improve AFP surveillance indicators to meet the recommended surveillance performance standards, especially for the stool adequacy rates, completeness and timeliness of reports and 60-day follow-up examination.

b. Considering additional special activities to increase surveillance sensitivity (e.g.: environmental surveillance in selected areas).

c. Conducting external surveillance reviews in selected high-risk areas based upon the regional risk assessment methodology and developing an action plan to address the gaps identified (Cambodia, Lao People's Democratic Republic, Philippines, Viet Nam).

d. Reporting on at least a bi-weekly basis on core surveillance indicators to the Regional Office for the Western Pacific to comply with the global reporting requirements.

3. Identify immunity gaps by age and geographic area based on AFP data analysis and risk assessment, and consider special activities to target under-vaccinated groups (strengthening routine, or adding OPV to any campaign).

4. Initiate implementation of Phase II of the laboratory containment plan in Western Pacific Region countries by 2014, according to the draft Global Action Plan for Poliovirus Laboratory Containment, Version III.

5. Initiate registration of IPV, bOPV and mOPVs as soon as possible.

6. Start developing a draft national polio endgame strategic plan of action. The global Polio Eradication and Endgame Strategic Plan 2013–2018 should serve as a blueprint for developing country-specific plans, with emphasis on introduction of at least one dose of IPV by October 2015 and replacing tOPV with bOPV by April 2016.

a. By November 2013, each country should provide to the RCC a provisional schedule for IPV and dates for introduction of IPV and bOPV to facilitate regional vaccine forecasting, and a provisional estimate of resource requirements.

b. The plan should include the financial resource requirements (FRR) needed to support implementation of the country endgame strategic plan.

c. The plan should include a timeline and reporting system to monitor the progress of country plan implementation.

d. A report on progress in developing the draft plan of action should be provided at the November 2013 RCC meeting.

<u>OPV-using countries and areas (17)</u>

1. The TAG encourages countries to initiate, as soon as possible, dialogue to develop national consensus with NITAGs and other relevant technical committees and multisectoral departments, and share information of the details of the national plan (including additional activities considered to fulfil immunity and surveillance gaps, national vaccine switch consensus: timeline, sequence, vaccine presentation, supply required, vaccine schedule).

2. The TAG recommends that countries planning introduction of IPV make provisions to secure long-term financing for the vaccine.

3. Following review of the regional risk assessment at the subnational level, the 18th RCC Meeting concluded that areas in several countries (Cambodia, Lao People's Democratic Republic, Papua New Guinea, Philippines, and Viet Nam) are vulnerable to poliovirus importation. In the current context of the polio endgame, The TAG urges each of these countries to develop a comprehensive plan of action to mitigate this risk, as part of the national polio endgame strategic plan.

WHO Regional Office for the Western Pacific

1. The TAG requests the Regional Office to develop a template and timeline for national polio endgame strategic plans of action and provide it to all Member States as soon as possible (see country recommendation #5).

2. The TAG requests the Regional Office and partners to provide technical support as needed in any Western Pacific Region countries to develop their national polio endgame strategic plans of action.

3. The TAG requests the Regional Office to develop a regional endgame strategic plan of action, including information on the licensure status by country of bOPV and IPV, and compiling the financial, human and technical resources required, by mid-2014.

WHO Headquarters and all WHO Member States

The TAG recommends that polio immunization be made a requirement for all travellers coming from and going to polio-infected countries, under the International Health Regulations.

3.2 Regional Framework for Implementation of the Global Vaccine Action Plan

3.2.1 General

Committing to immunization as a priority first and foremost means recognizing the importance of immunization as a critical public health intervention and the value that immunization represents in terms of health and economic returns for all countries of the Western Pacific Region. Moreover, the TAG recognizes that strong immunization systems are an integral part of a well-functioning health system and play a major role in improving child survival and the health and well-being of communities.

In this regard, the TAG has reviewed and appreciates the Secretariat's work to prepare a draft Regional Framework for Implementation of the GVAP in the Western Pacific.

The TAG notes that the draft Regional Framework for Implementation of GVAP in the Western Pacific reaffirms or updates the existing regional immunization goals and proposes regional immunization goals in order to ensure equity of immunization for every individual and every community and to protect them from vaccine-preventable diseases with existing and newly available vaccines.

Therefore, the TAG endorses the draft Regional Framework for Implementation of GVAP in the Western Pacific for supporting the countries to implement GVAP, achieving GVAP Strategic Objectives and accelerating progress towards achievement of the regional immunization goals.

*Recommendation*

The TAG requests the WHO Regional Office for the Western Pacific to finalize the draft Regional Framework for Implementation of GVAP in the Western Pacific in consultation with WHO country offices and Member States and to submit this framework to the Regional Committee for its endorsement.

3.2.2 Regional immunization goals

3.2.2.1 Sustaining polio-free status and implementing polio endgame strategy

The TAG welcomes the report of the 18th Regional Certification Commission that concluded that the Western Pacific Region retains its polio-free status after the 2011 Chinese polio outbreak. The TAG takes note of the Polio Endgame Strategic Plan 2013–2018 presented during the May 2013 World Health Assembly and the global timeline outlined. Because of their certified polio-free status, Western Pacific Region countries will be mainly focusing on objective 2 of this plan. Implementing the plan within the tight timeline will require a substantial coordinated multi-sectoral effort at all levels, especially for OPV-using countries. Limited financial and technical regional and country resources dedicated to the operationalization of this plan are currently the main challenge.

*Recommendations*

1. The TAG recommends that Western Pacific countries start developing national polio endgame strategic plans of action. These plans will include: formulating an advocacy and communications strategy, linking the endgame with routine immunization strengthening activities, evaluating bOPV and IPV demand and supply, determining technical assistance needs, identifying financing for IPV, and outlining a timeline for implementation.

2. In keeping with the Polio Eradication and Endgame Strategic Plan 2013-2018, the TAG reinforces the need to eliminate type 2 vaccine-derived poliovirus risk by introducing in OPV-using countries at least one dose of IPV by October 2015, and replacing tOPV with bOPV by April 2016.

3. The TAG recommends that the WHO Regional Office for the Western Pacific initiate and compile a regional endgame strategic plan of action including the resources required for its implementation by mid-2014.

3.2.2.2 Maternal and neonatal tetanus elimination

The TAG takes note of the global and regional progress towards maternal and neonatal tetanus elimination. The TAG congratulates China on its validation of neonatal tetanus elimination in 2012. As of May 2013, maternal and neonatal tetanus remains a problem in 28 countries globally and four countries in the Western Pacific Region. However, all four in the Western Pacific Region have completed assessments and are in the process of implementing various control measures. If these control measures are successful, the TAG feels confident that the four remaining countries should be able to eliminate maternal and neonatal tetanus by 2015.

*Recommendation*

The TAG recommends that the four remaining countries that have not yet validated the elimination of maternal and neonatal tetanus (Cambodia, Lao People's Democratic Republic, Papua New Guinea and the Philippines) continue implementing necessary actions to eliminate maternal and neonatal tetanus by 2015 with completion of validation assessments by 2016.

3.2.2.3 Measles elimination

The TAG notes that the Western Pacific Region has made remarkable achievements in eliminating measles with a >99% reduction in measles cases from 2003 (the year the measles elimination resolution passed) to 2012. Remaining challenges include the following: (i) in 2013, measles remains endemic in at least three countries; and (ii) several countries and areas have experienced endemic or imported outbreaks. Rapid and effective strategies and actions are needed to detect and interrupt measles virus transmission through more sensitive surveillance combined with immediate outbreak response and to close the remaining population immunity gaps across the age spectrum.

*Recommendations*

1. The TAG urges countries to make sustained, intensified efforts to accelerate progress towards achieving and sustaining measles elimination, in accordance with the Regional Committee Resolution WPR/RC63.R5.

2. The TAG encourages the WHO Regional Office for the Western Pacific and Member States to continue to use the Regional Verification Guidelines for Measles Elimination, and the roles of the Regional Verification Commission and national committees as an active means of monitoring progress and providing recommendations where needed to improve performance.

3.2.2.4 Hepatitis B accelerated control

The TAG is looking forward to the outcome of the 2013 Regional Committee Meeting where 2017 is proposed as the target year for the <1% Regional hepatitis B control goal. The significant achievements in reaching high birth dose and three-dose vaccination coverage bring an opportunity for hepatitis B control to support access to newborn care and increase of routine immunization coverage.

*Recommendation*

The TAG requests the WHO Regional Office for the Western Pacific to draft an updated strategic plan for reaching the Regional hepatitis B control goal of <1% seroprevalence in five-year-old children by the target year set by the Regional Committee, to be reviewed at the next TAG meeting.

3.2.2.5 Rubella and congenital rubella syndrome elimination

The TAG takes note of the following: (i) the feasibility of rubella elimination and the platform of measles elimination provide an opportunity to work toward simultaneous elimination of rubella; (ii) the remaining high burden of rubella and congenital rubella syndrome in the Western Pacific Region, noting that during 2011–2013, at least three countries in the Region (Japan, Mongolia and Viet Nam) have experienced large rubella outbreaks resulting in increased numbers of children born affected with congenital rubella syndrome; and (iii) the opportunity that as of 2013, six countries and areas have not yet introduced rubella vaccine into their routine immunization programmes, but that five of the six countries are eligible to apply for GAVI financial support to conduct wide age range catch-up campaigns with measles-rubella (MR) vaccine.

*Recommendations*

1. The TAG recommends establishing a regional goal of eliminating rubella, with a target date to be determined, and including it in the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific (2013–2020).

2. The TAG requests the Regional Director to advocate for endorsement of the regional rubella elimination goal (target date is yet to be determined) by Member States by including it as an agenda item in the Regional Committee Meeting in 2014.

3. The TAG requests all countries and areas to submit rubella case-based data on a monthly basis to the WHO Regional Office for the Western Pacific from January 2014.

4. The TAG requests the WHO Regional Office for the Western Pacific to provide comprehensive analysis of rubella epidemiology in the Region, including age-specific rubella case data, CRS data and serosurveys where available, and to dialogue with countries to develop a consensus on the appropriate target year for rubella elimination in the Region, for consideration during the 2014 TAG meeting.

5. The TAG requests the WHO Regional Office for the Western Pacific to provide technical assistance to Member States for developing tailored strategies to achieve the rubella elimination goal based on country-specific situations. The TAG also recommends that Member States develop joint action plans to synergize activities for eliminating measles and rubella.

6. To minimize the risk of CRS prior to achieving rubella elimination, the TAG urges those countries that have not introduced rubella-containing vaccine into the routine childhood immunization schedule to do so as soon as possible, in conjunction with a measles-rubella catch-up campaign in children under 15 years of age. All countries should consider targeted vaccination of rubella-susceptible older age groups, based on local epidemiology.

#### 3.2.2.6 Japanese encephalitis accelerated control

The TAG notes the importance of Japanese encephalitis (JE) virus as a cause of encephalitis in Asia, including risk areas in twelve countries of the Western Pacific Region. JE vaccine has been a highly successful tool in controlling JE in several countries of the Region, reducing the incidence to very low levels. While several countries in the Region produce JE vaccine, most are not marketed internationally and no vaccine is yet WHO-prequalified. However, WHO prequalification of one or more JE vaccines is anticipated in the next year, and GAVI support for vaccine purchase for eligible countries is anticipated. These developments make it possible to consider an accelerated control goal for JE in the Western Pacific Region. Expert consultation is needed to review the technical feasibility of achieving JE control across the Region, to determine the appropriate targets and timeframe for a goal, and to identify strategies for and cost of achieving it. Current weaknesses in surveillance, which limit efforts to estimate burden of disease, define target populations for vaccination, and measure impact of vaccination in some countries, are noted.

*Recommendations*

1. The TAG advises the WHO Regional Office for the Western Pacific to develop a Japanese encephalitis accelerated control goal and the targets, timeline and strategies to achieve it through consultation with experts and Member States during the coming year. The TAG requests that progress be reported during the 2014 meeting of the TAG.

2. The TAG recommends that JE surveillance should be further strengthened in endemic countries of the Western Pacific Region; sentinel surveillance should be systematized to facilitate reporting at the Regional level.

3. The TAG recommends that the WHO Regional Office for the Western Pacific continue efforts to strengthen laboratory diagnostic capacity for Japanese encephalitis.

3.2.2.7 Meeting regional vaccination coverage targets

With consideration of (i) the vaccination coverage targets set by the Global Vaccine Action Plan for national and district levels of all countries by 2020, (ii) the national vaccination coverage targets already set by countries in the Western Pacific Region, and (iii) coverage of MCV1 and MCV2 required at national and district levels for achieving and maintaining measles elimination, the TAG supports the following coverage targets proposed for the Western Pacific Region:

- Reach > 95% national coverage for each vaccine used in the national immunization programme; and

- Reach > 90% in every district or equivalent administrative unit for each vaccine used in the national immunization programme unless otherwise recommended.

The TAG reaffirms that the key challenges to meeting the above coverage targets raised by the Secretariat should be more actively addressed by all the countries and partners in the Western Pacific Region to ensure equitable access to immunization by all children. The TAG concurs that these challenges could be well addressed through pursuit of GVAP strategic objectives in the Regional Framework of GVAP Implementation in the Western Pacific. Documenting achievement of the coverage targets will rely on obtaining more accurate administrative coverage data.

*Recommendations*

1. The TAG urges countries, WHO and partners to work together in identifying provinces and districts with sub-optimal performance in routine vaccination programmes.

2. The TAG encourages countries, WHO and partners to work together in expanding "Reaching Every" District, Community or Child strategies to engage underserved and marginalized communities to participate in developing locally tailored, targeted strategies for reducing inequities.

3. The TAG encourages countries to adopt a life-course approach to immunization; school-entry screening and vaccination is an example of this approach.

4. The TAG urges WHO and countries to strengthen capacity for measurement of vaccination coverage to better identify immunity gaps by age and geographic area.

3.2.2.8 Evidence-based introduction of new vaccines

The TAG notes the potential of new vaccines to greatly increase the impact of national immunization programmes in the Region and recognizes the Decade of Vaccines goal for introduction of new and improved vaccines. Introduction of new vaccines in the Region has been slow due to a set of factors including cost, limited disease burden data, and competing priorities. The complexity of the new vaccine landscape makes it increasingly difficult for

countries to evaluate new vaccines for introduction. Evidence-based introduction of new vaccines requires evaluating data on disease burden including surveillance data, estimating costs and cost-effectiveness, assessing the role of other disease prevention and control measures, and considering vaccine characteristics, vaccine supply and immunization programme and health system strength. To facilitate a systematic approach to the process, and to achieve the Decade of Vaccines goal, countries need to have national plans for evidence-based introduction of new vaccines. WHO plays an important role in providing technical support and capacity building for the development and implementation of these national plans.

*Recommendations*

1. The TAG advises each Member State to develop a national plan for evidence-based introduction of new vaccines in coordination with NITAGs or similar groups (could be part of the comprehensive multi-year plan for immunization). This plan should take into consideration the use of disease burden data, cost and cost-effectiveness data and WHO recommendations for vaccine use; the role of comprehensive disease prevention approaches for pneumonia, diarrhoea and cervical cancer; vaccine characteristics, safety and supply; and immunization programme and health system strength. Progress in development of these plans should be reported to the TAG in 2014.

2. The TAG requests WHO to develop a template and guidance for development of national plans for evidence-based introduction of new vaccines.

3. The TAG requests WHO to provide technical support and capacity building for countries to develop and implement plans for evidence-based introduction of new vaccines. WHO will need to develop a pool of experts and obtain additional resources to implement this recommendation.

3.2.3 Priority actions for implementation of GVAP in the Western Pacific Region

The TAG acknowledges and supports the priority actions proposed by the WHO Regional Office for the Western Pacific in order to achieve GVAP strategic objectives in the Western Pacific and accelerate progress towards achievement of regional immunization goals.

*Recommendations*

1. The TAG urges WHO, countries and other stakeholders to actively coordinate and collaborate with each other in implementing priority actions proposed in the Regional Framework for the Western Pacific;

2. The TAG recommends that countries consider and, if necessary, incorporate priority actions proposed in the Regional Framework into planning, developing and implementing their national immunization programmes;

3. The TAG recommends that the WHO Regional Office for the Western Pacific and WHO country offices coordinate with national immunization programmes in estimating the annual cost to implement necessary priority actions proposed in the Regional Framework for the Region from 2014 to 2020;

4. The TAG recommends that WHO mobilize both technical and financial resources to support the Region to implement the necessary priority actions proposed in the Regional Framework; and

5. The TAG recommends that the WHO Regional Office for the Western Pacific foster alignment of Regional partners to advocate for allocation of additional financial and technical resources to support national immunization programmes in the Region.

3.2.3 Monitoring and Reporting GVAP Implementation in the Western Pacific Region

The TAG supports a framework proposed by the Secretariat for the Region to monitor and report the progress in implementation of GVAP in the Western Pacific Region.

*Recommendations*

1. The TAG recommends the WHO Regional Office for the Western Pacific and WHO country offices further work with countries in finalizing the proposed framework for monitoring and reporting the progress in implementation of GVAP;

2. The TAG recommends countries to provide the WHO Regional Office for the Western Pacific with necessary information on an annual basis for summary in an annual regional progress report on GVAP implementation in the Western Pacific to be submitted to the Regional Committee.

**Executive summary of the 11-12 June 2013 GAVI Alliance Board Meeting**

(Full report is available on the SAGE website)

- The GAVI Alliance Board recognized the importance of a strong partnership and complementarity between the GAVI Alliance and the Global Polio Eradication Initiative (GPEI) in eradicating polio based on a mutually agreed understanding of roles, responsibilities and results in countries and noted the comparative advantage of the GAVI Alliance in new vaccine introductions, the importance of routine immunization programmes and the integration of IPV into those programmes. The Secretariat was requested, as a matter of urgency, in collaboration with GPEI to initiate country dialogue on the introduction of IPV through national routine immunization in accordance with recommendations by WHO and SAGE, prioritizing countries most at risk for polio outbreaks and to initiate preparations with relevant partners, including countries, for IPV procurement and implementation support.

- The Board reaffirmed the complementary role of GAVI in supporting the introduction of IPV into routine immunization progammes in the 73 GAVI supported countries and requested GPEI and GAVI to urgently regroup to define roles and responsibilities, develop options for initiating country level dialogue and confirm funding outside of GAVI's current resources.

- On GAVI's next Vaccine Investment Strategy (VIS) the Board requested to narrow the choice of possible vaccine investment options for further analysis in Phase II by prioritizing vaccines based on health impact (mortality and morbidity), epidemic potential, and value for money (procurement cost per death averted). The Board further requested the phase II analysis outcomes to be benchmarked against the vaccines in GAVI's current portfolio. As modelled in Phase I of the VIS and subject to further analysis in Phase II, influenza (for maternal immunization), malaria and rabies vaccines are in the top tier of health impact outcomes; cholera and yellow fever vaccines are included on the basis of epidemic potential and value for money outcomes. Dengue, meningitis (serogroups CYW135) and measles (expanded investment), while diseases with epidemic potential, are excluded from further analysis because of a relatively high cost per death averted of the modelled strategy.

- On GAVI's funding, the Alliance is well funded through to 2015 in fulfilling all current commitments to countries with a potential gap of US$430M given the deferral of IFFIm proceeds beyond 2015.

- For 2016-2020, the process for defining GAVI's future strategy has been initiated including defining its new vaccine portfolio and positioning GAVI in the broader development context. The expected annual cruising altitude is about US$1.7 billion a year for 2016-2020, with a target of mobilizing an additional US$ 7.3 billion through its next replenishment.

- The plans for the midterm review meeting in Stockholm, Sweden on 30 October were discussed and towards preparing for GAVI's next replenishment likely towards the end of 2014 or early 2015.

World Health Organization

Organisation mondiale de la Santé

# Weekly epidemiological record
# Relevé épidémiologique hebdomadaire

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## Global Advisory Committee on Vaccine Safety, 12–13 June 2013

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO to provide independent scientifically rigourous advice on vaccine safety issues of potential global importance.[1] GACVS held its 28th meeting in Geneva, Switzerland, on 12–13 June 2013.[2] The committee reviewed 7 specific issues: (i) the experience of 4 Asian countries with the use of Hib-containing pentavalent vaccine; (ii) the safety profile of varicella vaccines; (iii) the safety of immunization during pregnancy; (iv) the monitoring of yellow fever vaccine safety during mass vaccination campaigns in Africa; (v) the safety profile of Japanese encephalitis vaccines; and (vi) updates on the risk of narcolepsy related to the use of the pandemic influenza vaccine Pandemrix® and (vii) recent data from the post-licensure monitoring of human papillomavirus vaccines.

### Pentavalent vaccine in Asian countries

Since 2008, *Haemophilus influenzae* type b (Hib) vaccine has been introduced progressively into Asian countries' immunization programmes. Hib vaccine has usually been introduced as a component of a combination pentavalent vaccine, which has replaced the traditional diphtheria–tetanus–

[1] See No. 41, 1999, pp. 337–338.

[2] GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: Bio-Manguinhos, Rio de Janeiro, Brazil; Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD, USA; Centers for Disease Control and Prevention, Atlanta GA, USA; Center for Drug Evaluation of China; Chengdu Institute of Biological Products, Chengdu, China; Crucell Holland, Leiden, The Netherlands; GlaxoSmithKline Biological, Wavre, Belgium; Intercell, Vienna, Austria; Merck & Co, Upper Gwynedd PA, USA; Ministry of Health and Family Welfare, India; National Centre for Disease Control, Canberra, Australia; National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam; University of Medical Sciences of Bhutan.

## Comité consultatif mondial de la Sécurité vaccinale, 12-13 juin 2013

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.[1] Le GACVS a tenu sa 28e réunion à Genève (Suisse), les 12 et 13 juin 2013.[2] Il a examiné 7 questions spécifiques: 1) l'expérience de 4 pays d'Asie dans l'utilisation du vaccin pentavalent contenant la valence *Haemophilus influenzae* type b (Hib); 2) le profil d'innocuité des vaccins antivaricelleux; 3) l'innocuité de la vaccination pendant la grossesse; 4) la surveillance de l'innocuité du vaccin antiamaril pendant les campagnes de vaccination de masse menées en Afrique; 5) le profil d'innocuité des vaccins contre l'encéphalite japonaise; 6) les mises à jour sur le risque de narcolepsie lié à l'utilisation du vaccin contre la grippe pandémique Pandemrix®; et 7) les données récentes sur la surveillance post-autorisation des vaccins anti-papillomavirus humain.

### Utilisation du vaccin pentavalent dans des pays asiatiques

Depuis 2008, le vaccin contre *Haemophilus influenzae* type b (Hib) a été introduit progressivement dans les programmes de vaccination des pays asiatiques. Il a généralement été introduit sous la forme d'un vaccin pentavalent combiné, qui remplace les vaccins classiques antidiphtérique-antitétanique-antico-

[1] Voir N° 41, 1999, pp. 337-338.

[2] 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: Bio-Manguinhos, Rio de Janeiro, Brésil; Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD, États-Unis d'Amérique; Centers for Disease Control and Prevention, Atlanta GA, États-Unis d'Amérique; Centre d'évaluation des médicaments de Chine; Institut des produits biologiques de Chengdu, Chengdu (Chine); Crucell Holland, Leiden, Pays-Bas; GlaxoSmithKline Biological, Wavre, Belgique; Intercell, Vienne, Autriche; Merck & Co, Upper Gwynedd PA, États-Unis d'Amérique; Ministère de la santé et du bien-être familial, Inde; National Centre for Disease Control, Canberra, Australie; Institut national d'hygiène et d'épidémiologie, Hanoï, Viet Nam; Université des sciences médicales du Bhoutan.

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whole-cell pertussis (DTwP) or DTPwP-hepatitis B vaccines. As with the introduction of any new vaccine, there has been particular attention to adverse events following immunization (AEFI), which presented challenges in several countries in the WHO South-East Asia and Western Pacific Regions. Four countries that introduced pentavalent vaccines from 3 different manufacturers presented their experience:

(1) Sri Lanka introduced the pentavalent vaccine from Crucell in January 2008. Within 3 months, 4 reports of deaths and 24 reports of suspected hypotonic-hyporesponsive episodes prompted regulatory attention and precautionary suspension of the initial vaccine lot. A subsequent death that occurred with the next lot in April 2009 led the authorities to suspend pentavalent vaccine use and resume DTwP and hepatitis B vaccination.

(2) Bhutan introduced pentavalent vaccine from Panacea in September 2009. The identification of 5 cases with encephalopathy and/or meningoencephalitis shortly after pentavalent vaccination prompted the authorities to suspend vaccination on 23 October 2009. Subsequently, 4 additional serious cases related to vaccine administered prior to suspension were identified and investigated.

(3) India introduced pentavalent vaccine from the Serum Institute of India in the states of Tamil Nadu and Kerala in December 2011. This was followed by expansion of vaccine usage in the states of Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat and Delhi during the second half of 2012 through the first quarter of 2013. To date, 83 AEFI cases, some of which were associated with mortality, have been reported after vaccine introduction from some states.

(4) Vietnam introduced pentavalent vaccine from Crucell in June 2010. Through May 2013, a total of 43 serious AEFI cases were investigated, including 27 with a fatal outcome. Following receipt of reports of 9 deaths following vaccination between December 2012 and March 2013, health authorities suspended use of the vaccine.

In each country the serious AEFIs were reviewed with independent national and international experts. Based on those reviews, none of the fatal cases could be classified as having a consistent causal association with immunization. In Sri Lanka, after a comprehensive investigation and review, the same pentavalent vaccine product was re-introduced in 2010. Since then and up to 2012, another 14 deaths were reported among infants who had received the Crucell pentavalent vaccine. In addition, 6 of 19 infant deaths were found at autopsy to have severe congenital heart disease. Following this finding, in Sri Lanka children with known severe congenital heart disease are now vaccinated under close medical supervision, and no additional deaths among children have since been reported in temporal association with pentavalent vaccine administration. In Bhutan, following a similar investigative process, the vaccine was reintroduced in 2011. Vietnam is currently reviewing clinical, epidemiological and vaccine quality issues.

quelucheux à cellules entières (DTCc) ou DTCc-hépatite B. Comme toujours lors de l'introduction d'un nouveau vaccin, une attention particulière a été accordée aux manifestations postvaccinales indésirables (MAPI) qui ont posé des problèmes importants dans plusieurs pays des régions OMS de l'Asie du Sud-Est et du Pacifique occidental. Quatre pays, ayant introduit l'un des vaccins pentavalents produits par 3 fabricants différents, ont présenté leur expérience.

(1) Le Sri Lanka a introduit le vaccin pentavalent fabriqué par Crucell en janvier 2008. En l'espace de 3 mois, 4 notifications de décès et 24 notifications d'épisode hypotonique-hyporéactif suspect ont attiré l'attention des autorités de réglementation et suscité la suspension par précaution du premier lot de vaccin. Un décès survenu ultérieurement avec le lot suivant, en avril 2009, a conduit les autorités à suspendre complètement l'utilisation du vaccin pentavalent et à reprendre la vaccination par le DTCc et contre l'hépatite B.

(2) Le Bhoutan a introduit le vaccin pentavalent produit par Panacea en septembre 2009. L'identification de 5 cas d'encéphalopathie et/ou de méningo-encéphalite peu de temps après l'administration de ce vaccin a incité les autorités à suspendre cette vaccination le 23 octobre 2009. Par la suite, 4 autres cas graves liés à l'administration du vaccin avant sa suspension ont été repérés et investigués.

(3) L'Inde a introduit le vaccin pentavalent fabriqué par l'Institut des sérums de l'Inde dans les États du Tamil Nadu et du Kerala en décembre 2011. L'utilisation de ce vaccin a ensuite été étendue aux États de Goa, Pondicherry, Karnataka, Haryana, Jammu et Kashmir, Gujarat et Delhi au cours de la deuxième moitié de l'année 2012 et du premier trimestre 2013. À ce jour, 83 cas de MAPI, dont certaines associées à des décès, ont été notifiés après l'introduction du vaccin dans certains États.

(4) Le Vietnam a introduit le vaccin pentavalent produit par Crucell en juin 2010. De cette période à mai 2013, 43 cas de MAPI grave, parmi lesquels 27 ont eu une issue fatale, ont été investigués. Après avoir enregistré la notification de 9 décès suite à cette vaccination entre décembre 2012 et mars 2013, les autorités sanitaires ont suspendu l'usage de ce vaccin.

Dans chacun de ces pays, les MAPI graves ont été examinées par des experts nationaux et internationaux indépendants. Sur la base de ces examens, aucun des cas mortels n'a pu être classé comme présentant un lien causal cohérent avec la vaccination. Au Sri Lanka, après des investigations et un bilan complets, le même vaccin pentavalent a été réintroduit en 2010. Depuis et jusqu'en 2012, 14 autres décès ont été signalés parmi les nourrissons ayant reçu le vaccin pentavalent de Crucell. En outre, on a constaté à l'autopsie que 6 nourrissons décédés sur 19 présentaient une maladie cardiaque congénitale sévère. Suite à cette constatation, les enfants que l'on sait atteints d'une maladie cardiaque congénitale sévère sont désormais vaccinés sous supervision médicale étroite au Sri Lanka et aucun décès supplémentaire n'a été notifié chez les enfants en association temporelle avec l'administration du vaccin pentavalent. Au Bhoutan, après un processus d'investigation similaire, le vaccin a été réintroduit en 2011. Le Vietnam est actuellement en train d'examiner des problèmes cliniques, épidémiologiques et de qualité vaccinale. Les 3 pays qui ont suspendu l'usage du vaccin

The 3 countries that suspended vaccine use also actively managed public communication about the observed events and their public health implications.

GACVS identified several common features among the countries that experienced significant vaccine safety concerns following pentavalent vaccine introduction. In all countries, the vaccination programme is well established and achieves high coverage (India introduced the vaccine in states with high vaccine coverage). Vaccine introduction was also accompanied by very thorough training of health-care staff about the benefits and risks of the vaccine. In Sri Lanka and Bhutan, discontinuation and resumption of pentavalent vaccine use did not significantly modify the pattern of serious AEFI reports following substitution of previously utilized vaccines. In addition, several limitations were noted in all 4 countries. Incomplete clinical information significantly complicated the causality assessment. For some cases, additional clinical information allowed another cause of death to be identified. For other cases, there remained insufficient clinical information to allow the cause of death to be ascertained, making it impossible to rule out sudden infant death syndrome (SIDS).

The diagnosis of SIDS requires clinical information and a thorough post-mortem examination (as described in the Brighton Collaboration case definition) that is not available in many settings. As peak incidence of SIDS occurs in early infancy, a close temporal relationship between SIDS and receipt of pentavalent vaccine is expected by simple chance. GACVS emphasized the need for thorough investigation of any reported serious AEFI and the importance of establishing standard investigation procedures. In the case of SIDS in particular, the possibility of conducting autopsies, or at least investigating and rapidly documenting the circumstances of death and collecting specimens and other clinical evidence, was highlighted.

New vaccine introductions associated with increased reports of deaths and other serious AEFI present a challenge to immunization programmes with respect to their ability to properly assess, manage and communicate about serious vaccine safety concerns. Identification of serious AEFI, including death, is to be expected in a temporal relationship with any infant vaccine even if no adverse events are causally associated with the vaccine.

The findings of investigations and expert review of deaths following pentavalent vaccine in the 4 countries are reassuring although not all cases could be fully assessed due to incomplete case information. The importance of thorough clinical investigation of AEFI (e.g. lumbar puncture and cerebro-spinal fluid examination for patients with suspected meningoencephalitis), and of adequate evaluation of deaths following vaccination including autopsy to identify underlying conditions and any potential alternative causes of death, was demonstrated by the experience of those countries.

pentavalent ont aussi activement géré la communication avec le public concernant les événements observés et leurs implications en termes de santé publique.

Le GACVS a identifié plusieurs caractéristiques communes aux pays ayant vécu des problèmes de sécurité vaccinale importants après l'introduction du vaccin pentavalent. Dans tous ces pays, le programme de vaccination est bien établi et permet d'atteindre une forte couverture (l'Inde a introduit le vaccin dans des États bénéficiant d'une bonne couverture vaccinale). L'introduction du vaccin a aussi été accompagnée d'une formation approfondie du personnel de santé sur les bénéfices et les risques du vaccin. Au Sri Lanka et au Bhoutan, l'arrêt et la reprise de la vaccination par le vaccin pentavalent n'ont pas significativement modifié la façon dont les notifications de MAPI graves se présentaient après le remplacement des vaccins précédemment employés. En outre, plusieurs limitations à l'exploitabilité de ces notifications ont été constatées dans les 4 pays. L'incomplétude des informations cliniques a notablement compliqué l'évaluation du lien de causalité. Dans certains cas, des informations cliniques supplémentaires ont permis d'identifier une autre cause de décès. Dans d'autres, les informations disponibles restaient insuffisantes pour déterminer de manière sûre la cause du décès, ce qui laissait la possibilité qu'il s'agisse d'un syndrome de mort subite du nourrisson (MSN).

Le diagnostic de MSN nécessite des informations cliniques et un examen post mortem approfondi (comme indiqué dans la définition de cas établie par la Brighton Collaboration), qui n'est pas réalisable dans de nombreux contextes. Comme le pic d'incidence de la MSN intervient dans la petite enfance, on s'attend à ce qu'une relation temporelle étroite entre ce syndrome est l'administration du vaccin pentavalent relève simplement du hasard. Le GACVS souligne la nécessité d'investiguer de manière approfondie toute MAPI grave notifiée et l'importance d'établir des procédures d'investigations standard Dans le cas de la MSN en particulier, il insiste sur la possibilité de réaliser une autopsie, ou tout au moins d'enquêter et de rassembler rapidement des éléments sur les circonstances du décès, et de recueillir des échantillons et autres preuves cliniques.

L'association entre l'introduction d'un nouveau vaccin et une augmentation des notifications de décès et d'autres MAPI graves met à l'épreuve les capacités d'évaluation, de gestion et de communication au sujet des problèmes de sécurité vaccinale graves des programmes de vaccination. On s'attend à l'identification des MAPI graves, y compris des décès, en relation temporelle avec tout vaccin administré à des nourrissons, même si aucun effet indésirable n'est associé par un lien de causalité à ce vaccin.

Les résultats des investigations et de l'examen par des experts des décès faisant suite à l'administration du vaccin pentavalent dans les 4 pays sont rassurants, même si tous les cas n'ont pu être complètement évalués en raison de l'incomplétude des informations disponibles. L'importance d'une investigation clinique approfondie des MAPI (ponction lombaire et examen du liquide céphalorachidien par exemple pour les patients que l'on suspecte d'être porteurs d'une méningo-encéphalite) et d'une évaluation adéquate des décès survenus après la vaccination, y compris l'autopsie des corps pour identifier d'éventuelles pathologies sous-jacentes et toute autre cause potentielle du décès, a été démontrée grâce à l'expérience acquise dans ces pays.

In the context of evaluating a safety signal, it is important that countries understand their own infant mortality rates and underlying causes. If a particular serious AEFI is identified as a concern, additional epidemiological studies should be conducted to ascertain factors that can be used to evaluate the evidence for risk hypotheses. SIDS, among other causes of infant mortality, would benefit from detailed epidemiological studies. This is particularly important when new vaccines such as those against Hib, pneumococcus and rotavirus are introduced in resource-poor countries and where there is increasing attention to safety concerns. GACVS also emphasized the fact that in a context of decreasing risk related to the diseases prevented by vaccines and increasing attention to AEFI, the capacity of countries that introduce new vaccines to rapidly assess and communicate using a risk communication approach should be reviewed and enhanced accordingly.

In conclusion, pentavalent vaccine introduction in Asian countries has illustrated how legitimate increased attention to AEFI can pose new challenges to national decision-makers. The review of the experience of 4 countries, their willingness to openly discuss all case information with external experts, the consistent causality assessment conclusions reached in the countries, and the carefully managed reintroduction of pentavalent vaccines in Sri Lanka and Bhutan are valuable examples of the successful maturation of national vaccine safety systems. Pentavalent vaccines provide great public health benefits that accrue from the ability to protect against 5 major threats to health in a single injection. Currently, pentavalent vaccines from 5 different manufacturers are prequalified by WHO and considered to be safe, effective and of assured quality.

## Zoster vaccine safety and varicella vaccine safety in immunocompromised populations

### Zoster vaccine safety

In a follow-up to the December 2012 GACVS meeting at which a general summary of varicella vaccine safety was presented, experts from the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) presented systematic post-licensure safety reviews of the zoster vaccine (Zostavax®) and safety of varicella vaccine in immunocompromised populations. The FDA completed a 7-year safety update of Zostavax® by summarizing key post-licensure observational studies conducted by CDC and Merck, a literature review from the date of licensure (May 2006) through February 2013, and analysis of reports from the Vaccine Adverse Event Reporting System (VAERS) from May 2006 through February 2013. The CDC Vaccine Safety Datalink study on Zostavax®, together with 3 post-licensure studies conducted by Merck as FDA regulatory commitments, included a total of >190 000 vaccinated study subjects. No new safety signals were identified in these studies. More than 12 000 reports

S'ils veulent évaluer un signal de sécurité, il importe que les pays puissent interpréter leur propres taux de mortalité des nourrissons et comprendre les causes sous-jacentes de cette mortalité. Si une MAPI particulièrement grave est identifiée comme préoccupante, d'autres études épidémiologiques devront être menées afin de déterminer les facteurs utilisables pour évaluer les preuves à l'appui des hypothèses concernant les risques. Des études épidémiologiques détaillées devraient se révéler utiles pour mieux connaître et comprendre la MSN, parmi d'autres causes de mortalité du nourrisson. Cette démarche est particulièrement importante lorsqu'on introduit de nouveaux vaccins, tels que ceux visant le Hib, le pneumocoque et les rotavirus, dans des pays qui disposent de ressources limitées, mais accordent une attention grandissante aux problèmes de sécurité. Le GACVS souligne aussi qu'avec la diminution du risque de contracter les maladies évitables par la vaccination et la plus grande attention accordée aux MAPI, la capacité des pays qui introduisent de nouveaux vaccins à évaluer rapidement la situation et à communiquer à l'aide d'une stratégie de communication des risques doit être examinée et renforcée en conséquence.

En conclusion, l'introduction du vaccin pentavalent dans certains pays asiatiques illustre comment la façon dont le surcroit d'attention légitimement accordé aux MAPI peut poser de nouvelles difficultés aux décideurs nationaux. L'examen de l'expérience de ces 4 pays, leur volonté de discuter ouvertement de toutes les informations concernant les cas avec des experts externes, les conclusions cohérentes de l'évaluation de la causalité auxquelles ils sont parvenus et la réintroduction prudemment gérée des vaccins pentavalents au Sri Lanka et au Bhoutan sont des exemples utiles d'une progression vers la maturité réussie des systèmes de sécurité vaccinale nationaux. Les vaccins pentavalents apportent au public de d'importants bénéfices sur le plan de la santé publique, qui résultent de leur capacité à protéger les humains de 5 grandes menaces pour la santé par une simple injection. Actuellement, des vaccins pentavalents produits par 5 fabricants différents sont préqualifiés par l'OMS et considérés comme sûrs, efficaces et de qualité garantie.

## Innocuité des vaccins contre le zona et la varicelle chez des populations immunodéprimées

### Innocuité du vaccin contre le zona

Dans le cadre du suivi effectué après la réunion du GACVS de décembre 2012, qui avait donné lieu à la présentation d'un résumé général de l'innocuité du vaccin antivaricelleux, des experts de la *Food and Drug Administration* (FDA) et des *Centers for Disease Control and Prevention* (CDC) des Etats-Unis ont exposé des examens post-autorisation systématiques de l'innocuité du vaccin anti-zona (Zostavax®) et l'innocuité du vaccin antivaricelleux chez des populations immunodéprimées. La FDA a achevé une mise à jour sur 7 ans des connaissances sur l'innocuité du Zostavax® en résumant les principales études d'observation post-autorisation menées par les CDC et Merck, une revue de la littérature depuis de la date d'autorisation du vaccin (mai 2006) jusqu'à février 2013 et l'analyse des rapports du Vaccine Adverse Event Reporting System (Système de notification des manifestations postvaccinales indésirables, VAERS) de mai 2006 à février 2013. Le projet d'étude Vaccine Safety Datalink, mené par les CDC sur le Zostavax®, combiné à 3 études post-autorisation réalisées par Merck dans le cadre de ses engagements réglementaires auprès de la FDA, a couvert au

were submitted globally for Zostavax® to VAERS from May 2006 through February 2013, of which 1057 were considered serious. The 3 most frequent terms for serious adverse events were herpes zoster, pain, and rash. FDA data mining using disproportionate analysis revealed adverse events predominantly associated with vaccine failure (i.e. herpes zoster despite vaccination), as well as accidental exposure and inappropriate vaccine administration (i.e. use of Zostavax® in subjects younger than the FDA approved age of ≥50 years). In summary, although safety data on the subpopulation of individuals aged ≥80 remains limited, no new safety risks have been identified or confirmed since initial licensure.

### Safety of varicella vaccine in immunocompromised populations

Because diseases caused by wild type VZV are more severe and fatal in persons with defects in cell-mediated immunity, varicella vaccine has been studied for safety and efficacy in select immunocompromised populations. Studies of the safety and effectiveness of varicella vaccines were conducted in children with cancer, HIV, and post-organ transplant. All but one of the studies was conducted in developed countries. Compared to healthy children, varicella vaccine is associated with a higher risk of adverse reactions, some severe, in selected subpopulations of children with deficiencies in cell-mediated immunity. Varicella vaccine is contraindicated or should be used with caution, under strict protocol, in persons with leukaemia. Two doses of varicella vaccine are effective and safe in preventing varicella in children with HIV with CD4 T-cell count ≥15%. Case reports were identified describing other immunocompromised children primarily due to natural killer T-cell deficiency discovered after vaccination. In countries with routine childhood varicella vaccination programmes, children are likely to be vaccinated without knowledge of their immune deficiency states. The size of this group will depend largely on the prevalence of undetected and untreated HIV infection. This fact is an important consideration in introducing varicella vaccination, but should be balanced against the benefits of reducing more severe wild-type varicella disease in this subpopulation.

## Immunization during pregnancy

Vaccine-preventable infectious diseases are responsible for significant maternal, neonatal, and young infant morbidity and mortality. Maternal immunization can protect the mother directly against vaccine-preventable infections, and provide a cocooning effect that can potentially protect the fetus. It can also provide further direct fetal/infant protection against infection via the transport of specific antibodies to the fetus prior to birth.

total >190 000 sujets vaccinés. Aucun nouveau signal de sécurité n'a été identifié dans ces études. Plus de 12 000 notifications ont été soumises à l'échelle mondiale au VAERS à propos du Zostavax® entre mai 2006 et février 2013, parmi lesquelles 1057 ont été considérées comme graves. Les 3 termes les plus fréquemment employés pour qualifier les manifestations indésirables graves étaient zona, douleur et éruption. L'exploration des données de la FDA par une analyse avec sondage non proportionnel a révélé que les manifestations indésirables étaient associées de manière prédominante à un échec vaccinal (apparition d'un zona malgré la vaccination), à une exposition accidentelle ou à une administration inappropriée du vaccin (utilisation du Zostavax® chez des sujets plus jeunes que l'âge approuvé par la FDA pour recevoir ce vaccin, soit ≥50 ans). En résumé, bien que les données d'innocuité concernant la sous-population des ≥80 ans restent limitées, aucun nouveau risque pouvant compromettre l'innocuité du vaccin anti-zona n'a été identifié ou confirmé depuis l'autorisation initiale.

### Innocuité du vaccin antivaricelleux chez des populations immunodéprimées

Les maladies causées par le VZV de type sauvage étant plus sévères, voire fatales, chez les personnes présentant des défauts de l'immunité à médiation cellulaire, l'innocuité et l'efficacité du vaccin antivaricelleux ont été étudiées chez des populations immunodéprimées. Des études sur l'innocuité et l'efficacité des vaccins de ce type ont été menées chez des enfants cancéreux, porteurs du VIH ou ayant subi une transplantation d'organe. Toutes ces études sauf une ont été réalisées dans des pays développés. Par comparaison avec des enfants en bonne santé, le vaccin antivaricelleux est associé à un plus grand risque de réactions indésirables, pouvant parfois être sévères, chez les enfants appartenant à des sous-populations présentant des défauts de l'immunité à médiation cellulaire. Ce vaccin est contre-indiqué ou doit être utilisé avec précautions, en respectant un protocole strict, chez les personnes leucémiques. Deux doses de ce vaccin sont efficaces et sans risque pour prévenir la varicelle chez les enfants porteurs du VIH dont la numération des cellules T CD4 est ≥15%. On a repéré des notifications de cas décrivant d'autres enfants immunodéprimés en raison principalement d'un déficit en cellules T tueuses naturelles, découvert après la vaccination. Dans les pays dotés de programmes de vaccination systématique comprenant l'administration du vaccin antivaricelleux pendant l'enfance, il est probable que ces enfants seraient vaccinés sans que leur état d'immunodéficience soit connu. La taille de ce groupe dépendra dans une large mesure de la prévalence des infections à VIH non détectés et non traitées. L'existence de ce groupe est un élément important à prendre en compte dans l'introduction de la vaccination antivaricelleuse, mais doit être mis en balance avec les bénéfices apportés par la réduction de la morbidité plus sévère due au virus sauvage de la varicelle dans cette sous-population.

## Vaccination pendant la grossesse

Les maladies infectieuses évitables par la vaccination sont responsables d'une charge de morbidité et de mortalité importante chez les mères, les nouveau-nés et les jeunes enfants. La vaccination maternelle peut protéger la mère directement de ces infections et fournir un effet «cocon» susceptible de protéger le fœtus. Elle peut en outre apporter une protection fœtale/infantile directe par le biais du transfert d'anticorps spécifiques au fœtus avant la naissance.

At its meeting in December 2011, the Strategic Advisory Group of Experts (SAGE) asked GACVS to provide support to the review of current evidence on the safety of vaccinations in pregnant and lactating women. This request related to uncertainties about the safety of vaccination – whether intended or inadvertent – of pregnant women during mass vaccination campaigns. Such evidence would be particularly important in situations where manufacturers do not recommend the vaccination of pregnant women on precautionary grounds.

Given the broad spectrum of vaccines currently available, GACVS prioritized vaccines for review based on 2 key criteria: their potential to reduce morbidity for the pregnant woman and her fetus; and their use (or projected use) in vaccination campaign settings, which have the potential for inadvertent vaccination of pregnant women. GACVS evaluated relevant data from interventional and non-interventional studies and spontaneous reporting systems on the safety of immunization of pregnant women for several viral, bacterial inactivated vaccines, toxoid and live attenuated vaccines.

Based on the reviewed data, GACVS concluded that there is no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus, bacterial, or toxoid vaccine. Therefore, pregnancy should not preclude women from immunization with the assessed vaccines if medically indicated.

Live vaccines may pose a theoretical risk to the fetus. However, there is substantial literature available describing the safety of live attenuated vaccines including monovalent rubella vaccines, combined measles-mumps-rubella vaccines, and oral polio vaccines. No significant adverse effects to the fetus following these live attenuated vaccines have been reported. Thus, the contraindication of measles-mumps-rubella (MMR)-containing vaccines is considered a purely precautionary measure. Inadvertent vaccination of pregnant women with MMR-containing vaccines is not considered an indication for pregnancy termination.

The benefits of vaccinating pregnant women generally outweigh the potential risks of exposure to a particular infection to the mother or her fetus/newborn if the vaccine is unlikely to cause harm. The use of selected vaccines in pregnancy is an important aspect of prenatal care, which not only improves maternal health but also benefits the neonate.

## Yellow fever vaccine safety during mass immunization campaigns in sub-Saharan Africa

The introduction of the yellow fever 17D vaccine in the 1930s provided an effective preventive measure resulting in a significant decline of the disease. However, there has been a resurgence of yellow fever resulting from changes in population dynamics, urbanization, defores-

Lors de sa réunion de décembre 2011, Le Groupe stratégique consultatif d'experts (SAGE) a demandé au GACVS d'aider à l'examen des données actuelles sur l'innocuité des vaccinations chez la femme enceinte ou allaitante. Cette demande était liée aux incertitudes quant à l'innocuité de la vaccination – qu'elle soit intentionnelle ou par pratiquée par inadvertance – des femmes enceintes pendant les campagnes de vaccination de masse. De telles données seraient particulièrement importantes dans les situations où les fabricants ne recommandent pas la vaccination des femmes enceintes pour des motifs de précaution.

Compte tenu de la large palette de vaccins actuellement disponibles, le GACVS classe ces produits selon la priorité de leur examen en fonction de 2 critères clés: leur capacité à réduire la morbidité chez les femmes enceintes et leur fœtus; et la possibilité que leur usage (ou usage prévu) dans le cadre des campagnes de vaccination puisse donner lieu à la vaccination par inadvertance de femmes enceintes. Le GACVS a évalué des données pertinentes provenant d'études d'intervention ou non-interventionnelles et des systèmes de notification spontanée sur l'innocuité de la vaccination des femmes enceintes par plusieurs vaccins viraux ou bactériens inactivés, contenant une toxine ou vivants atténués.

Sur la base des données examinées, le GACVS a conclu qu'il n'y avait pas de preuve d'une issue défavorable de la grossesse due à la vaccination des femmes enceintes par un virus inactivé, bactérien ou contenant une toxine. Par conséquent, la grossesse ne doit pas priver les femmes de la vaccination par les vaccins évalués si ceux-ci sont médicalement indiqués.

Les vaccins vivants peuvent comporter un risque théorique pour le fœtus. Néanmoins, il existe une abondante littérature décrivant l'innocuité des vaccins vivants atténués, et notamment des vaccins antirubéoleux monovalents, des vaccins combinés antirougeoleux-anti-ourliens-antirubéoleux et des vaccins antipoliomyélitiques oraux. Aucun effet indésirable notable pour le fœtus n'a été rapporté suite à l'administration à la mère de vaccins vivants atténués. Ainsi, la contre-indication des vaccins contenant les valences rougeole, oreillons et rubéole (ROR) est considérée comme une mesure relevant purement de la précaution. La vaccination par inadvertance de femmes enceintes avec des vaccins contenant les valences ROR n'est pas considérée comme une indication pour l'avortement thérapeutique.

Les bénéfices de la vaccination des femmes enceintes outrepassent généralement les risques potentiels de l'exposition à une infection particulière de la mère ou du fœtus/nouveau-né s'il est peu probable que le vaccin soit nocif. L'administration pendant la grossesse de vaccins sélectionnés est une composante importante des soins prénatals, qui non seulement améliore la santé de la mère, mais bénéficie également au nouveau-né.

## Innocuité du vaccin antiamaril dans le cadre des campagnes de vaccination de masse en Afrique sub-saharienne

L'introduction du vaccin 17D contre la fièvre jaune dans les années 1930 a constitué une mesure préventive efficace entraînant un déclin important de cette maladie. Cependant, on a ensuite assisté à une résurgence de celle-ci sous l'effet d'évolutions dans la dynamique des populations, de l'urbanisation, de

tation coupled with other agricultural and developmental activities, climate changes and a decline in population immunity. In 2006, the Yellow Fever Initiative led by the WHO in partnership with UNICEF and GAVI was launched to control this resurgence in order to reduce the risk of epidemics in sub-Saharan Africa. This entailed a mass preventive vaccination campaign against the backdrop of other WHO-UNICEF yellow fever control strategies.

The recent (2007–2010) preventive yellow fever (YF) vaccination campaigns in West and Central African countries provided an opportunity for surveillance of AEFIs, thus further characterizing the safety of the vaccine. Nine countries were involved – Benin, Burkina Faso, Cameroun, Guinea, Liberia, Mali, Senegal, Sierra Leone and Togo. GACVS reviewed the recently published findings of surveillance of AEFIs conducted during those campaigns. In all, 38 million doses of the vaccine were administered, and 3116 AEFIs were observed (2952 non-serious and 164 serious). Of the serious AEFIs, 22 were classified as related to the YF vaccine and 142 were not related; of the 22, 6 clinical cases resembled acute neurotropic disease (YEL-AND), 5 clinical cases resembled acute viscerotropic disease (YEL AVD) and a further 11 involved hypersensitivity reactions. The attack rates per 100 000 vaccinated people obtained from the study therefore were 0.016, 0.013 and 0.029 for YEL-AND, YEL-AVD and hypersensitivity reactions respectively. These rates were lower than those seen with recipients of a first dose of YF vaccine in more developed settings. The median time to onset (days) was observed as 8 (YEL-AND), 4 (YEL-AVD) and 1.8 (hypersensitivity reactions). Vaccine virus identification, however, was not successful for acute cases.

The authors noted the challenges and limitations of the study to account for a relatively low specificity and sensitivity of active case findings due to many coincidental cases, operational issues with inadequate collection, storage and transportation of specimens, poor laboratory and investigation facilities, cultural practices hindering post-mortem examination, misclassification of cases, and inadequate prioritization of pharmacovigilance, amongst others. Despite the limitations, the authors concluded that the study has had impact on the countries in ensuring a proactive surveillance system as well as reinforcing the safety profile of YF vaccine in this particular setting.

GACVS noted the enormous challenges of conducting a pharmacovigilance study in a resource-limited setting. The committee suggested that enhanced vaccine safety monitoring, including additional resources to provide adequate capacity and expertise, should be included in planning vaccination campaigns. It observed that the criteria for case definition were very strict and difficult to apply appropriately in such settings. It therefore suggested that more operational criteria could be proposed that would be adapted to local clinical practice or that additional dedicated efforts be conducted to meet existing criteria. There is also a need to put standard oper-

la déforestation couplée à d'autres activités d'exploitation agricole ou de développement, du changement climatique et de la disparition progressive de l'immunité des populations. En 2006, l'Initiative contre la fièvre jaune, dirigée par l'OMS en partenariat avec l'UNICEF et l'Alliance GAVI, a été lancée pour endiguer cette résurgence et réduire le risque d'épidémie en Afrique subsaharienne. Cette initiative a fait appel à une campagne de vaccination de masse à visées préventives, ayant pour toile de fonds les autres stratégies OMS-UNICEF de lutte contre la fièvre jaune.

Les campagnes préventives de vaccination antiamarile menées récemment (de 2007 à 2010) dans des pays d'Afrique centrale et d'Afrique de l'Ouest ont offert une opportunité de surveiller les MAPI, permettant ainsi une caractérisation plus poussée de l'innocuité du vaccin. Neuf pays ont été impliqués (Bénin, Burkina Faso, Cameroun, Guinée, Libéria, Mali, Sénégal, Sierra Leone et Togo). Le GACVS a examiné les résultats dernièrement publiés de la surveillance des MAPI pendant ces campagnes. Globalement, 38 millions de doses de vaccin ont été administrées et 3116 MAPI ont été observées (2952 sans gravité et 164 graves). Sur l'ensemble des MAPI graves, 22 ont été classées comme liées à la vaccination antiamarile et 142 comme sans lien avec elle; il s'agissait pour la première catégorie de 6 cas cliniques ressemblant à une maladie neurotrope aiguë (YEL-AND), de 5 cas cliniques ressemblant à une maladie viscérotrope aiguë (YEL-AVD) et de 11 autres cas de réaction d'hypersensibilité. Cette étude a donné un taux d'atteinte pour 100 000 personnes vaccinées de 0,016 pour les YEL-AND, de 0,013 pour les YEL-AVD et de 0,029 pour les réactions d'hypersensibilité. Ces taux sont plus faibles que ceux observés chez des personnes recevant une première dose de vaccin antiamaril dans des pays plus développés. On a relevé un délai médian d'apparition (en jours) de 8 pour les YEL-AND, de 4 pour les YEL-AVD et de 1,8 pour les réactions d'hypersensibilité respectivement. Néanmoins, on n'a pas réussi à identifier le virus vaccinal dans les cas aigus.

Les auteurs ont noté que les difficultés et les limites rencontrées par l'étude expliquaient la sensibilité et la spécificité relativement faibles de la recherche active des cas, dues entre autre à de nombreux cas coïncidents, à des problèmes opérationnels de collecte, de conservation et de transport des échantillons, aux faibles performances des installations d'analyse et d'investigation, aux pratiques culturelles s'opposant à l'examen postmortem, aux erreurs de classification des cas et à la priorité inadéquate donnée à la pharmacovigilance. Malgré ces limites, les auteurs ont conclu que l'étude avait eu un impact sur les pays en fournissant un système de surveillance proactif et en renforçant le profil d'innocuité du vaccin antiamaril dans le contexte considéré.

Le GACVS a aussi pris note des énormes difficultés que rencontre la conduite d'une étude de pharmacovigilance dans un contexte où les ressources sont limitées. Le Comité a suggéré qu'une surveillance renforcée de la sécurité vaccinale, y compris les moyens supplémentaires pour garantir des capacités et une expertise suffisantes, soit prévue lors de la planification des campagnes de vaccination. Il a observé que les critères de définition des cas étaient très stricts et difficiles à appliquer correctement dans un tel contexte. Il a donc suggéré également de proposer des critères plus opérationnels, qui seraient adaptés aux pratiques cliniques locales, ou de consacrer des efforts ciblés supplémentaires au respect des critères existants. Il est

ating procedures or tiered instructions in place to strengthen pharmacovigilance and address technical and logistic issues. GACVS also recommended that clinical and laboratory findings even if limited be more systematically correlated with post-mortem examinations.

## Safety profile of Japanese encephalitis vaccines

GACVS considered recent data on the safety profiles of a cell culture based on live attenuated and 2 inactivated Japanese encephalitis (JE) vaccines. The live attenuated SA 14-14-2 JE vaccine manufactured by the Chengdu Institute of Biological Products was licensed 25 years ago and is now in routine use in several countries including China, where it is given routinely at 8 months and 2 years. Worldwide, >400 million doses of the vaccine have been administered. GACVS previously reviewed this vaccine and found it to be generally safe. The Committee recommended studies in special populations, on viraemia, and post-marketing surveillance.[3] Subsequently, studies on a few hundred children in the Philippines and Sri Lanka examined the safety of the SA-14-14-2 and found that the vaccine produces only mild local and systemic reactions. A study in India on 19 adults previously unexposed to Japanese encephalitis found no evidence of viraemia up to 2 weeks after SA-14-14-2 administration.

Post-marketing surveillance carried out by the Chinese Centre for Drug Evaluation during 2009–2012 reported 6024 AEFI of which 70 were considered severe. The severe events included a range of disorders including febrile convulsions, thrombocytopenic purpura and encephalitic/meningitic illness. Of the 9 encephalitis cases, one was considered vaccine related while the others were classified as coincidental illnesses. There were 4 recorded deaths, none of which were considered related to vaccination on expert review. The GACVS reviewed these data and noted that although there was no evidence of a safety signal, the number of events recorded in the AEFI reporting system was low given that >70 million doses of vaccine have been administered.

Limited data demonstrating safety in HIV-infected individuals were available for the inactivated mouse-brain vaccine, which was marketed as either Biken® or JE-Vax®. The production and distribution of this vaccine has ceased, and the last lots of the vaccine expired in May 2011. GAVCS recommended that studies in immunocompromised populations, particularly individuals with HIV, should be carried out with the new inactivated vaccines, starting with those with CD4 T-cell counts >200. Additional data on the recently licensed inactivated vaccines, Ixiaro®, made by Intercell SA, and Jeev®, made by Biological E Ltd, in India were presented by the manufacturers. Those vaccines are based on

[3] See No. 4, 2008, pp. 37–44.

aussi nécessaire de mettre en place des modes opératoires normalisés ou des instructions par étapes pour renforcer la pharmacovigilance et répondre aux problèmes techniques et logistiques. Le GACVS a aussi recommandé que les résultats cliniques et analytiques soient plus systématiquement corrélés avec les examens post mortem, même s'ils sont limités.

## Profil d'innocuité des vaccins contre l'encéphalite japonaise

Le GACVS a examiné les données récentes sur les profils d'innocuité d'un vaccin vivant atténué préparé sur culture cellulaire contre l'encéphalite japonaise (EJ) et de 2 vaccins inactivés contre cette maladie. Il y a 25 ans déjà que le vaccin vivant atténué SA 14-14-2 JE, fabriqué par l'Institut des produits biologiques de Chengdu, a été autorisé et ce vaccin est actuellement utilisé en routine dans plusieurs pays dont la Chine, où il est administré de manière systématique à 8 mois et 2 ans. À l'échelle mondiale, >400 millions de dose de ce vaccin ont été administrées. Le GACVS avait déjà procédé auparavant à un examen de ce vaccin et l'avait trouvé sûr d'une manière générale. Le Comité avait recommandé que l'on consacre des études à des populations spéciales, à la virémie et à la surveillance post-commercialisation.[3] Par la suite, des études portant sur quelques centaines d'enfants philippins et sri-lankais ont examiné l'innocuité du vaccin SA-14-14-2 et ont constaté qu'il ne produisait que des réactions locales ou systémiques bénignes. Une étude menée en Inde sur 19 adultes auparavant non exposés à l'encéphalite japonaise n'a relevé aucune preuve de la présence d'une virémie jusqu'à 2 semaines après l'administration de ce vaccin.

La surveillance post-commercialisation effectuée par le Centre chinois pour l'évaluation des médicaments sur la période 2009-2012 a signalé 6024 MAPI, parmi lesquelles 70 ont été considérées comme sévères. Les manifestations jugées sévères incluaient une série de troubles, dont des convulsions fébriles, un purpura thrombocytopénique et des affections encéphalitiques/méningitiques. Sur les 9 cas d'encéphalite, un seul a été considéré comme lié à la vaccination, tandis que les autres étaient classés comme des maladies coïncidentes. Quatre décès ont été enregistrés, mais aucun d'eux n'a été considéré comme en lien avec la vaccination après examen des cas par des experts. Le GACVS a examiné ces données et constaté qu'en l'absence de preuve d'un signal de sécurité, le nombre d'événements enregistrés par le système de notification des MAPI était faible comparé aux 70 millions de doses et plus administrées.

On disposait de données limitées démontrant l'innocuité chez des personnes infectées par le VIH du vaccin inactivé préparé sur cellules cérébrales de souris et commercialisé sous les noms de Biken® ou JE-Vax®. La production et la distribution de ce vaccin ont cessé et les derniers lots ont atteint leur date de péremption en mai 2011. Le GACVS a recommandé de réaliser des études sur des populations immunodéprimées, en particulier sur des personnes porteuses du VIH, avec les nouveaux vaccins inactivés, en commençant avec les individus présentant une numération des cellules T CD4 >200. Des données supplémentaires sur les vaccins inactivés récemment autorisés, Ixiaro®, fabriqué par Intercell SA, et Jeev®, fabriqué par Biological E Ltd en Inde, ont été présentées par les fabricants. Ces

[3] Voir N° 4, 2008, pp. 37-44.

inactivation of the SA 14-14-2 strain. Both vaccines were licensed on the basis of serologic correlates and have not been evaluated against disease. Ixiaro® was evaluated in 1869 children from 2 months to 18 years in a Phase III trial in the Philippines, a JE-endemic area. Study participants received either full (6 µg) or half (3 µg) doses of Ixiaro® (2 doses 1 month apart), Havrix® hepatitis A vaccine for children > 1year or Prevnar® 7-valent pneumococcal conjugate vaccine for children aged <1 year. The safety profile was generally comparable with the age-specific control vaccines. In children aged <1 year, the dominant local reaction was redness; in the older ages pain and tenderness were most common. The predominant systemic reaction was fever, mostly ≤39.3 °C. Immunogenicity and safety of Ixiaro® compared to JenceVac® (a mouse brain inactivated vaccine made by Korean Green Cross) were investigated in 60 healthy Indian children aged 1 to 3 years. No difference was seen in the safety profiles of these vaccines.

Overall, GAVCS noted that the live attenuated and the inactivated vaccines based on SA-14-14-2 appear to have an excellent safety profiles. The Committee emphasized the need for building post-marketing surveillance systems in countries where disease is endemic and vaccines are used, and currently only limited data are collected post-licensure. GACVS recommended more detailed study of the safety profile of those vaccines in pregnant women, on viral shedding of the live vaccine, and the implications for the efficacy and safety of the vaccine in infants with high maternal antibodies against JE virus.

## Update on human papillomavirus vaccines

The Committee reviewed updated information about the safety of human papillomavirus vaccines (HPV) vaccines. The last review was conducted in June 2009,[4] and GACVS noted at the time that accumulating evidence on the safety of HPV vaccines was reassuring and that studies on HPV immunization had been initiated, along with capacity-building for adverse events monitoring. GACVS continues to place a high priority on the ongoing collection of high-quality safety data in settings where the vaccine is being introduced.

In the past 4 years, safety data continued to accumulate as countries have initiated or expanded their immunization programmes. The GAVI Alliance has also begun taking steps to make HPV vaccine available to women in developing countries where the burden of cervical cancer is considerable. To date, some 175 million doses of HPV vaccines have been distributed. A review of adverse events reported to the US Vaccine Adverse Event Reporting System following the distribution of >23 mil-

2 vaccins sont préparés à partir de la souche SA 14-14-2 inactivée. Ils ont été autorisés sur la base de corrélats sérologiques et n'ont pas été évalués contre la maladie. Le vaccin Ixiaro® a été évalué chez 1869 enfants de 2 mois à 18 ans dans le cadre d'un essai de phase III aux Philippines, une zone d'endémie de l'encéphalite japonaise. Les participants à l'étude ont reçu soit une dose entière (6 µg) ou une demi-dose (3 µg) d'Ixiaro® (2 doses à 1 mois d'intervalle), soit le vaccin Havrix® contre l'hépatite A pour les enfants de >1 an ou le vaccin antipneumococcique conjugué heptavalent Prevnar® 7, pour les enfants de <1 an. Le profil d'innocuité était en général comparable avec celui du vaccin témoin adapté à l'âge du bénéficiaire. Chez les enfants de <1 an, la réaction locale dominante était la présence de rougeurs, tandis qu'à un âge un peu plus avancé, la douleur et la sensibilité à la palpation étaient les effets les plus couramment observés. La réaction systémique prédominante était la fièvre, le plus souvent ≤39,3 °C. L'immunogénicité et l'innocuité du vaccin Ixiaro® par rapport à celles du vaccin JenceVac® (un vaccin inactivé préparé sur cellules cérébrales de souris par le fabricant coréen Green Cross) ont été étudiées chez 60 enfants indiens en bonne santé âgés de 1 à 3 ans. Aucune différence n'a été observée entre les profils d'innocuité de ces vaccins.

Globalement, le GAVCS a noté que les vaccins vivants atténués et les vaccins inactivés préparés à partir de la souche SA-14-14-2 semblaient avoir d'excellents profils d'innocuité. Il a insisté sur la nécessité de mettre en place des systèmes de surveillance post-commercialisation dans les pays où la maladie est endémique et qui utilisent des vaccins et sur le fait qu'on ne collecte actuellement que des données limitées dans la phase post-commercialisation. Il a recommandé des études plus détaillées sur le profil d'innocuité de ces vaccins chez les femmes enceintes, sur l'excrétion virale suite à l'administration du vaccin vivant et sur les conséquences sur l'efficacité et l'innocuité du vaccin de la présence chez les nourrissons de titres élevés d'anticorps maternels contre le virus de l'EJ.

## Mise à jour sur les vaccins contre le papillomavirus humain

Le GACVS a examiné les données actualisées sur l'innocuité des vaccins contre le papillomavirus humain (PVH). Le dernier examen de ces vaccins avait été effectué en juin 2009,[4] et le GACVS a constaté à ce jour que les données accumulées sur l'innocuité des vaccins contre le PVH étaient rassurantes et que des études sur la vaccination contre ce virus avaient été lancées, en parallèle avec la constitution de capacités pour la surveillance des manifestations indésirables. Le Comité continue d'accorder une forte priorité à la collecte en cours de données d'innocuité de grande qualité dans les pays ou les régions où le vaccin est en cours d'introduction.

Pendant les 4 dernières années, les données d'innocuité ont continué de s'accumuler à mesure que les pays lançaient et étendaient leurs programmes de vaccination. L'Alliance GAVI a aussi commencé à prendre des mesures pour mettre le vaccin anti-PVH à la disposition des femmes des pays en développement où le cancer du col de l'utérus représente un fardeau considérable. À ce jour, quelque 175 millions de doses de vaccin anti-PVH ont été distribuées. Un examen des événements indésirables signalés au Système de notification des manifestations

[4] See No. 5, 2009, pp. 30–36.

[4] Voir N° 5, 2009, pp. 30-36.

lion doses was published in 2009.[5] Both manufacturers have developed pregnancy registries and are maintaining long term safety studies in conjunction with efficacy.

The Committee reviewed data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). Updates from the United States included an extension of the spontaneous reports to VAERS since the published review in 2009 as well as completed and planned studies from the Vaccine Safety Datalink. In Australia, a new programme targeting males started in February 2013 and data are starting to become available. Data from all sources continue to be reassuring about the safety of both vaccines.

The data from VAERS now includes >50 million doses distributed and the profile has not changed since the review in 2009. Reported adverse events not identified at the time of the first review, namely syncope and venous thromboembolism (VTE), were further investigated. Syncope continues to be reported but remains an event with a plausible relationship given the population and settings in which HPV vaccine is used. Adherence to a 15-minute observation period following vaccination has thus been strengthened as a recommendation. For VTE, while a rapid cycle analysis in the VSD did not find an increased risk, this is being further investigated with appropriate control for confounders such as oral contraceptive use, smoking and other risk factors in this population. Similarly, the VSD did not find any increased risk of Guillain-Barré syndrome or stroke. In Australia, safety surveillance has been enhanced and an expert group evaluated early reported events, including a signal regarding anaphylaxis. To date, with almost 7 million doses distributed, the previously investigated concern of increased anaphylaxis was not confirmed. Following the extension of the vaccination programme in males and enhanced surveillance since 1 February 2013, preliminary results show the safety profile of Gardasil® to be similar to the profile among females. Finally, there have been no further concerns regarding demyelinating disease or other chronic conditions also investigated earlier by the expert group.

Surveillance from the 2 manufacturers found no signals suggesting any necessary revisions to product labelling. Both have maintained surveillance of pregnancy outcomes following inadvertent vaccination during pregnancy. Detailed analyses of results have not found any new adverse outcomes related to HPV vaccination. For Gardasil®, long term follow-up has now extended to

postvaccinales indésirables des États-Unis après la distribution de >23 millions de doses a été publié en 2009.[5] Les 2 fabricants ont mis en place des registres des grossesses et poursuivent des études d'innocuité à long terme en parallèle avec des études d'efficacité.

Le Comité a examiné des données provenant des États-Unis, d'Australie, du Japon et des fabricants du Cervarix® (GlaxoSmithKline) et du Gardasil® (Merck). Les mises à jour émanant des États-Unis incluaient une suite au bilan des notifications spontanées du VAERS depuis celui publié en 2009, ainsi que des études achevées ou prévues par le projet Vaccine Safety Datalink. En Australie, un nouveau programme ciblant les hommes a débuté en février 2013 et des données commencent à être disponibles. Les informations provenant de l'ensemble des sources continuent d'être rassurantes quant à l'innocuité des 2 vaccins.

Les données émanant du VAERS couvrent maintenant >50 millions de doses distribuées et le profil n'a pas évolué depuis l'examen de 2009. Les manifestations indésirables rapportées qui n'avaient pas été identifiées lors du premier examen, à savoir les syncopes et les thromboembolies veineuses (TEV), ont fait l'objet d'investigations plus poussées. Des syncopes continuent d'être signalées et restent un événement dont la relation avec la vaccination est plausible compte tenu de la population et des contextes dans lesquels le vaccin anti-PVH est employé. Une force plus grande a donc été affectée à la recommandation invitant à respecter une période de 15 minutes d'observation après la vaccination. Pour ce qui concerne la TEV, bien qu'une analyse à cycle rapide du Vaccine Safety Datalink (VSD) n'ait fait apparaître aucune augmentation du risque, elle fait l'objet d'études plus approfondies maîtrisant correctement les facteurs de confusion tels que la prise d'un contraceptif oral, le tabagisme et d'autres facteurs de risque présents dans la population concernée. De même, le VSD n'a pas mis en évidence d'augmentation du risque d'apparition du syndrome de Guillain-Barré ou d'un AVC. En Australie, la surveillance de la sécurité vaccinale a été renforcée et un groupe d'experts a évalué les événements récemment signalés, y compris un signal relatif à l'anaphylaxie. Aujourd'hui, avec près de 7 millions de doses distribuées, la possibilité préoccupante d'une augmentation des réactions anaphylactiques antérieurement investiguée n'a pas été confirmée. Après l'extension du programme de vaccination aux hommes et le renforcement de la surveillance depuis le 1er février 2013, les résultats préliminaires montrent un profil d'innocuité du Gardasil® chez l'homme similaire à celui observé chez la femme. Enfin, il n'est pas apparu de préoccupation supplémentaire concernant la maladie démyélinisante ou d'autres affections chroniques ayant aussi fait l'objet d'investigations antérieures par le groupe d'experts.

Dans le cadre de la surveillance qu'ils exercent, les 2 fabricants n'ont relevé aucun signal laissant envisager la nécessité de réviser l'étiquetage du produit. Chaque fabricant a également maintenu une surveillance des issues de la grossesse après une vaccination par inadvertance au cours de celle-ci. Les analyses détaillées des résultats n'ont identifié aucune nouvelle issue défavorable de la grossesse en rapport avec la vaccination anti-

[5] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*, 2009, 302(7):750-757. [doi: 10.1001/jama.2009.1201]

[5] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*, 2009, 302(7):750-757. [doi: 10.1001/jama.2009.1201]

>8 years in the longest cohort, and no significant increase in newly diagnosed health events have been identified among those vaccinees. Updated analyses of the pregnancy registry have also been reassuring in that no adverse pregnancy outcomes have been observed beyond background expected rates. For Cervarix®, the data have been similarly reassuring regarding pregnancy outcomes and specific events of interest such as immune mediated diseases. Risk of syncope and anaphylaxis have been added to the label to warn of these potential events, the former being also possibly related to conditions around the vaccination experience itself.

Cases initially resembling complex regional pain syndrome (CPRS) were reported from Japan where >8 million doses of HPV vaccines have been distributed. CPRS is a painful condition that emerges in a limb usually following trauma. Cases have been reported following injury or surgical procedures. It remains of unknown etiology and may occur in the absence of any documented injury. CPRS following HPV vaccines has received media attention in Japan and the number of reported cases has risen to 24, only 7 of which were reported through usual post-marketing surveillance channels. Review by an expert advisory committee could not ascertain a causal relationship to vaccination given lack of sufficient case information and inability to reach a definitive diagnosis in many cases. While these are under investigation, Japan has continued to provide HPV vaccine in their national programme but is not actively recommending its use.

In summary, 4 years after the last review of HPV vaccine safety and with >175 million doses distributed worldwide and more countries offering the vaccine through national immunization programmes, the Committee continues to be reassured by the safety profile of the available products. Anaphylaxis and syncope, outcomes previously identified as concerns, have been addressed through further studies and appropriate revisions were made to the product labelling. Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions – many using rapid cycle analysis in the VSD in the United States. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

The cases of chronic pain being reported from Japan deserve specific mention. To date there is little reason to suspect the HPV vaccine, given its growing use worldwide, in the absence of a similar signal from elsewhere. Recognizing the public concerns voiced, the Committee urges careful documentation of each case and a thorough search for a definitive diagnosis by

PVH. Pour le Gardasil®, la durée du suivi à long terme a maintenant dépassé 8 ans pour la cohorte bénéficiant du plus long suivi et aucune augmentation significative des événements sanitaires nouvellement diagnostiqués n'a été repérée chez les personnes vaccinées. Les analyses actualisées des registres des naissances sont aussi rassurantes dans la mesure où aucune issue défavorable de la grossesse n'a été observée au-delà des taux de fonds attendus de ces issues. Concernant le Cervarix®, on obtient également des données rassurantes concernant les issues de la grossesse et des événements spécifiques considérés tels que les maladies à médiation immunitaire. Les risques de syncope et de réaction anaphylactique ont été ajoutés à la liste figurant sur l'étiquette pour avertir de la potentialité de ces réactions, la première pouvant aussi être liée aux conditions dans lesquelles la personne subit la vaccination.

Des cas ressemblant au départ à un syndrome douloureux régional complexe (SDRC) ont été signalés au Japon où >8 million de doses de vaccin anti-PVH ont été distribuées. Le SDRC est une affection douloureuse qui se manifeste dans un membre habituellement suite à un traumatisme. Des cas ont été rapportés après une blessure ou une opération chirurgicale. L'étiologie de ce syndrome reste inconnue et il peut apparaître en l'absence de tout traumatisme enregistré. La survenue d'un SDRC après l'administration d'un vaccin anti-VPH a attiré l'attention des médias au Japon et le nombre de cas signalés a atteint 24, parmi lesquels 7 seulement ont été notifiés par les canaux de surveillance post-commercialisation habituels. L'examen par un comité consultatif d'experts n'a pu déterminer une relation causale avec le vaccin compte tenu de l'insuffisance des informations concernant les cas et de l'impossibilité de parvenir à un diagnostic définitif pour nombre d'entre eux. Bien que ces cas soient encore en cours d'investigation, le Japon continue de délivrer le vaccin anti-PVH dans le cadre de son programme national, mais ne recommande pas activement son utilisation.

En résumé, 4 ans après le dernier examen de l'innocuité du vaccin anti-PVH, avec >175 millions de doses distribuées dans le monde et un nombre accru de pays proposant le vaccin par le biais de leur programme de vaccination national, le Comité continue d'être rassuré par le profil d'innocuité des produits disponibles. Les réactions anaphylactiques et les syncopes, manifestations antérieurement identifiées comme préoccupantes, ont été examinées dans le cadre d'études supplémentaires et l'étiquetage des produits a été revu en conséquence. Les manifestations indésirables graves rapportées comme des signaux potentiels ont été investiguées plus en détail, y compris le syndrome de Guillain-Barré, les convulsions, les AVC, les thromboembolies veineuses, les réactions anaphylactiques et autres réactions allergiques – dans nombre de cas par une analyse à cycle rapide pratiquée par le VSD aux Etats-Unis. La surveillance des issues de la grossesse chez les femmes vaccinées par inadvertance lorsqu'elles étaient enceintes par le biais des notifications spontanées et des registres n'a repéré aucune issue défavorable dont la fréquence serait supérieure aux taux attendus.

Les cas de douleur chronique rapportés au Japon méritent une attention spéciale. À ce jour, il y a peu de raisons de suspecter le vaccin anti-PVH, compte tenu de son usage de plus en plus répandu partout dans le monde et de l'absence de signal similaire émanant d'un autre lieu. Reconnaissant les préoccupations émises par la population, le Comité a incité à documenter avec soin chaque cas et à demander à des médecins spécialistes

medical specialists in order to best guide treatment. A timely clinical assessment and diagnosis of each case followed by appropriate treatment is therefore essential.

## Update on pandemic influenza vaccine (Pandemrix®) and narcolepsy

The committee has previously reviewed data from studies on the use of the pandemic influenza vaccine (monovalent A(H1N1)pdm09 vaccine) in Finland, Sweden, Ireland, the UK and France which all demonstrated an increased risk of narcolepsy following Pandemrix® vaccination in children and adolescents. The studies in Sweden and France also found evidence of an increased risk in adults. The Committee reviewed newly available data from Finland about the safety of Pandemrix® vaccine in adults. The retrospective cohort study linked vaccination data of the whole adult population to incident cases of narcolepsy identified through the national care register during the follow-up period from 1 January 2009 to 31 December 2011. The comparison of incidence rates indicated a 3–5-fold (after sensitivity analysis 2–4-fold) risk of narcolepsy among vaccinated compared to unvaccinated adults. The increased risk was seen 8 months post vaccination; thereafter, no increased risk was observed. The reports from Sweden, France and Finland concur that young adults have an increased risk of narcolepsy after Pandemrix® vaccination. GACVS acknowledges this finding suggesting a possible risk of narcolepsy among adults, although it remains lower than that seen among children. Further follow-up research is required to confirm the strength of the observed association and size of the risk. Because of the continued threat of emergence of new pandemics and the expected need for new pandemic vaccines, the Committee reiterated the urgency of continued research to identify the underlying biological mechanisms of this association. ■

d'effectuer une étude approfondie pour poser un diagnostic définitif et ainsi mieux guider le traitement. Une évaluation et un diagnostic cliniques en temps utile de chaque cas, suivis d'un traitement approprié, sont donc essentiels.

## Mise à jour sur le vaccin contre la grippe pandémique (Pandemrix®) et la narcolepsie

Le Comité a précédemment examiné des données tirées d'études sur l'utilisation du vaccin contre la grippe pandémique (vaccin monovalent anti-virus A(H1N1)pdm09) en Finlande, en France, en Irlande, au Royaume-Uni et en Suède, qui toutes mettent en évidence un risque accru de narcolepsie après l'administration du Pandemrix® à des enfants et des adolescents. Des études menées en Suède et en France ont aussi trouvé des preuves d'une augmentation de ce risque chez les adultes. Le Comité a aussi examiné de nouvelles données provenant de Finlande sur l'innocuité du Pandemrix® chez l'adulte. L'étude rétrospective de cohorte avait mis en relation les données de vaccination pour l'ensemble de la population adulte avec les cas incidents de narcolepsie identifiés par le registre national des soins sur la période de suivi allant du 1er janvier 2009 au 31 décembre 2011. La comparaison des taux d'incidence a fait apparaître une augmentation d'un facteur 3 à 5 (2 à 4 après l'analyse de sensibilité) du risque de narcolepsie chez les adultes vaccinés par rapport aux adultes non vaccinés. L'augmentation du risque a été observée 8 mois après la vaccination, après quoi aucun accroissement supplémentaire du risque n'a été relevé. Les rapports émanant de Finlande, de France et de Suède s'accordent sur une augmentation du risque de narcolepsie chez les jeunes adultes après une vaccination par le Pandemrix®. Le GACVS reconnaît que ce résultat amène à suspecter également un risque accru de narcolepsie chez les adultes, quoique plus faible que celui observé chez les enfants. D'autres travaux de recherche comprenant des phases de suivi sont nécessaires pour confirmer la force de l'association observée et l'ampleur du risque. En raison de la menace permanente d'une nouvelle pandémie et des besoins attendus en nouveaux vaccins pandémiques, le Comité a rappelé l'urgence de poursuivre les recherches pour identifier les mécanismes biologiques sous-jacents à cette association. ■

### How to obtain the WER through the Internet

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

(2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to **listserv@who.int**. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

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2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à **listserv@who**.int en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh.

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**FOR DISCUSSION**

**How may the risk-benefit balance of maternal immunization be best taken into account?**

SAGE has long recognized the need for maternal immunization to be better supported whenever it is the best – or the only – strategy to effectively protect mothers and neonates. The GACVS recent review articulates what is known and not known about risks (or lack of risk) from various specific vaccines and substantiates confidence of lack of associated risk with inactivated products. This review is by definition limited to assessing the collected evidence, which remains limited as long as vaccines are contra-indicated during pregnancy.

The following elements may have to be discussed in addition to the vaccine-specific GACVS review.

- Pregnant women have traditionally been excluded from biomedical research because of the lack of knowledge about the potential risks of drugs or vaccines in population perceived as vulnerable. The fear of litigation and the limited expected financial benefits (small market size) has led the pharmaceutical industry to generally deny the enrollment of pregnant women into clinical trials. Consequently, the regulatory files leading to licensing do generally not include information on pregnant women, postponing their acquisition to slow and complex post-marketing surveillance activities or to investigator-driven trials of limited size.

- The same precautionary attitude leads regulatory authorities to exclude pregnant women from the populations to whom drugs or vaccines may be given: “in the absence of data, formulation X should not be given to pregnant women”. Consequently, the use of drugs/vaccines in pregnant or lactating women is traditionally off-label.

- This off-label status creates uncertainties among vaccine recipients and health-care workers about the possibility of using the drug or vaccine. For example, despite a WHO recommendation for off-label use during the roll-out of meningococcal A vaccines in Burkina Faso and neighboring countries, vaccine uptake ended-up being substantially lower among pregnant women than in the rest of the eligible population. Another example is pertussis immunization during pregnancy, recommended in a growing number of countries, despite no vaccine being approved for this use.

**However:**

- Pregnant women, compared to both the general population and also non-pregnant women of similar age, are at equal or in some cases at increased risk of mortality and serious morbidity from vaccine preventable diseases.

- The early life period, *in utero* or early after birth, is associated with risks of vaccine-preventable diseases which may only be avoided by immunizing pregnant women (tetanus, influenza, pertussis, etc.).

- Decades of vaccine use and a growing number of studies have shown the safety of traditional non-live vaccines (e.g. tetanus or influenza) during pregnancy. To date, not a single licensed non-live vaccine formulation has been associated with enhanced risks of adverse outcome for the

mother, the fetus or the child. Although live attenuated viral vaccines (e.g. measles, rubella or even yellow fever vaccines) or novel adjuvanted vaccines (e.g. squalene-based vaccines used during the H1N1/09 pandemic) have not shown evidence of harm, their pathogenic profile is theoretically higher.

- The enhanced understanding of the mode of action of non-live vaccines (mild transient inflammation and antigen-specific immune activation) provides the biological bases which supports the safety of vaccines in pregnant women. The likelihood that similar non-live vaccines (e.g. dTpa compared to T) would eventually be shown to cause harm if used during pregnancy is thus extremely small.

- The immunomodulatory condition that prevails during pregnancy (minor decrease of cell mediated immunity) does not prevent pregnant women from raising protective vaccine responses providing a direct benefit for them and their fetus or child.

- Waiting for post-marketing surveillance data or investigators-driven trials to provide sufficient high-quality data to result into the licensing of a given vaccine for use in pregnant or lactating women deprives this population, and their offspring, of beneficial effects during many years or decades.

- The current communication by health authorities that vaccines should in general not be used in pregnant women (with a few exceptions such as tetanus or influenza vaccines) generates the wrong message that vaccines may cause harm, and thus markedly reduces their acceptance by physicians and women.

**Thus, the current assessment of the risk-benefit balance of maternal immunization is not optimal.**

**Which strategies could SAGE consider?**

- **A traditional approach restricted to vaccine-specific evaluations and recommendations.** The current strategy of collecting vaccine-specific data (mostly from post-marketing studies) is in accordance with the ”doing nothing unless proven safe” principle. It could be considered as the only way to go.

- **The introduction of class-specific evaluations and recommendations.** SAGE could encourage vaccines to be classified among generic groups *(e.g. protein-based vaccines, polysaccharide or conjugated vaccines, vaccines including novel adjuvants, live-attenuated vaccines)* and the degree of confidence on lack of expected risk or possibility of risk be specified by such categories. This would generate permissive or non-permissive recommendations, which would accelerate the recommendation process for the “expected-as-safe” vaccines. A landscape assessment of which novel vaccines (live products, adjuvants, chimeric products, other novel vaccines) may eventually have to be given during pregnancy could be encouraged to include a risk assessment early in the process and thus avoid continuing having important new vaccines but no information about their potential risks in pregnancy.

- **A better consideration of the expected benefits in the evaluations and recommendations.** Although postponing immunization to the post-partum period may be an optimal risk-benefit assessment in certain situations, it becomes inappropriate if the risk of exposure during pregnancy is high (outbreaks, high disease incidence). The risk of missed opportunities, if immunizations are only provided during campaigns, could also be considered. SAGE could recommend that the risks of not immunizing pregnant women be included in the recommendation process.

- **A strengthening of data collection for maternal immunization safety.** SAGE could recommend reinforcing the greater use of registries or other strategies likely to accelerate data collection.

- **The inclusion into the preparation of each immunization trial or program a formal analysis of the expected benefits-risks of maternal immunization instead of automatically excluding pregnant women**. SAGE could recommend to WHO and its partners to include into each new immunization trials or programs a formal analysis of the expected benefit/risks of a priori excluding pregnant women. This evaluation could be supported by a class-specific approach.

- **The recommendation to include new elements (class-specific approach, expected population benefits, etc.) in the WHO prequalification and other regulatory approval processes**. SAGE could recommend this issue to be brought to the International Conference of Drug Regulatory Agencies (ICDRA) and to approach major agencies such as FDA and EMA for possible ways forward. Similarly to pediatric medicines, which required regulators worldwide to take action for studies of medicines in children to be undertaken, some process may be needed.

- **The encouragement of NITAGs and national authorities to actively support maternal immunization,** e.g. with vaccines considered as safe based on class-specific evaluations.

- **The strengthening of communication** on the safety of maternal immunization, when recommended, to reach as many health authorities, physicians and women as possible.

- **Other strategies to be defined.**

# REPORT ON THE IMMUNIZATION AND VACCINES RELATED IMPLEMENTATION RESEARCH (IVIR) ADVISORY COMMITTEE MEETING

*Geneva, 26-28 June 2013*
(Draft version 16 October 2013)

*Immunization, Vaccines and Biologicals (IVB)*

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# Abbreviations

| | |
|---|---|
| CFR | Case-fatality rate |
| CDC | Centers for Disease Control |
| DALY | Disability Adjusted Life Year |
| GMP | Global Malaria Programme |
| HBsAg | Hepatitis B serum antigen |
| HBV | Hepatitis B vaccine |
| HPV | Human papilloma virus |
| IARC | WHO International Agency for Research on Cancer |
| IVB | WHO Department of Immunization, Vaccines and Biologicals |
| IVIR-AC | Immunization and Vaccines-related Implementation Research Advisory Committee |
| IVR | Initiative for Vaccine Research |
| JTEG | Joint Technical Expert Group on Malaria Vaccines in PivotalPhase III Trials and Beyond |
| LiST | Lives Saved Tool |
| LMICs | Low and middle income countries |
| MPAC | Malaria Policy Advisory Committee |
| QUIVER | Quantitative Immunization and Vaccines related Research |
| SAGE | Strategic Advisory Group of Experts |
| Swiss TPH | Swiss Tropical and Public Health Institute |
| WHO | World Health Organization |
| WPR | WHO Western Pacific Region |

# Executive summary

- WHO is funding a project to provide new data on hepatitis B disease, vaccination and infection measures in relation to vaccine implementation levels, in order to update evidence-based vaccine recommendations. The proposal was well-received by IVIR-AC, although the committee made some suggestions that will be taken into account in a revised proposal. Two IVIR-AC members have also agreed to join the project working group.
- A malaria vaccine (RTS,S/AS01) has shown efficacy over 12 months of follow-up in a large Phase 3 trial, with full trial results expected in late 2014. Five modelling groups have used preliminary trial data to explore the impact and cost-effectiveness of malaria vaccination. IVIR-AC will provide experts on health economics and health systems to advise on these issues to ensure that they are comprehensively captured in the models. IVIR-AC is also considering providing methodological guidelines around how projected demographic changes in LMICs (represented population mobility) should be handled in models. IVIR-AC will be available to review model findings and conclusions before they are presented to SAGE.
- A model to explore the case for investing in measles eradication has been revised to perform analyses at the country-level following feedback from IVIR-AC in 2012. However, IVIR-AC registers concern that the model does not capture within-country heterogeneities in coverage and transmission adequately. Hence, the current model may be insufficient to assess measles elimination goals. Further work that incorporates within country heterogeneity is critical to adequately assess elimination at country, regional and global levels. The modeling group agreed to build in sub-national heterogeneity in their model and will present this to the IVIR-AC subgroup on measles eradication.
- A model has been constructed to re-evaluate the burden of yellow fever in Africa, estimating 850,000-2 million infections with yellow fever virus, yielding 85,000-200,000 cases and 30,000-70,000 deaths per year. The case-fatality rate is higher than previously estimated. The remaining burden is concentrated in countries which were not targeted for investment by the GAVI Alliance. IVIR-AC felt that the model is adequate for yellow fever disease burden estimation across the Africa region.
- A model for varicella burden has been constructed in order to inform SAGE recommendations for varicella zoster vaccination in low and middle income countries. IVIR-AC finds the model to be appropriate although it could be strengthened by capturing uncertainties in data around seroprevalence, case-fatality ratios and morbidity estimates. Better data on disease incidence and outcomes in LMICs are needed before the model can be used to estimate global disease burden. Extending the work to calculate cost-effectiveness of vaccination across a range of possible estimates of disease burden would also be useful for priority setting.
- An exercise is being conducted by WHO in order to develop and prioritise a research agenda for implementation research. A bank of potential research questions was developed from a broad solicitation of experts and reviews of existing reports or reports from relevant advisory committees, for prioritization by an ad-hoc expert group. IVIR-AC is supportive of the effort to make priority setting for implementation research questions more systematic and believes that the overall analytical approach was well-designed. However, contextual variability and considerations will require that the findings not be used as the sole criterion for decision making. Input from a range of stakeholders at different levels besides global and regional will be beneficial in validating the exercise and defining the application of the results.

# Introduction

*(R. Breiman)*

Dr. R. Breiman opened the second meeting of the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC evolved from WHO's Quantitative Immunization and Vaccines-related Research (QUIVER) advisory committee, expanding its remit to include implementation research. The key objectives of IVIR-AC are:

- To appraise methods to estimate disease burden and resolving differences in disease burden estimates.
- To characterise critical factors around vaccine demand and hesitancy.
- To advance techniques to assess cost-effectiveness of vaccines.
- To develop behavioural research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.

WHO's Department of Immunization, Vaccines and Biologicals (IVB) has conducted an analysis of areas where IVIR-AC has a comparative advantage compared to other WHO committees.

# Hepatitis B impact evaluation framework

## Introduction

*(A. Hall)*

Hepatitis B vaccine (HBV) has been available for 32 years but hepatitis B serum antigen (HBsAg) prevalence (reflecting exposure to HBV) in adult males has only recently decreased substantially, due to slow vaccine introduction and the long interval during which hepatitis B carriage can persist. The experience of early adopters in WHO's Western Pacific Region (WPR) suggests that vaccination can bring substantial herd protection against child-to-child transmission. Most cases of carriage acquisition in WPR are now from perinatal transmission. Countries in WPR have mostly advanced from monitoring vaccine coverage to estimating vaccine impact on HBsAg prevalence in children, to reach a target of <2% HBsAg prevalence in children under 5. However, some countries have expressed concern that they may lose funding if they report having controlled hepatitis B. There is also variability in schedules, especially for the birth dose, which affects perinatal transmission.

This project aims to provide new evidence on hepatitis B disease, vaccination and infection in relation to vaccine implementation levels, to provide evidence for updating vaccine recommendations. The project is intended to contribute to ongoing refinement of HBV programmes to minimise disease, as well as sustain political will in supporting these programmes. It has three parts:

- Global disease impact of HBV vaccination – estimating infection prevalence, vaccine coverage, economic measures and trends in liver cancer based on systematic reviews and modelling of health and economic outcomes. A report to SAGE will be prepared.
- Country-level impact of vaccination and strategy in selected countries – epidemiological data in early adopters with good data on HBV and liver cancer epidemiology, allowing between-country comparisons using a standard tool.
- Communication and data sharing – setting up an online database and journal publications to make all information accessible.

Management will be led by Prof. A. Hall, with representatives from IARC, WHO and CDC, as well as oversight by IVIR-AC. An outline of the steps in more detail will be prepared following the current IVIR-AC meeting, and the committee will report back to IVIR-AC and SAGE in 2014.

## Review

*(P. McIntyre)*

The objective of the project is to conduct a comprehensive review of hepatitis B impact evaluation which may be worth narrowing down to a few key objectives, including identifying barriers to implementation. The country-level work should focus on a template for impact assessment or implementation. For instance, justification for delivery of birth dose in settings where this is logistically difficult may be important.

*(G. Kang)*
Prevalence needs to be defined more precisely – it can refer to acute disease, chronic infection or hepatocellular carcinoma. It is good to stratify countries in the analysis by time of vaccine introduction and performance of immunisation systems and that success in delivering the birth dose within 24 hours of birth as performance indicator for immunisation systems is included in the project proposal. In high income settings, treatment effects also have an impact on transmission.

## Discussion

J. Edmunds declared a conflict of interest; he is currently bidding to do the modelling component of the work.

The value of the modelling work is that it allows the impact of HBV on carriage and liver cancer to be measured and demonstrated to decision makers. In many countries this is not obvious from monitoring

liver cancer incidence, because increases in cancer incidence have occurred as a result of population growth and life expectancy improvements (allowing more people to reach the ages at which they may acquire cancer).

The main prevalence measure is seroprevalence, as used by WPR. There are no plans to evaluate catch up campaigns, but they may have limited impact if acute HBV is excluded since their effect on perinatal transmission is minimal. Treatment effects are limited outside high income settings. Liver cirrhosis is not being assessed because of poor surveillance data. Liver cancer is being estimated using data from countries with good registries; the strength of a country's registry is assessed through a partnership with IARC. Most regions have many countries with good registries apart from sub-Saharan Africa where there are only a few. It may be possible to explore within-country variations (eg rural vs urban).

WHO recommends that HBV is delivered as a birth dose, but many countries do not follow this, and those which do often have low birth dose coverage. Given the administrative and economic obstacles to birth dose vaccination, it may be worth examining the relative benefits and costs of a monovalent birth dose compared to a pentavalent dose. Other issues to examine are the number of primary doses needed after a birth dose, the impact of catch-up campaigns, particularly in children, and the cost-effectiveness and long-term budget impact of different vaccination strategies.

## Summary and recommendations

IVIR-AC is broadly supportive of the framework, and welcomes in particular the assessment of the implementation of a birth dose and its potential impact of hepatitis B transmission. To improve the communication of the project's objective to the broader community it is important that some of the terms and objectives are further spelled out such as the definition of seroprevalence, immunization schedules to be evaluated, estimation of the contribution of hepatitis B to hepatocellular carcinoma, criteria for selection of countries and the project timelines.

IVIR-AC requested that the team incorporates the IVIR-AC suggestions and comments into the proposal, and then circulates to the committee by e-mail within one month, with a final statement within 6-8 weeks.

IVIR-AC suggests that two members of IVIR-AC (Philippe Beutels and Fernando de la Hoz Restrepo) join the project working group to ensure that IVIR-AC provides continued input into the project. Progress will be presented at the 2014 IVIR-AC meeting.

# Malaria vaccine impact and cost-effectiveness

## Introduction

*(P. Smith, JTEG chair)*

There is only one advanced malaria vaccine candidate (RTS,S/AS01), which is currently undergoing phase III trials and has demonstrated efficacy in children. Higher efficacy is seen when giving the vaccine to older children (5-17 months) compared to infants as part of the EPI schedule (6-12 weeks). Mathematical modelling using trial results with 12 month follow-up from the Phase 3 trial suggests that efficacy may also vary with local transmission intensity. By late 2014, all trial results will be available including a 30-month follow-up study with a booster dose at 18 months. Final results will help to address remaining unresolved issues such as the effect on vaccine efficacy of changes over time, transmission intensity, maternal antibodies, impact of co-administration of pentavalent vaccine, and prior administration of HBV vaccine. The results will inform discussion by SAGE and the Malaria Policy Advisory Committee (MPAC), ultimately leading to a WHO position paper to guide country-level decision making. Because trial results are also critical for licensure, the manufacturer (GlaxoSmithKline) has faced restrictions in altering its analytical plan in response to WHO requests.

Several models of malaria vaccination have been developed and will help to inform decision making in 2015 by giving an indication of the long-term impact of vaccination. WHO IVR and the Global Malaria Programme (GMP) have organised a Joint Technical Expert Group (JTEG) to evaluate the current status of the models, which met in May 2013. Five groups were represented: three with stochastic, individual-based, dynamic transmission models (Swiss Tropical and Public Health Institute (Swiss TPH), Imperial College and Intellectual Ventures), as well as two with static models (GlaxoSmithKline, and the Lives Saved Tool or LiST group). The first three groups have already published results on vaccine impact; the Swiss Tropical and Public Health Institute have in addition also published cost-effectiveness results.

The modelling groups have been given a standard set of input data in order to generate comparable impact and cost-effectiveness predictions for 2017-2030. The Swiss TPH and Imperial College were able to provide the full range of outputs requested. The most important remaining uncertainties include the duration of vaccine protection and site-specific efficacy for the two potential target age groups. Vaccine price is unknown, with analyses currently assuming the price of $5/dose based on the GAVI Alliance's vaccine investment strategy.

Models predict that vaccine efficacy against clinical malaria wanes more quickly in high transmission settings, so the most favourable cost-effectiveness is seen in medium transmission settings. However, vaccination is still cost-effective in high transmission settings at a range of $50-$200 per disability adjusted life year (DALY) averted in many African malaria-endemic settings. The greatest impact and most favourable cost-effectiveness can be seen in vaccinating children rather than infants (assuming no difference in delivery costs). Analyses suggest that investment in long-lasting insecticide treated nets is still more cost-effective than vaccination, so vaccination should be considered as an add-on to existing preventive strategies rather than a replacement.

The modelling groups were encouraged to further harmonise key parameters such as vaccine costs, vaccine efficacy, demographics and baseline disease burden as far as possible. Uncertainty around vaccine efficacy will be reduced after publication of full trial results in 2013-14. The next iteration of modelling will incorporate 18 month follow-up data, site-specific efficacy and booster dose data. WHO will then organise another meeting to enable comparative assessment of model predictions, which can inform the WHO policy process, post-marketing surveillance and tools for national decision-making. WHO policy recommendations for malaria vaccines in 2015 will focus on clinical trial data wherever available with the use of modeling as an adjunct to inform questions for which there are no clinical trial data available.

## Review

*(E. Sinanovic)*

It would be useful to reach some general conclusions for policy makers as was recently done in WHO model comparison exercises for other vaccines such as HPV, rotavirus and pneumococcal vaccines.

Besides epidemiological modelling, there is also a need to consider economic and health systems aspects such as indirect costs, affordability and possible impact of health systems. A budget impact analysis may also be useful to see if the vaccine is affordable as well as cost-effective, and if funding is sustainable after removal of donor support.

## Discussion

JTEG currently lacks expertise on health economics and health systems, so it would be useful to have an IVIR-AC member with such experience to join the group. Models do not currently incorporate price maturity so it may be helpful to explore this in sensitivity analyses. Cost-effectiveness results compared to a GDP per capita threshold are not always useful for decision making in these settings; another useful type of evaluation may be to present net costs in terms of the total health care budget of a country. Indirect (herd) effects are not expected to be substantial because of the low target age range for vaccination and short duration of protection. However, the overall impact of vaccination is difficult to determine precisely, partly because many malaria-attributable deaths are due to the interaction of malaria and other diseases.

The current models also have different ways of capturing demographic change, which are difficult to accurately represent in sub-Saharan Africa because of high birth rates. IVIR-AC may need to take a general view on how methodological issues such as these should be handled.

## Summary and recommendations

IVIR-AC looks forward to new vaccine trial data and their impact on the output of the models. IVIR-AC is available to review and comment on the results of the malaria models before they are presented to SAGE.

IVIR-AC is considering providing methodological guidelines around how demographic factors in low and middle income countries should be handled in these and other infectious disease models.

The WHO Policy process for malaria vaccines may benefit from having expertise in health economics and health systems from IVIR-AC. Aparnaa Somanathan and Edina Sinanovic have agreed to join the working group (in addition to the IVIR-AC Chair).

# Measles investment case

## Introduction

*(K. Thompson)*

Six WHO regions have committed to eliminating measles, and a further two regions have committed to eliminating rubella. The GAVI Alliance has offered investment for measles catch-up campaigns, with or without rubella. However, the world is currently not expected to meet Global Vaccine Action Plan targets for measles and rubella elimination.

WHO is funding a model to explore the case for investment in measles control, elimination and eradication. The model is an age-structured MSLIRV (maternal-susceptible-latent-infected-recovered-vaccinated) transmission model. Currently, it looks at six options for control, elimination and eradication and it integrates the economics and transmission dynamics of measles and rubella. The model assumes that countries will coordinate work towards their commitments from 2014 onwards with secure vaccine supply, financing and political will.

In 2011 and 2012, IVIR-AC emphasised the need to incorporate both between-country and within-country heterogeneity in the model. In response, the unit of analysis in the model has been changed from World Bank country income group to individual country. Results are then aggregated to regional and global levels. Population dynamics are matched to United Nations Development Programme estimates and projections for the years 1950 – 2100. The model is simulated from 1954 to 2013 using historical population and immunisation data, with the model at endemic equilibrium in 1954. Some coverage assumptions have to be made about historical coverage data. Stochastic importatations are incorporated; eventually these will be linked to regional and global levels of transmission.

For the rubella component, potential increases in the age of infection will be investigated. However, previous studies suggest that in most countries, the overall rubella burden will be reduced as long as coverage of about 80% is achieved, although the exact threshold is dependent on the birth rate. Work is also being done to develop a DALY weight for rubella. Development of the integrated economic and dynamic disease model for the investment case has taken longer than expected because of challenges associated with the data quality for some inputs (such as historical SIA coverage data) and the shift to a country-specific modeling, and further adaptation to include subnational modeling to account for heterogeneity will lead to some further delay.

## Review

*(J. Edmunds, S. Sow)*

The reviewers received a set of papers that do not represent an investment case, so the review could only consider whether the main questions and guidelines for constructing such a case as presented are adequate. A large number of parameters are needed for every country in the world to parameterise a model, but most of them are unknown so there is a danger they will be filled in by extrapolation or assumption. Hence some kind of prioritisation around the list may be needed to ensure appropriate data collection activities for the most important parameters. Also, the total cost of investment may be more useful than cost-effectiveness, since the main need is to understand the resource and health systems implications of various measles vaccination strategies.

Within-country heterogeneity in contact patterns and vaccine coverage is crucial, particularly since the herd immunity threshold for measles is high (about 95%). The current model does not address this because it assumes mixing within a country is homogeneous. This is not of theoretical interest only; measles outbreaks in the Netherlands occurred in 1999/2000 and 2008 despite MMR1 coverage exceeding 95% in cohorts born since 1986, due to low coverage in particular subpopulations i.e. the “Bible belt”.

A further issue is the extent to which rubella dynamics need to be incorporated. In principle rubella should be eliminated before measles if the MR vaccine is used, since rubella has a lower R0 compared to measles. However, there is a danger that the burden of congenital rubella syndrome will increase at intermediate levels of vaccine coverage due to shifts in the average age of infection. Even if the overall burden does not

decrease, health inequalities may worsen since the burden will be concentrated on the unvaccinated population. Hence if MR vaccination is used, there is a need to explore the use of broad immunization campaigns. The role of civil society in supporting eradication efforts also needs to be considered.

## Discussion

Within-country heterogeneities could be handled by identifying groups with low coverage and considering appropriate social and behavioural interventions, rather than assuming they will never be reached. The affected groups are very diverse (migrants, underserved peoples, vaccine objectors etc.) The modellers indicated that they can incorporate heterogeneity explicitly in their model in the context of characterizing undervaccinated subpopulations, as they do for polio modeling. They indicated that they will add this capacity to the model, and expressed that this adds more complexity to the process of estimating input parameters (i.e., it adds parameters related to relatively poorly-characterized parts of the population).

The effect that measles eradication activities have on routine vaccination programmes (such as rotavirus and pneumococcal vaccines) is a key uncertainty. In countries like India, it is difficult to see how levels of coverage needed to maintain measles control can be achieved without compromising other services. On the other hand, India still experiences a high burden of measles which had led to intensified efforts to increase routine measles immunization coverage, add a routine second dose of measles vaccine and complete a catch-up vaccination in 14 low coverage States. The investment case also needs to take account of the cost of surveillance, contact tracing and outbreak response, and the model will need to comprehensively consider costs. The success of measles eradication activities is also dependent on events and trends that are difficult to predict such as changes in breastfeeding habits, political upheavals and natural disasters.

## Summary and recommendations

IVIR-AC considers that the work as described cannot be recommended as the model does not sufficiently capture all the uncertainties and risks of measles eradication. Concerns that IVIR-AC outlined at its previous meetings in 2011 and 2012 still exist in particular with respect to within-country heterogeneities in coverage and transmission. Variability in coverage can occur within sub-populations with substantial implications for eradication, making a global model using country-level data only problematic.

Additional work that addresses the key concerns and incorporates subnational heterogeneity in the model is required prior to its use for assessing global .measles eradicationThe modellers have agreed to incorporate these IVIR-AC suggestions and comments and will submit the updated approach for discussion with some IVIR-AC members in about 4-6 weeks.

# Estimating the burden of yellow fever across Africa

## Introduction

*(N. Ferguson)*

In 1990, it was estimated that there were around 200,000 cases and 30,000 deaths due to yellow fever. In October 2011, QUIVER recommended revisiting these estimates in order to inform investment decisions about yellow fever vaccination by the GAVI Alliance. An expert committee convened by WHO commissioned a group led by Imperial College to carry out this assessment.

Work began in 2012 with an initial review of data, with a decision to focus on sub-Saharan Africa in the initial assessment. A list of available data on seroprevalence, outbreaks, surveillance database trends, vaccine coverage, population estimates and environmental variables was compiled. A model was then fitted to incidence data (with environmental and other variables as covariates) to estimate transmission intensity and hence overall disease burden.

In most countries, an age-independent force of infection fits data well. Overall burden estimates are similar to previous ones (850,000-2,000,000 infections, 85,000-200,000 cases and 30,000-70,000 death). However, the CFR is higher than previously estimated (35% compared to 15%). GAVI Alliance support for vaccination is estimated to have reduced incidence by 26% across Africa, and 56% in the targeted countries. The largest remaining burden is in countries not targeted by GAVI (particularly Nigeria). High infant vaccine coverage needs to be maintained in the targeted countries in order to maintain current levels of disease reduction.

Key limitations include uncertainties in demographics, vaccine coverage reports and interpretation of serosurveys. It is also not possible to distinguish between sylvatic, intermediate and urban transmission. Also, vaccine impact estimates are conservative because they do not take into account indirect protection. Key strengths are the use of a coherent framework making use of available data, quantification of uncertainty and ability to evaluate vaccine impact (including prospectively).

## Discussion

The model suggests that the burden of yellow fever increases across Africa from east to west; the mechanism behind this effect is unclear. Models without longitude fit data more poorly. It is possible that this is due to different regions having different vectors, but there are insufficient data on vectors to investigate this hypothesis. The CFR varies depending on the vector cycle and level of endemicity. Also, it may be inflated if only severe cases are detected. However, the historical range is around 20-65%. Changes in forestation levels affect the population of animal vectors but could not be taken into account, partly due to poor quality of data sets in the past.

The GAVI Alliance will need to make a decision about yellow fever vaccination by the end of 2013. The work will be important to inform decisions about continued investment in the targeted countries, extension to new countries and use of mass campaigns. The model needs to be sustainable because the GAVI Alliance may need to know in the future whether investment has made an impact.

## Summary and recommendations

IVIR-AC requested further clarification about how the generalised linear model captures the effect of vaccination. In follow up discussions after the meeting through a conference call with IVIR-AC chair, two members and the project team, outstanding issues were satisfactorily addressed, and discussed hence IVIR-AC felt that the model was adequate for yellow fever disease burden estimation across the African region.

# Varicella and zoster vaccination in low and middle income countries

## Introduction

*(M. Brisson)*

There are three concerns around varicella vaccination: (i) high rate of breakthrough cases among vaccinees, particularly if they only receive one vaccine dose, (ii) shifts in the age of infection to adults in whom disease severity is greater, and (iii) vaccine induced reduction of wild virus circulation in the population with consecutive decrease in natural boosting of immunity might increase the risk of reactivation of latent varicella-zoster-virus. These concerns are particularly pronounced in LMICs because of poor data and greater risk of age shifts due to likely mixing and coverage patterns. A SAGE working group is developing recommendations for varicella and zoster vaccination in low and middle income countries. Conclusions will be presented to SAGE for discussion.

Modelling has been conducted to inform SAGE deliberations. This uses a previously described transmission dynamic model (Brisson et al, 2000, 2010)[1] fitted to age-specific seroprevalence from countries representing a range of seroprevalence values and geographical regions. However, the validity and generalisability of the available serological data is unknown, as the data are not always nationally representative. Empirical contact matrices from Europe (POLYMOD) did not fit LMIC data well so a range of parameterised matrices were used instead. CFRs by age were extrapolated from Brazilian data.

Results suggest that at post-vaccination equilibrium, breakthrough cases occur most frequently in countries with medium to high seropositivity and intermediate coverage. In these countries, at intermediate levels of coverage the number of varicella deaths will increase after vaccination. In low seropositivity countries, deaths will decrease as vaccine coverage increases. Brazil and Singapore are outliers where the number of breakthrough cases always seems to increase with increasing coverage.

Remaining work to be done includes conducting sensitivity analyses on assumptions about contact patterns and vaccine efficacy, exploring the effect of varicella vaccination on herpes zoster, examining 2-dose vaccination, modelling African countries and estimating global burden.

## Review

*(P. Beutels)*

The current work offers a good pragmatic approach but should be considered a prelude to a more elaborate analysis. Key parameters that drive results are seropositivity and CFR. It would also be useful to show the cost-effectiveness and affordability of varicella vaccination compared to other vaccination programmes.

Fitting to seroprevalence data could be improved by considering the sample size of each data point, so that older age groups (which are typically undersampled) are given less weight. It would also be useful to fit to the original datasets; the IVIR-AC secretariat could write to the authors to request these. There may be other serological studies which are unpublished or in the gray literature which WHO regional offices could try to obtain. The functions used for fitting to seroprevalence data (gamma and Farrington) are unimodal; POLYMOD-like contact patterns often require multimodal functions. The assumption of time homogeneity may also be an issue in multiple time point seroprevalence studies that needs to be examined. Also, it is important to allow the status of immune individuals to vary continuously with age rather than to summarise seroprevalence data to binary outcomes.

The most important concern with varicella vaccination is the potential shift in the average age of infection; this is well represented in the model. However, the importance of this age shift relies on estimates of CFR which depend on an evaluation of varicella primary cause deaths in Brazil. This is subject to uncertainties in both the numerator (varicella and zoster deaths may have been mixed up in adults) and denominator (the total number of varicella cases over the time period may be small in some age groups). However, the most

[1] Brisson et al. Vaccine. 2010 Apr 26;28(19):3385-97; Brisson et al. Epidemiol Infect. 2000 Dec;125(3):651-69

important use of the analysis is simply to get the overall shape of the age-dependent CFR curve. For this purpose, the pragmatic approach taken seems acceptable. Also the age profile appears fairly similar to UK and Canadian data.

Another concern is a potential increase in zoster. However, there is a poor understanding of the underlying mechanism for such an increase. Post-vaccination observational data, modelling work and immunological studies investigating this effect have shown mixed results. Demographic change in LMICs may play a critical role, but there was not time to investigate this within available timelines. Lastly, breakthrough varicella cases may be important since vaccine efficacy in LMICs is poorly documented.

*(J. Edmunds)*
Overall the model uses an appropriate approach to address the question. The shapes of the force of infection and morbidity curves are probably the most important inputs to the model. They are likely to show similar patterns to those in high income settings, but it is possible that varicella is more serious in older adults in LMICs. Meta-analyses combining available data sets may offer a means to increase statistical power. To obtain a reliable global burden estimate requires more than simply extrapolating data from Brazil and high income settings.

## Discussion

Vaccine effectiveness data from China was used; this has performed at the same effectiveness level as vaccines in high income countries and uses the same Oka strain.

LMICs are not homogeneous; a model designed for Brazil or China cannot always be extrapolated to other countries. In low income countries, there are a number of barriers to vaccine introduction: lack of data, cost-effectiveness issues, competing demands on health care resources and the potential for negative outcomes. Hence it may be useful to focus the exercise mainly on middle income countries, where private sector use is important (and may on its own bring coverage to intermediate levels where the potential for harm is greatest), and WHO guidance is likely to be most influential. For low income countries, due to the potential for harm, it may be better to focus on improving access to care.

Despite data uncertainties, it is unlikely that overall mortality due to varicella is high compared to more severe vaccine-preventable diseases like measles. The incidence of varicella deaths is likely to range between 1-10 deaths per million, based on data from the two outlier countries in terms of CFR (Brazil and Sri Lanka). It would be useful to see cost-effectiveness results for different CFR assumptions. In terms of guidance, SAGE has already recommended that vaccination programmes should only be introduced if coverage of at least 80% is achievable. It would be useful to incorporate into guidance the level of private sector uptake that would trigger a cause for concern.

## Summary and recommendations

IVIR-AC believes that the model is suitable and appropriate for varicella vaccine impact modelling and to examine potential concerns prior to vaccination with regard to breakthrough cases and shifts in the age of infection in LMICs. However, some minor technical improvements can be made such as around the functional forms used to represent the force of infection and mixing patterns. A better acknowledgment of the uncertainties in the data that are used in the model such as seroprevalence, CFRs and morbidity estimates is also recommended.

IVIR-AC believes that more data are needed about the burden of varicella in low and middle income countries for the model to be of optimal use. IVIR-AC considers that the model is not designed to estimate global burden of varicella. If additional modelling exercises on varicella burden of disease are undertaken, IVIR-AC would like the opportunity to review and provide comments.

Extending the work to calculate cost-effectiveness of vaccination across a range of possible estimates of disease burden will have substantial utility for priority setting.

potential users of the results, but each will have a different set of priorities. Local or regional exercises producing lists of priorities tailored to local needs may be more useful, but may require a lot of work. Preliminary results show higher priority for research questions that are widely applicable and generalisable, and less priority for topics in specific areas. However, it was noted that the exercise was geared toward broadly generalisable research questions while specific questions and research topics may still have relevance for particular conditions, vaccines and geographical areas. The experts who rated the questions were mainly generalists; disease-specific experts may have given a different set of rankings.

One immediate use of the results is to prioritise the agenda of IVIR-AC. However, the list of priorities is unlikely to have wider impact unless if affects priorities of funders. Most funders are interested in funding disease-specific projects rather than the broader set of topics that were highest rated.

For the GAVI Alliance, specific questions on research priorities to fill critical information needs are more helpful than general questions. While a lot is known about general barriers to vaccine uptake, it is important to understand particular pathways more precisely.

## Summary and recommendations

IVIR-AC is supportive of the effort to make priority setting for implementation research questions more systematic. IVIR-AC believes that the overall analytical approach is well-designed. While the findings provide a basis for decision making, IVIR-AC recognizes that contextual variability and considerations will require that the findings are not used as the sole criterion for decision making. Input from a range of stakeholders at different levels besides global and regional will be beneficial in validating the exercise and defining the application of the results. IVIR-AC recommends that IVB develop a well-formulated strategy for the next steps in priority setting.

# Implementation research priority setting framework

## Introduction

*(J. Clemens)*

Barriers to increasing vaccination coverage are often not technical. Implementation research focuses on understanding bottlenecks and barriers that impede uptake of new vaccines or improved coverage for existing vaccines, and finding solutions to overcome them. In early 2012, WHO started work to develop a systematic process for formulating an implementation research agenda to increase vaccine uptake. In September 2012, IVIR-AC made some suggestions for methodological improvements which have been incorporated. Preliminary results were presented pending completion of the prioritization exercise and a final report.

An ad-hoc working group was convened with 21 independent experts to develop a prioritisation framework to review a list of candidate research questions from a broad solicitation of experts and existing reports in order to help define the final list of questions to undergo a systematic prioritisation.. Input from the group and from a pilot prioritization criteria was used to formulate pilot questions, which were then narrowed down to a final set of 84 questions. An additional 21 members were later added following IVIR-AC recommendations.

For the prioritisation framework used, adapted from the Essential National Health Research (ENHR) methodology incorporates four categories (appropriateness, relevance, chance of success and impact), consisting of nine criteria with three response levels each. Responses are weighted to derive an additive numerical score across the nine criteria using the PAPRIKA (Potentially All Pairwise Rankings of All Possible Alternatives) method and software developed by 1000 Minds[2].

The preliminary results from (from 26 raters who completed ratings for weights to the criteria and 15 who completed the rating of candidate questions) showed that the most important criterion identified was whether a study can be conducted ethically. The prioritization criteria and PAPRIKA methodology were found to be feasible and relevant, although the final rating of questions was limited by low response rate and small numbers of raters per domain.

The next steps will be to try to achieve a higher response rate (using phone reminders and trying to determine reasons for dropouts), analyse the final dataset and share it for stakeholder comments, and finally to disseminate a list of priorities to relevant stakeholders. IVIR-AC guidance was sought on the robustness of the method and analytical strategies,

## Review

(M. Weiss)

The method used has appeal because it is based on an accepted decision theory framework, taps the authority of experts and simplifies complex multiple comparisons to binary choices. While the process uses explicit criteria to guide decision making, it is important that it does not displace the decision makers. It should be used as a hypothesis generating exercise; the next step is to shift from the technical process of conducting the exercise to reflecting on the priorities it produces and their implications.

## Discussion

In general, the exercise was well conducted and the methodology appears sound. But the results need to be brought back to decision makers and re-evaluated for face validity. It is also important to have more grassroots input; although regional representation has now been included in the exercise it may be necessary to get feedback from national and district levels officers as well. There are different kinds of

[2] See Hanssen et al. J. Multi-Crit. Decis. Anal. 15: 87–107 (2009)

# Executive Summary

# Immunization Implementation Research Priority Setting

Adwoa Bentsi-Enchill[1] and John Clemens[2] on behalf of the Ad Hoc Working Group on Immunization Implementation Research Prioritization

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## 1. Background

Despite significant achievements over the last decade to strengthen national immunization programmes, and significant donor support to introduce new vaccines in resource-limited countries, major challenges remain in reaching and maintaining high vaccine coverage in several countries or regions[1]. Many of the challenges contributing to this are known to be related to health systems and immunization program management issues as well as socio-cultural factors that impede the delivery or scale up of cost-effective immunization interventions[2,3]. Implementation research to understand these and other barriers and bottlenecks is increasingly recognized as a critical tool to improve the delivery of immunization services and uptake of new vaccines as well as the effective use of new immunization technologies. As such, implementation research is an integral component of the work of WHO's Department of Immunization, Vaccines & Biologicals, (IVB). Against this background, in 2012, IVB initiated an activity in consultation with its key partners to develop priorities for a global immunization implementation research agenda.

The overall goal was to create an enabling environment for all stakeholders to participate actively in supporting implementation research that has the potential to drive immunization policy and maximize the impact of vaccines and immunization, and to help define and implement a collaborative process to facilitate efforts at country level aimed at generating relevant and credible evidence to support decision-making for national immunization programmes.

An ad hoc working group was established to guide IVB in the priority setting exercise. The scope of ***research needs*** covered was quite broad and included initial submissions of broad topics and specific research questions. For consistency, all such research needs considered were framed as questions for review. However, the process to evaluate priorities among these "research questions" was not aimed at making decisions to fund or support specific research studies and did not include the more detailed review of research proposals that would be required for that purpose.

Other related components, aimed at ensuring a dynamic and ongoing global implementation research agenda, were proposed and were to be informed by the outcomes of the prioritization exercise: (a) mapping of global research activities and monitoring of progress in the field; (b) assessing the quality, relevance and potential policy implications from emerging implementation research; (c) to build

[1] WHO-UNICEF estimates: In 2012, 22.6 million children < 1 year of age did not receive DTP3 vaccine worldwide and 1.5 million children died from diseases preventable by vaccines currently recommended by WHO. (http://www.who.int/immunization_monitoring/Global_Immunization_Data_v2.pdf)
[2] http://www.who.int/immunization/sage/CDC_UNVACC_REPORT_FINAL_v2.pdf
[3] Swiss Tropical and Public Health Institute. Gender and Immunization (Report to WHO), 2010

scientific consensus around useful implementation research outputs, and develop best practices and guidelines in accordance with WHO's normative role; and (d) to support implementation research capacity in countries and regions in collaboration with partners.

The methodology and preliminary findings of the prioritization exercise were reported to WHO's Immunization and Vaccine-Related Implementation Research Advisory Committee (IVIR-AC) which provided further guidance to the work. In addition, the working group took note of the critical work by the Decade of Vaccines (DoV) Collaboration Research and Development Working Group which defined an implementation research framework that could serve to evaluate the application of results from this prioritization exercise.[4]

## 2. Methods

### *2.1 Ad hoc working group*

The working group comprised 41 immunization experts (chaired by Dr John Clemens) who represented a broad range of expertise; public health, academic and research backgrounds; perspectives from all 6 WHO Regions and representation from both high and low resource settings. Working group members were selected based on their expertise and did not represent their affiliated organization or agency other than the WHO Regional staff. The composition of the final working group is detailed in Annex 1.

As one of its first tasks, the working group developed a conceptual framework which defined the focus of its work to be: research to improve coverage of recommended vaccines and to facilitate introduction of new, licensed or near-to-licensing vaccines; research to understand the barriers and bottlenecks against improving vaccine coverage and uptake, and to identify and test attractive strategies to overcome such barriers; research that addresses low and middle income countries (LMIC) with a specific emphasis on low performing and low resource settings; research with a broad scope (i.e., as applicable as possible to immunization or vaccines in general rather than vaccine-specific); and research that can be completed in less than a five-year timeframe (once the priorities are finalized and disseminated in the public domain). In addition, it was decided that the research needs to be considered should be relevant to one or more guiding principles relating to equity, integration, innovation and partnerships. The group also defined eight domains under which research needs would be grouped as listed below.

| | |
|---|---|
| **Domain A: Health and Immunization Systems** | • Financing, human resource, infrastructure, immunization services, governance |
| **Domain B: Social determinants of vaccination & Communication** | • Gender, vulnerable population, socio-economic factors, geographic distribution (including urban/rural, hard-to-reach groups etc.), power/social hierarchy, community engagement, knowledge, attitude and behavior, communication and advocacy |
| **Domain C: Vaccine product profile** | • Vaccine effectiveness, vaccine presentations, delivery devices/technologies, vaccine safety including perceptions about safety |
| **Domain D: Vaccination and Coverage** | • Policy, introduction decisions, schedules, immunization strategies, immunization practices, vaccine refusal and drop-out |

[4] Arora NK et al. The need for targeted implementation research to improve coverage of basic vaccines and introduction of new vaccines. Vaccine 2013;31S: B129-36.

| | |
|---|---|
| **Domain E: Cold chain and logistics management** | • Cold chain space, equipment and related technology, vaccine and dry stores management, waste management |
| **Domain F: Programme Management** | • Performance/programme monitoring, capacity building, supervisory practices, job aids, checklists |
| **Domain G: Programme monitoring and Impact assessment** | • Surveillance standards and practices, economic impact, disease burden reduction, use of monitoring data for decision making |
| **Domain H: Research capacity and application** | • Research capacity strengthening, linking research to policy and practice |

### *2.2. Identifying the candidate research questions*

Potential research questions and topics were identified through a widespread consultation with technical staff of IVB; WHO Regional Immunization Advisers, and through the latter with national immunization programme managers; vaccine and immunization experts and through selected regional and global meetings in 2012[5]. Additional potential implementation research needs were identified through reviews of several key documents, including reports of the WHO Strategic Advisory Group of Experts (SAGE) meetings from 2007 to 2011; technical reports to SAGE and WHO on the analysis of specific issues[6]; the Global Vaccine Action Plan; reports of the Global Vaccine Research Forum meeting (2011); national research priorities of 23 selected countries[7], technical reports of immunization programme reviews (such as EPI reviews, post-introduction evaluation of new vaccines, vaccine management assessments) and Project Optimize activities.

An initial list of 404 potential research needs (questions and broad topics) was obtained from the multiple sources described above. All research needs were framed as research questions from which, following a series of review steps undertaken by the working group and with inputs of the relevant IVB technical staff, a final list of candidate questions to be rated was compiled. Questions were included to be rated if they were consistent with the conceptual framework and guiding principles and it was felt that results of the proposed research could potentially strengthen immunization programmes at the country level. Suggested research questions specific to a vaccine for which a more detailed research agenda existed (e.g. polio eradication), or with an agenda setting process ongoing (e.g. for measles and rubella), and those considered to have been adequately addressed by previous research or for which ongoing work was identified (for example under Project Optimize) were excluded. Where necessary, questions were edited to ensure both clarity and consistency in terminology, harmonization among the domains and elimination of duplicates in the master list. A final list of 84 candidate research questions was subjected to the systematic rating method described below. The eight domains within which questions were grouped were defined after the process to solicit potential research questions had started and no specific efforts were made to achieve a balance in the final number of questions per

[5] Targeted meetings in 2012 included the South-East Asia Immunization Technical Advisory Group meeting (29-30 March), the Africa Advisory Committee on Health Research Meeting (27-28 April), the Global NUVI meeting (15–17 May), and the WHO/AFRO Task Force on Immunization (TFI) meeting (21-22 June).

[6] Epidemiology of the unvaccinated child, Impact of new vaccine introduction and Gender and immunization.

[7] 23 national health research prioritization reports, accessed from the Health Research Web initiative of the Council on Health Research for Development (http://www.healthresearchweb.org/) were reviewed to identify Immunization-related research issues.

domain (ranging from 5 to 19).

### *2.3 Prioritization criteria*

At its June 2012 meeting, the working group considered several systematic prioritization criteria and methods: the Essential National Health Research (ENHR) method[8]; Child Health and Nutrition Research Initiative (CHNRI) method[9]; 3D Combined Approach Matrix method[10]; and Delphi and nominal group techniques. The group decided on an approach using absolute ranking (based on an aggregate score for each question) as the most appropriate and feasible for the number of questions under consideration in this exercise.

The ENHR method was selected to be adapted for use in this exercise. The method is based on four fundamental questions to assess the suitability of a proposed research question: *Appropriateness* (Should we do it?); *Relevance* (Why should we do it?); *Chances of success* (Can we do it?); and *Impact of the research outcomes* (What benefit will be achieved?). A final set of nine prioritization criteria adapted from the ENHR criteria was used, each with three response levels of "no", "not sure" and "yes" which were assigned nominal values of 0, 0.5 and 1 respectively (Annex 2). A response of "don't know" (meaning the rater felt that he/she was not sufficiently well informed to assess the research question on a particular criterion) was allowed but treated as missing data and omitted from the calculation of scores.

### *2.4 Method for weighting of criteria and rating of questions*

A web-based tool for multi-criteria decision-making[11] was selected for use (after a pilot test[12]) in a 2-step process involving (a) weighting of the prioritization criteria based on raters' value judgments about the relative importance of the criteria and (b) rating of the candidate questions from which a weighted aggregate score was calculated from each rater's responses to the nine criteria. The weighting of criteria and question rating were carried out between 23 May to 20 August 2013.

In the first step, all experts in the working group were invited to complete a "decision survey", in which a scoring system, called the *Potentially All Pairwise Rankings of All Possible Alternatives (PAPRIKA) method,* was used to derive each rater's *preference values* (i.e., weights) for the pre-defined criteria according to their stated preferences when presented with a series of paired criteria (with differing responses) at a time to be ranked on importance. In the PAPRIKA method, each time the expert ranks a pair, all undominated pairs implicitly ranked as corollaries are identified and discarded. In this way the PAPRIKA method limits the number of pairwise rankings to a small fraction of all potential pairs and the process is repeated until potentially all undominated pairs are ranked. From the explicitly ranked pairs, preference values for each criterion are obtained via linear programming and expressed as a percentage. Each criterion's relative importance (i.e., weight), relative to the other criteria, is represented by the value of its highest ranked level ("yes" response). For a question to achieve a 100% rating it would need a "yes" response on all nine criteria. Similarly, a question would be rated worst if it received a "no"

[8] COHRED. A Manual for Research Priority Setting using ENHR Strategy, COHRED document 2000.3, March 2000

[9] CHNRI. A New Approach for Systematic Priority Setting In Child Health Research Investment

[10] Global Forum for Health Research. The 3D Combined Approach Matrix: An improved tool for setting priorities in research for health, 2009.

[11] Hansen P and Ombler F. A new method for scoring multi-attribute value models using pairwise rankings of alternatives. Journal of Multi-Criteria Decision Analysis. 2008; 15: 87-107.

[12] The tool was tested with a pilot group including six WHO staff and two external experts who completed the decision survey to weight the criteria and rated all candidate research questions.

response on every criterion. The mean preference values of the group therefore represent the relative importance of the nine criteria to the group.

In the second step of the exercise, the rating of questions was designed to address two potential challenges that were earlier identified, and confirmed as important through the pilot test, namely how to ensure that an individual rater had the relevant expertise to provide valid responses for questions across multiple areas of immunization, and the need to limit the rating exercise to a reasonable and feasible duration that would not hinder the response rate. To address those concerns, each rater was requested to identify their top four areas of expertise according to the domains by which questions were grouped,. Raters were then matched to rate questions in specific domains (on average 3-4 domains) corresponding to their areas of expertise. Raters were kept blinded to the weights calculated for the criteria.

### *2.5 Analysis of scores*

Each rater's responses to the nine prioritization criteria for each question were weighted (by *mean preference values* from the PAPRIKA method) and a mean of the weighted individual scores for each criterion was calculated as a criterion-specific score for that criterion. Each research question therefore received nine criterion-specific scores. The nine criterion-specific scores were then summed to give an aggregate score for the question (ranging between 0 to 100%[13]) by which research questions in each domain were ranked in decreasing order.

## 3. Results

### *3.1 Response rate*

Of the 41 experts who were invited to participate in the prioritization exercise, 28 completed the weighting of the criteria (68% response rate) while 29 completed the rating of their assigned research questions (71% response rate). All non-respondents on the question rating survey (and those experts who had started but not completed) received up to five reminders through a combination of emails and phone calls. The distribution of respondents by WHO Region was approximately representative of the distribution in the working group (AMR 24%, SEAR 22%, EUR 20%, AFR 12%, EMR 12%, and WPR 10%), however with slightly lower response rate from the African Region (with only 4% and 7% of experts completing the weighting and rating respectively).

Five experts who completed weighting of the criteria did not complete the rating of questions. Conversely, six of those who completed rating of the questions did not contribute to the criteria weights. Overall, four experts did not respond to either the weighting or the question rating . There was no systematic process to document reasons for delayed or non-response, however lack of time and/or other competing commitments were reported by several non-respondents or respondents who completed the exercise with significant delay (after an initial start).

### *3.2 Criteria weights*

Annex 2 shows the weights (by mean preference values) assigned by the group to the response levels for each of the nine criteria. Not unexpectedly, criterion 1.2 (ethical conduct of the study) was deemed to be the most important relative to the other criteria (i.e., highest weight on a "yes" response). Criterion 3.2 (availability of endpoints/results in <5 years) was judged to have the lowest relative importance.

[13] To score 100%, a question had to have a "yes" response on each of the nine criteria.

### *3.3 Rating of the research questions*

The number of experts who completed the rating per domain ranged from 9 to 19. However, the completion rate varied in relation to the number of experts assigned to each domain. For example, while there was comparatively more expertise on the working group in programme management (Domain F with 60% completion rate), and in health and immunization systems (Domain A, 64% completion) not all the eligible experts in those domains contributed to the final ranking. The top 5 ranked questions per domain, based on weighted aggregate scores, is presented in Table 1[14] (the full list of ranked questions in each domain is available in the full report).

While one of the goals of this exercise was to focus on research questions that are broadly applicable rather than vaccine-specific ones, a few exceptions were made for the latter. Five of the six vaccine-specific questions included were rated in the bottom third of their respective domains, which could suggest that the panel of raters may not have been sufficiently well informed to assess those vaccine-specific questions on the given criteria. It is also possible, but difficult to confirm, that the *a priori* decision to exclude vaccine-specific questions could have biased raters against such questions.

There were missing data (i.e., "don't know" responses) in all domains with the exception of Domain F (in which none of the questions generated a "don't know" response to any of the criteria). However, in general there was no tendency for questions with a higher proportion of missing data (across all nine criteria for all raters combined) to rank lower on the final aggregate score. For example, in domains with the highest frequency of missing data (>20% of all possible responses to the criteria for all questions by all domain raters), questions with relatively higher or lower proportions of missing data were equally distributed in the ranking order. Comments provided by raters (optional) suggested that lack of clarity or the rater's judgment that it was "not a research question" were frequent reasons for missing data.

## 4. Discussion

In this exercise, a pool of "research questions" was gathered from multiple sources in an effort to identify potential research needs for addressing barriers to improving vaccine coverage for existing recommended vaccines or uptake of newly licensed or soon-to-be licensed vaccines. The questions were categorized *post hoc* into eight domains as presented in the report. Given that questions were ranked within each domain, the results are not useful for making choices between research needs in one area versus another (e.g., health systems versus social determinants of vaccine acceptance and uptake). The ranking of all questions in each domain provides a reference list of the relative importance assigned to the identified research needs by this group of experts. Given the close range of scores it would be difficult with these data to identify, for example in funding decisions, a true set of "lowest ranked" research needs that should not receive support. It is possible that a larger group or a different group of raters could result in a different rank order of research needs. Furthermore, different stakeholder groups that may use such a list are likely to have different priorities and apply additional factors in selecting among these research needs.

The ENHR criteria proved to be adaptable to the prioritization of immunization implementation research needs. In addition, the PAPRIKA method served as a useful tool for a transparent decision-making

[14] In different analyses, aggregate scores were weighted by (a) working group mean preference values (averaged across responses given by all experts who completed the decision survey) and (b) domain mean preference values (averaged across responses given by only those experts who were assigned to rate the given domain according to their expertise). The rankings were identical with limited changes in overall ranking and the results in this report are based on the working group weights only.

process in that it enabled empiric weighting of our prioritization criteria according to judgments by the actual raters and yielded weights that exhibited face validity. Importantly, changing the weights applied to the criteria from the overall weights to those derived by raters in a specific domain did not result in significant changes in the overall ranking. Limitations of this prioritization exercise include relatively small numbers of raters per domain, less than optimal completion rate (in part this is likely attributable to the prolonged duration of the exercise) and potential biases in selecting (through the multiple stages of review) the final list of candidate research questions for systematic rating.

IVIR-AC guidance was sought on the robustness of the overall methods used and the analytical approach. IVIR-AC was supportive of the effort to make priority setting for immunization implementation research needs more systematic and found the analytical approach to be appropriate. The committee also found that the method is attractive in that it is based on an accepted decision theory framework and tapped the authority of relevant experts while also simplifying complex multiple comparisons to binary choices in the weighting process. Nonetheless, the committee cautioned that the outcomes of this prioritization should not be used as the sole measure for decision-making on implementation research needs given the importance of contextual factors to implementation research and the variability of such factors in different settings. Dissemination to and inputs from a range of stakeholders (public health communities, researchers, donors and policymakers at national, regional and global levels) – all of whom may have different priorities - will be beneficial in defining the application of the results from this exercise.

Implementation research needs in immunization have been identified and categorized in different dimensions by the DOV R&D Working Group[15] and other groups. It will be particularly interesting to review the research needs identified through this exercise against five implementation research domains developed by the DOV R&D Working Group: Bringing immunization closer to the community; Demand for vaccination; Services at fixed sites; Program management, and Policy and governance. The latter also provide a useful framework for monitoring the outcomes of this prioritization exercise in terms of the broader acceptance of the research needs identified as well as the number and outcomes of future research activities conducted.

[15] See footnote 4

**Table 1: Top 5 ranking research questions per domain – aggregate score (based on number of raters in the given domain) weighted by working group mean preference values**

*Note: The full ranking for all questions per domain is available in the complete report.*

| **Domain A (Health and Immunization Systems) – 15 questions** | | | |
|---|---|---|---|
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=9 raters) |
| A13: Unvacc_ delivery strategies | What are the specific barriers to immunization among children not reached by immunization services and what are the service delivery strategies (including specific package of services) to respond effectively to those barriers? | 1st | 95.1% |
| A04: HCP competence/KA | How do the level of professional competence, knowledge and attitudes of vaccinators (e.g., trained nurses vs. 'lay' health workers) impact on the quality of vaccination services, vaccine acceptance, vaccination coverage, and occurrence and management of AEFIs etc.? | 2nd | 91.6% |
| A03: Sustainability barriers | What are the barriers to sustained financing for routine immunization in low and middle income countries and what are the successful financing and advocacy mechanisms both internal (i.e., governmental) and external (i.e., donors) for countries in different categories (GAVI-supported vrs. non-GAVI etc.) in terms of long term sustainability? | 3rd | 89.9% |
| A06: PPPs_service quality | What public-private partnerships (and specific interventions) can be developed and leveraged to improve the quality of routine immunization services and to increase vaccination coverage? | 4th | 88.9% |
| A01: Sustainability tools | What are the optimum tools to assess and sustain vaccine purchases and operational costs after donor funding ends? | 5th | 87.8% |
| **Domain B (Social determinants of vaccination & Communication) – 8 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=12 raters) |
| B1: High risk communities | What are the profiles of high risk communities (such as gender, vulnerable populations, socio-economic factors etc), how do these profiles influence vaccine uptake, and what are the best strategies to identify and vaccinate such groups? | 1st | 91.0% |
| B5: Low public demand | What are the factors that influence levels of demand for immunization (context, vaccine and vaccination specific issues, individual and social group influences)? | 2nd | 88.3% |
| B7: Media education/training | What is the impact of education/training of the media in enhancing (a) community knowledge and perceptions about vaccination, and (b) greater media accountability in reporting immunization-related issues? | 3rd | 87.4% |
| B4: HCP capacity on trust issues | Do policymakers, doctors, nurses, and other frontline workers have adequate relevant (as per their responsibilities) tools, knowledge, and capacity to address trust issues in order to increase (or maintain already high levels of) vaccine uptake? | 4th | 87.3% |
| B8: Strategies_vacc hesitancy | What strategies are effective (with the public, health care workers, health system) to address vaccine hesitancy? | 5th | 84.7% |
| **Domain C (Vaccine product profile) – 6 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=14 raters) |
| C4: LLD feasibility_safety | What is the feasibility of establishing (regional) dynamic, large-linked databases for use in assessing vaccine safety concerns? | 1st | 87.6% |
| C1: Perceptions_impac t | How do perceptions about vaccine effectiveness and safety influence vaccine introduction and coverage, and what are the most effective strategies to address negative inaccurate perceptions in order to improve coverage? | 2nd | 83.9% |

| | | | |
|---|---|---|---|
| C6: Quality AEFI systems | What are the most effective strategies for management of AEFIs and to have high quality AEFI surveillance systems? | 3rd | 83.1% |
| C5: Needle-free routes LMIC | What are the effectiveness, efficiency, appropriateness and potential risks of novel needle-free routes of vaccine administration (e.g., sublingual, jet injectors, micro-needle patches) in low- and middle-income countries and what is the impact of their use on reducing injection waste? | 4th | 81.3% |
| C3: Vaccine presentations_impact | What is the impact of different vaccine presentations (e.g., single dose vs. multiple dose or combo vs. non-combo vaccines) on vaccine wastage, costs, acceptability and vaccine introduction and coverage? | 5th | 75.8% |
| **Domain D (Vaccination and Coverage) – 12 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=19 raters) |
| D09: Vacc cov_special populations | How should vaccination services be adapted to increase coverage of specific populations e.g. in context of HPV (different target group); cholera vaccines (home intake of the second dose distributed when the first dose is administered under supervision); private sector availability of some oral vaccines (e.g., cholera, typhoid); or marginalised population (slums, migrants, etc.) ? | 1st | 93.0% |
| D06: IntegratSed Vacc programs | Does integration of childhood and adolescent immunization programmes with other health programmes improve vaccination coverage and if so, which other health programmes (e.g., Primary Health Care, PMTCT) provide the most effective models for integration (e.g., what is the optimal package of services and the cost-effectiveness of different packages, and what additional resources are needed to achieve successful and sustainable integration)? | 2nd | 89.1% |
| D01: Unvacc_active measures | How effective are active measures to supplement routine EPI in capturing children at risk of non-vaccination and/or poor compliance? | 3rd | 88.3% |
| D07: Health/immunization cards | How can child health cards and child immunization cards (or equivalent) be designed and used as cost-effective monitoring tools to track service delivery (i.e. linked with registers and tracking systems) and improve vaccination coverage, and as communication tools for caregivers? | 4th | 87.4% |
| D03: Survey methods | How can survey methods be standardized to reduce heterogeneity between vaccination coverage estimates from different surveys and/or system reports, and to improve accuracy and timeliness of coverage data at all levels? | 5th | 85.3% |
| **Domain E (Cold chain and logistics management) – 10 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=10) |
| E10: Integrated logistics mxmnt | What would be an effective 'common operating platform' for integrated logistics management of all public health activities at district level, including the validation of a trained logistics manager to lead the activity? | 1st | 89.3% |
| E02: Solar refrigerators | What is the performance in use and the reliability of solar refrigerators in health facilities without electricity and why have repair/maintenance systems worked or failed? | 2nd | 88.1% |
| E07: Controlled Room Ambient | What is the potential impact of equipping medicines supply chains with storage at Controlled Room Ambient (+15/+25C) on future vaccine storage (i.e., to enable vaccine storage out of the cold chain)? | 3rd | 86.9% |
| E05: Centralized destruction | How can sharps collection systems be best integrated within vaccine delivery systems, in environmentally acceptable, practical and affordable ways, and using centralized destruction technologies? | 4th | 83.7% |
| E03: Passive transport containers | Which technologies and practices will provide the necessary protection against heat and freezing for vaccine carried in passive transport containers and what is likely to be the burden of introduction? | 5th | 83.1% |

| **Domain F (Programme Management) – 9 questions** | | | |
|---|---|---|---|
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=12 raters) |
| F5: Tools_missed opportunities | What tools are needed for health workers to effectively assess and correct missed opportunities for children whose immunization has been delayed or whose schedules have been interrupted? | 1st | 91.4% |
| F6: Minimum supervisory criteria | What are the supervisory capacities and practices in different countries/settings, and what is the minimum set of criteria for supervisory workforce planning and supervisory practices in immunization programmes? | 2nd | 89.1% |
| F1: Minimum enabling elements | What is the minimum set of "enabling elements" required for a successful immunization programme, and what indicators can be best used to monitor the quality of immunization services and immunization programme management? | 3rd | 88.1% |
| F3: Barriers_RED | What are the barriers to implementation of the RED (Reaching Every District) strategy in low performing countries? | 4th | 86.8% |
| F8: Strategies_REC | What are the implementation and management strategies, and the outcomes/impact of the 'Reaching every Community' strategy (in countries where this is implemented)? | 5th | 83.8% |
| **Domain G (Programme monitoring and Impact assessment) – 19 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=18 raters) |
| G02: Estimating target population | Can improvements be made to methods for estimating the size of the target populations, at national and subnational levels? | 1st | 90.4% |
| G01: Technologies_data recording | How can new or innovative information and communication technologies be used to improve the recording and reporting as well as the use of immunization data? | 2nd | 89.6% |
| G04: Sub-national data | Can better tools be developed to facilitate the use of sub-national (district level) immunization data (stock, surveillance and coverage) to take timely action to improve programme performance? | 3rd | 85.9% |
| G10: Rapid methods_sensitivity | Can rapid methods be developed to assess reporting sensitivity of VPDs in national health management information systems? | 4th | 85.5% |
| G11: Rapid methods_BOD | In countries with inadequate surveillance capacity, can rapid assessment methods be developed to estimate burden of disease using data from hospital records or national health management information systems? | 5th | 85.5% |
| **Domain H (Research related issues) – 5 questions** | | | |
| **Short title** | **Proposed research questions** | **Rank** | **Aggregate score** (n=15 raters) |
| H5: NITAGs | How frequently is evidence-based information used to support NITAG (or other equivalent national) recommendations? What are the barriers and challenges to the effective functioning of NITAGs and how can they be addressed to strengthen NITAGs and vaccine policy-making at country level? | 1st | 87.3% |
| H1: Strategies_IMR capacity | What strategies can be used to strengthen vaccine implementation research capacity in countries and the translation of research to policy? | 2nd | 82.4% |
| H2: IMR capacity_Policy | To what extent is in-country research critical in driving immunization policy? How is it influenced by presence or absence of local research capacity/institutions and their relationships with policy makers and local/national advisory bodies such as NITAGs? | 3rd | 80.6% |
| H4: Requirements_Governance | What are the technical cooperation and research capacity requirements to facilitate establishment of immunization governance mechanisms? | 4th | 77.4% |
| H3: ICC roles | What role can interagency coordinating committees play in improving immunization financing, governance and partnership? | 5th | 66.7% |

**Annex 1: Composition of the Ad Hoc Working Group on Immunization Implementation Research**

The table lists the technical experts on the ad hoc working group as well as each member's affiliation (at the start of the prioritization exercise) and selected areas of expertise for rating the research questions.

| Name | Affiliation | "Top areas" of immunization expertise selected (Domains assigned for rating) |
|---|---|---|
| Abdoulreza Esteghamati | Tehran University of Medical Sciences, Iran | Health and Immunization Systems, Social determinants of vaccination & Communication, Cold chain and logistics management, Programme Management, Research capacity and application |
| Andrew J. Hall | London School of Hygiene and Tropical Medicine | Vaccine product profile, Vaccination and Coverage, Research capacity and application |
| Asad Ali | The Aga Khan University, Pakistan | Vaccine product profile, Vaccination and Coverage, Programme monitoring and Impact assessment, Research capacity and application |
| Auguste Ambendet | WHO AFRO | Health and Immunization Systems, Programme Management, Programme monitoring and Impact assessment, Research capacity and application |
| Adalid Zamora | National Immunization Technical Advisory Group for Immunization, Bolivia | Social determinants of vaccination & Communication, Cold chain and logistics management, Programme Management, Programme monitoring and Impact assessment |
| Carolina Danovaro | PAHO | Vaccination and Coverage, Programme Management, Programme monitoring and Impact assessment, Research capacity and application |
| Christian Schaetti | Swiss Tropical & Public Health Institute | Health and Immunization Systems, Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Research capacity and application |
| Dicky Akanmori | WHO AFRO | Social determinants of vaccination & Communication, Vaccination and Coverage, Programme Management, Programme monitoring and Impact assessment |
| David Durrheim | University of Newcastle, Australia | Vaccination and Coverage, Programme monitoring and Impact assessment, Research capacity and application |
| David Sack | Johns Hopkins Bloomberg School of Public Health | Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Programme monitoring and Impact assessment |
| Fussum Daniel | WHO AFRO | Health and Immunization Systems, Programme Management, Programme monitoring and Impact assessment |
| Gabriela Montorzi | Council on Health Research for Development | Research capacity and application |
| Helen Oh | Changi General Hospital, Singapore | Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management |
| Irtaza Chaudhri | WHO EMRO | Social determinants of vaccination & Communication, Cold |

| | | |
|---|---|---|
| | | chain and logistics management, Programme Management, Programme monitoring and Impact assessment |
| John Clemens (Chair) | UCLA (subsequently icddr,b, Bangladesh) | Vaccine product profile, Programme monitoring and Impact assessment |
| John Grundy | Nossal Institute for Global Health | Health and Immunization Systems, Social determinants of vaccination & Communication, Programme Management, Research capacity and application |
| John Lloyd | Independent consultant | Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management, Programme Management, |
| Lee Jong-Koo | Seoul National University College of Medicine | Health and Immunization Systems, Vaccine product profile, Vaccination and Coverage, Programme Management |
| Lauri Markowitz | US CDC | Vaccine product profile, Vaccination and Coverage, Programme monitoring and Impact assessment, Research capacity and application |
| Manoj K. Das | INCLEN Trust International | Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management |
| Myriam Henkens | Médecins Sans Frontières | Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management, Programme monitoring and Impact assessment |
| Mark LaForce | Independent consultant | Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management, Research capacity and application |
| Nihal Abeysinghe | WHO SEARO | Health and Immunization Systems, Vaccine product profile, Programme monitoring and Impact assessment |
| Niyazi Cakmak | WHO EURO | Health and Immunization Systems, Social determinants of vaccination & Communication, Vaccination and Coverage, Programme Management |
| Nonhlanhla Dlamini | Department of Health, South Africa | Social determinants of vaccination & Communication, Vaccination and Coverage, Cold chain and logistics management, Programme Management |
| Nehemie Mbakuliyemo | WHO AFRO | Health and Immunization Systems, Social determinants of vaccination & Communication, Vaccination and Coverage, Programme Management |
| Pritaporn Kingkaew | Health Intervention and Technology Assessment Program, Department of Health, Thailand | Social determinants of vaccination & Communication, Vaccine product profile, Programme monitoring and Impact assessment, Research capacity and application |
| Pem Namgyal | WHO SEARO | Health and Immunization Systems, Vaccine product profile, Vaccination and Coverage, Programme Management |
| Paba Palihawdana | Ministry of Healthcare and Nutrition, Sri Lanka | Health and Immunization Systems, Programme Management, Programme monitoring and Impact assessment |

| | | |
|---|---|---|
| Rajendra Bohara | WHO SEARO | Social determinants of vaccination & Communication, Vaccine product profile, Vaccination and Coverage, Programme monitoring and Impact assessment |
| Rana Hajjeh | US CDC | Vaccination and Coverage, Programme monitoring and Impact assessment, Research capacity and application |
| Robert Steinglass | Maternal and Child Health Integrated Program, USA | Health and Immunization Systems, Social determinants of vaccination & Communication, Cold chain and logistics management, Programme Management |
| Renato Valenzuela | National Autonomous University of Honduras | |
| Shams Al Arifeen | International Centre for Diarrhoeal Disease Research, (icddr,b) | Health and Immunization Systems, Vaccination and Coverage, Programme monitoring and Impact assessment |
| Salah Al Awaidy | Ministry of Health and Social Welfare, Oman | Health and Immunization Systems, Cold chain and logistics management, Programme monitoring and Impact assessment, Research capacity and application |
| Shahin Huseynov | WHO EURO | Vaccination and Coverage, Programme Management, Programme monitoring and Impact assessment |
| Sudath Peiris | Ministry of Healthcare and Nutrition, Sri Lanka | Vaccine product profile, Vaccination and Coverage, Cold chain and logistics management, Programme Management, Research capacity and application |
| Theresa Diaz | UNICEF | Social determinants of vaccination & Communication, Vaccination and Coverage, Programme monitoring and Impact assessment, Research capacity and application |
| Vusala Allahverdiyeva | WHO EURO | Vaccination and Coverage, Cold chain and logistics management, Programme Management, Programme monitoring and Impact assessment |
| Yot Teerawattananon | Health Intervention and Technology Assessment Program, Department of Health, Thailand | Social determinants of vaccination & Communication, Programme Management, Programme monitoring and Impact assessment, Research capacity and application |
| Zulfiqar Ahmed Bhutta | The Aga Khan University, Pakistan | |

**Annex 2: Prioritization criteria**

Each criterion was assigned the following response levels:

**Yes/No:** The rater is *sufficiently informed* to assess and score the research question as "Yes" or "No"
**Not sure (Maybe):** The rater is *sufficiently informed* to assess and score the research question, but *cannot decide* "Yes" or "No"
**Don't know:** The rater feels that s/he is *not well informed* to assess the research question on the criterion. In these cases, raters were instructed to leave the response as *blank* ("not rated" in the online surveys). Don't know responses were treated as missing data and removed from the calculation of scores (see sections 2.4 and 2.5).

| Description of category | Specific criteria | Weights assigned to response levels |
|---|---|---|
| **1. Appropriateness**<br>The purpose of this category is to determine if the proposed research is well suited to the target population and if it duplicates past studies or addresses knowledge that is known already.<br>The key question is "Should we do it?" | 1.1. Would you say there is a significant knowledge gap on this issue to be addressed by research? | Yes = 12.0%<br>Not sure = 6.7%<br>No = 0% |
| | 1.2. Do you think that a study to answer the proposed research question can be conducted in an ethical fashion? | Yes = 14.9%<br>Not sure = 9.1%<br>No = 0% |
| **2. Relevance**<br>The purpose of this category is to make sure that the proposed research is of the right kind for the right people, is pertinent to the health problems and immunization issues of the population/community and also addresses the equity issues.<br>The key question is "Why should we do it?" | 2.1. Would you say that the size and/or severity of the problem being addressed by the proposed research is significant?<br>*(An indicator of significance of the size and severity of the problem may be any of these: burden of the disease, disability, years of potential life lost, disability-adjusted life years, economic burden, social burden, contribution to low coverage, difficulties in introducing new vaccines, etc.)* | Yes = 9.9%<br>Not sure = 5.1%<br>No = 0% |
| | 2.2. Do you think the proposed research can respond to the population needs and national or global health policies or goals? | Yes = 12.2%<br>Not sure = 7.3%<br>No = 0% |

| | | |
|---|---|---|
| | 2.3. Do you think the proposed research can contribute to greater equity in immunization? *(Indicator of equity may be on any, or a combination, of these factors: socio-demographic, economic, health service access/delivery, gender, etc.)* | Yes = 11.9%<br>Not sure = 6.6%<br>No = 0% |
| **3. Chances of success**<br>The purpose of this category is to evaluate the possibility and feasibility of undertaking the proposed research considering the resources (technical, financial) available and timeframe.<br>The proposed research is to be evaluated within the specific context (low and middle income countries) and a time frame of 5 years.<br>The key question is "Can we do it?" | 3.1. Is it possible to design a study to appropriately answer the proposed research within the specific context and time frame (as defined above)? | Yes = 9.2%<br>Not sure = 5.4%<br>No = 0% |
| | 3.2. Do you think the endpoints of the proposed research are likely to be achieved, i.e., results will be available, within the specific context and time frame (as defined above)? | Yes = 6.8%<br>Not sure = 4.2%<br>No = 0% |
| **4. Impact of the research outcome(s)**<br>The purpose of this category is to estimate the benefit of using or implementing the proposed research results by assessing their potential merit and usefulness.<br>The key question is "What benefit will be achieved?" | 4.1. Do you think that the proposed research is likely to produce knowledge that will lead to affordable and sustainable interventions and/or policies? | Yes = 11.0%<br>Not sure = 6.2%<br>No = 0% |
| | 4.2. Do you think that the proposed research is likely to produce knowledge that will lead to any or all of the following: improved coverage, improved quality of immunization services, improved new vaccine introduction, or improved policy/decision-making? | Yes = 12.3%<br>Not sure = 6.2%<br>No = 0% |

Draft: 14 October 2013

# CONSIDERATIONS FOR THE TIMING OF A SINGLE DOSE OF IPV IN THE ROUTINE IMMUNIZATION SCHEDULE

## INTRODUCTION

In May 2012, the World Health Assembly declared the completion of polio eradication to be a global public health emergency and called for the development of a comprehensive polio endgame strategy. In response, the *Polio Eradication and Endgame Strategic Plan 2013-2018* was developed.

This plan contains four objectives, and objective 2 outlines the activities and timelines necessary to strengthen routine immunization, introduce at least one dose of inactivated poliovirus vaccine (IPV) into routine immunization schedule, and withdraw Sabin type 2 strains for the oral poliovirus vaccine (OPV).

The subsequent SAGE meeting (November 2012) recommended that all country should introduce at least one dose of IPV, prior to the OPV2 cessation, in order to a) prevent polio if exposed to a VDPV2 or WPV2, b) improve response to mOPV2 in an outbreak, c) reduce transmission of a reintroduced type 2, and d) boost immunity to WPV1 & 3[1].

This communication provides the key elements and supporting scientific data for the timing of the IPV dose.

## GENERAL CONSIDERATIONS

There are a number of general considerations that may influence policy decisions for poliomyelitis prevention.

Schedule: The vast majority of OPV-using countries use one of three routine schedules: DTP/OPV at age 6, 10 and 14 weeks (AFRO and some Asian countries); at age 2, 3, and 4 months (China, Indonesia), or at age 2, 4, and 6 months (mostly PAHO, but also Bangladesh) [2, 3].

OPV immunogenicity: The immunogenicity of OPV varies greatly between industrialized and developing countries [3]. Even within developing countries, the immunogenicity of OPV shows major differences. For example, Northern India has very low immunogenicity [4-6], other tropical countries, such as Thailand [7] and Indonesia [8], have high immunogenicity.

In those countries with low immunogenicity, OPV is not “effective” in a substantial proportion of children until later doses in the series are given. This is in contrast to industrialized countries where much higher seroconversion rates are achieved with the initial dose of OPV.

Vaccine-associated paralytic poliomyelitis: No standardized global surveillance system exists for vaccine-associated paralytic poliomyelitis (VAPP), although countries may detect VAPP cases as part of their acute flaccid paralysis (AFP) surveillance system. Given the complexities of VAPP diagnosis

and classification [9], additional follow-up and review by national expert classification committees is necessary, and consequently, most data on VAPP come from industrialized countries.

Maternally-derived antibody: Newborns from many currently- OPV-using developing countries have a high prevalence of maternally-derived antibody against poliovirus [10-14] because their mothers are relatively more likely to have had recent exposure to wild poliovirus and/or OPV viruses.

**SPECIFIC CONSIDERATIONS FOR THE TIMING OF AN ADDITIONAL IPV DOSE**

Two considerations represent critical factors with respect to decisions about the timing of an additional IPV dose to the existing national OPV schedule: (1) Immunogenicity of IPV at possible age / schedule; and (2) coverage & drop out between DTP1-DTP3 Some countries have been concerned about VAPP as well in their decision making about IPV.

However, in the context of the new endgame strategy, there is a clear hierarchy for policy decision-making. Although VAPP and coverage & drop-out rates may be important in some countries, the over-riding objective is to ensure that the "highest possible immunity" can be achieved with the single additional dose of IPV, given in the context of an "unchanged OPV routine schedule", strictly additional to, and simultaneous with the OPV dose.

Immunogenicity: In general, the immunogenicity of IPV is inversely related to levels of maternally-derived antibodies [7, 14, 15]. In terms of seroconversion, early IPV administration at 6-8 weeks of age results in lower seroconversion rates [10]. Reviews of limited existing scientific data, a dose of IPV seroconverts between 32-39% against poliovirus type 2 at age 6-8 weeks, compared with 63% at age 16 weeks [3, 16, 17]. In terms of priming, one study of IPV birth dose administration in Israel provides limited evidence that IPV administered at birth is apt to induce immunologic memory, [18],

In Cuba, 98% of 4-month old infants in Cuba that didn't previously seroconvert with OPV responded with a priming immune response with one dose of IPV [16].

**Please note that the additional IPV dose would be co-administered with OPV and DTP at the selected age.*

*Interpretation: A dose of IPV given at older age (14-16 weeks)appears to induce almost double the seroconversion rate compared with an early dose (6-8 weeks).*

Coverage & drop out between DTP1-DTP3: Program evaluation data suggest that coverage varies by WHO Region, with the lowest in AFRO, and the highest in EURO, WPRO and PAHO. Drop-out rates between DTP1-DTP3 show similar patterns. Improving routine immunization coverage is a long-term health system development priority, as well as a key priority in the new Strategic Plan for Polio Eradication, 2013-2018 [18]. During the period, 2009-2011, only three countries had massive drop-out rates >35% between DTP1-DTP3 (Chad, Equatorial Guinea & Gabon), and the vast majority of countries had drop-out rates below 10% [WHO web].

*Interpretation: Drop-out rates from DTP1-DTP3 do not constitute a major consideration with respect to the timing of the introduction of an additional IPV dose to a national immunization schedule.*

Vaccine-associated paralytic poliomyelitis: Our review of VAPP suggests different epidemiology for developing and industrialized countries. In industrialized countries, VAPP occurs primarily in early

infancy associated with the first dose of OPV. In contrast, in some developing countries, VAPP is associated with subsequent doses of OPV, with the age distribution concentrated among 1-4 year old children [20]. This difference in epidemiology most likely reflects the low immunogenicity of OPV in some tropical developing countries [4-6], which delays the actual immunizing dose to later in life [20, 21], and the prevalence of maternally-derived antibody in recently polio-endemic countries, which also impedes OPV vaccine "takes".

In Iran, a total of 12 cases of VAPP were reported between 2005-present, with an age distribution of ≥5-25 months, mostly among immunodeficient individuals, and associated with Sabin type 2 (97%) (personal communication, Shahmahmoodi, 2013; data shared with SAGE WG).

In India, further analysis suggested that <10% of VAPP cases occur prior to age 12 weeks. The most recent analysis refined this estimate to only 6.4% of VAPP cases occurring before age 12 weeks. Data from India [21, and unpublished data] and Iran [personal communication, S Shahmahmoodi, 2013] suggest that early IPV administration (age 6-8 weeks) would only further decrease the risk of VAPP by <10% compared with later IPV administration (age 14-16 weeks).

Countries that adopted sequential schedules using IPV followed by OPV rapidly eliminated VAPP, and introducing IPV as a first dose offers the greatest potential to reduce VAPP, as long as interference with maternal antibodies does not impact take rates for IPV. Theoretically, in developing countries, 25-40% of VAPP could be prevented by OPV2 withdrawal, although uncertainty remains about the actual magnitude of the change.

For OPV-using countries with a documented VAPP age distribution similar to that of industrialized countries, early administration of IPV (age 6-8 weeks) or a sequential schedule of IPV followed by OPV may represent the best option. For example in Thailand, 55% (6/11) of VAPP cases reported during 2001-2012 followed the administration of the first dose of OPV ; and a further 18% (2/11) followed the administration of a second dose of OPV [personal communication, Dr Piyanit, MOH/Thailand]. For countries with distribution of VAPP cases that occur at relatively older ages, later introduction of IPV will most likely offer the best chance of minimizing the impact of maternal antibodies and increasing take rates.

*Interpretation: OPV administration (delayed to age14-16 weeks) should prevent the vast majority of VAPP (>90%) in most tropical developing countries. However countries with a demonstrated VAPP burden following the first dose of OPV may wish to consider relatively earlier introduction of IPV.*

**PROPOSED RECOMMENDATIONS**

Given these considerations, weighting the evidence, and quantifying the trade-offs, the SAGE WG made the following preliminary recommendations during their October 2013 meeting (to be endorsed by the full SAGE in November 2013):

- *All countries should introduce at least one dose of IPV into their immunization schedules by the third quarter of 2015.*
- *In OPV-only using countries which are introducing one dose of IPV, IPV should be administered in addition to the 3-4 doses of OPV in the primary series. The dose should be administered during the immunization contact at or after 14 weeks.*

- *The timing of the IPV dose is as follows:*
    - *6, 10, 14 weeks or 2, 3, 4 months schedule: add IPV dose at the DPT3/OPV3 (or OPV 4 in countries administering a birth dose of OPV) contact;*
    - *2, 4, 6 months schedule: add IPV dose at the DPT3-OPV3 contact (although the DPT2-OPV2 can be considered).*
- *For children starting the routine immunization schedule late (age >14 weeks) the IPV dose should be administered at the first immunization contact. The minimum age for IPV is 14 weeks.*
- *When communicating this recommendation, the following should be highlighted:*
    - *IPV is an additional dose to OPV and not a replacement (the combined schedule gives the optimal immunity);*
    - *The primary :purpose of IPV introduction is to mitigate the cVDPV type 2 following OPV2 withdrawal (it will also prevent VAPP due to OPV types 1 and 3.);*
    - *The immunization visit in which DTP3 and OPV3 (OPV4 if there is a birth dose) are administered was selected over DTP1/OPV1 because of the gains in immunogenicity of IPV at 14 weeks compared to earlier administration. The later visit gives time to allow decrease in the levels of maternally-derived transplacental polio antibodies in the infant, which can interfere with an immune response to IPV; and*
    - *The potential risk of an IPV only schedule should be explained to any country considering such a change (including the evidence from Israel, an IPV only using country, of prolonged transmission of wild poliovirus type 1 probably related to the inferior intestinal immunity IPV induces compared to OPV)*

Countries with documented VAPP risk prior to 4 months of age may decide to consider alternative schedules as outlined in the previous WHO position paper [22].

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**BRIEFING NOTE**

*for*

**DONOR MEETING ON IPV FINANCING**

London | September 10, 2013

**Updated 11 October for sharing with SAGE members**

*Note: a full set of the background materials that were shared with donors in early September can be found online at [http://tinyurl.com/IPV-Donor-Meeting](http://tinyurl.com/IPV-Donor-Meeting)*

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Since mid-April 2013, GAVI and GPEI have been working together through the Immunization Systems Management Group (IMG), utilizing their complementary strengths to ensure that the IPV introduction as well as existing vaccine introduction plans for other vaccines-- including those supported by GAVI-- can be achieved. The IMG's work has also focused on the broader objective 2 of the Endgame strategy and includes opportunities to strengthen routine immunisation services, through the use of polio human resources and through greater coordination between polio, GAVI and routine immunization programmes.

As the group responsible for the management and coordination of partners' activities to achieve Objective 2 of the Polio Eradication Endgame Strategic Plan 2013-2018, the IMG's work focuses on the following:

- Introducing IPV
- Withdrawing OPV2 from Routine and Supplementary Immunization Activities
- Ensuring the availability of appropriate IPV and bOPV products
- Increasing immunization coverage in 10 GAVI and WHO/UNICEF focus countries *(Afghanistan, Chad, the Democratic Republic of the Congo (DRC), Ethiopia, India, Nigeria, Pakistan, Somalia, South Sudan, Angola)*
- Ensuring clear recognition and understanding of the rationale for and urgency of the Endgame and the Objective 2 activities across their respective agencies

In preparation for the IPV donor meeting, a series of working meetings had been held to more clearly articulate points of alignment, and define how to best work together to deliver on shared mandates most efficiently and effectively. Central in these discussions was the definition of the appropriate coordination and accountability mechanisms to support IPV implementation. The partners also sought to understand the incremental investments and changes to current operating models that would need to be made in order to ensure currently planned activities and vaccine introductions aren't derailed.

The outcomes of these discussions include decisions on how to tackle each of the key priority issues for both GAVI and non-GAVI countries, through the coordinating mechanism of the IMG: **jointly** *(in which activities are implemented through a single process, with one partner serving as 'lead')*, in a **coordinated fashion** *(activities are implemented separately, but with regular discussion and collaboration)* or s**eparately** as indicated in the table below:

| Topic | GAVI Countries | Non-GAVI Countries |
|---|---|---|
| **Demand forecasts** | Joint | Coordinated |
| **Supply** | Joint | Coordinated |
| **Procurement** | Joint | Coordinated |
| **Regulatory** | Joint | Separate |
| **Implementation / TA** | Joint | Coordinated |
| **Communications & programmatic reporting** | Coordinated, often joint | Coordinated |
| **Financial projections** | Coordinated | Coordinated |
| **Financial flow** | Coordinated | Separate |
| **Financial reporting** | Separate | Separate |

A series of background documents summarizing the current state of plans for IPV introduction have been made available for your review, along with some more general documents—such as the IMG workplan—which highlight the inter-linkages between IPV introduction and the other Endgame objective 2 workstreams.

These documents are works in progress, and will evolve as more information becomes available and further planning is completed. Nonetheless, they highlight the progress that has been made since the IMG was established , providing a venue for the expertise in GAVI and GPEI to collaborate on key areas such as planning for country introduction, revising policies, and issuing a strategic demand forecast.

These background documents are summarized in the next pages, and their full versions can be accessed online at: http://tinyurl.com/IPV-Donor-Meeting.

## 1. Background on the IMG and its workstreams

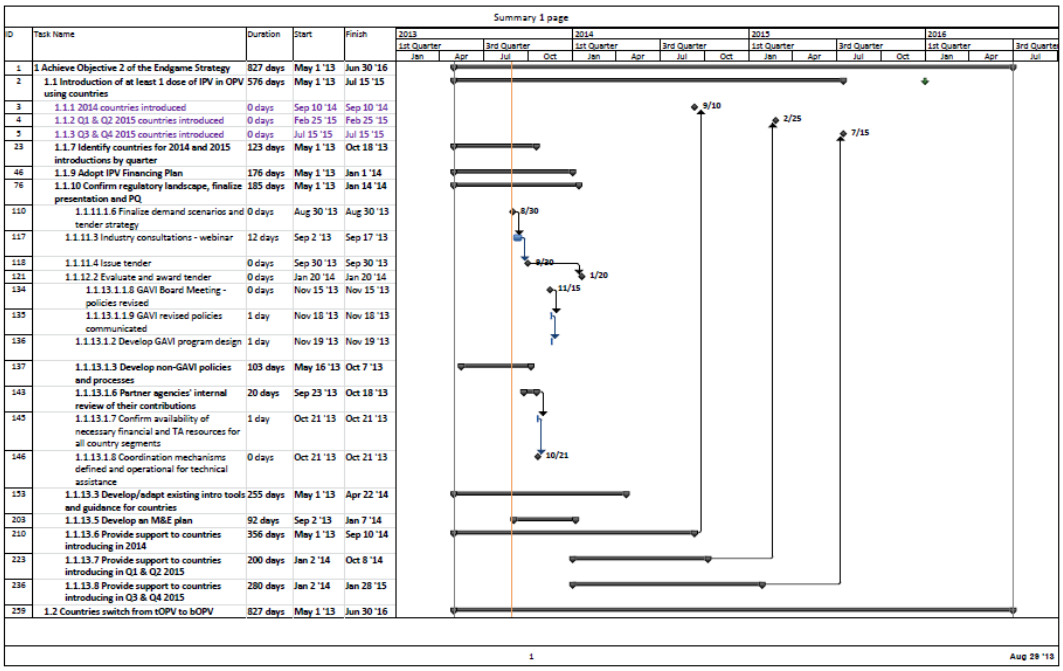
(Full document title: 1_IMG and its workstreams.pdf)

The IMG is comprised of representatives from both the polio program and routine immunization program from each of the GPEI core partners: WHO, UNICEF, BMGF, Rotary, and US-CDC, with the addition of the GAVI Secretariat. UNICEF and WHO regional offices are also invited to participate in IMG calls. The IMG is co-chaired by WHO and UNICEF on a rotating basis. While other key groups such as NGOs and implementing partners are not core members of the GPEI partners group and are not represented on the IMG, their input is critical. Discussions are on-going to determine what form and level of representation would be useful. The IMG has five sub-groups, each representing an IMG workstream. These include: Regulatory issues, Implementation (including country readiness, supply and demand), Financing, Communications and Routine Immunization Strengthening.

## 2. Current draft of the IMG Workplan

(Full document title: 2_Summary IMG Workplan.pdf. *Note that the workplan prints best in A3 or 11X17"*)

The IMG has through its sub-groups and workstreams developed a workplan to address objective 2 of the Endgame strategy. This is the guiding document for the IMG activities and serves as a key tool for coordination of all partner efforts. This workplan, which is still under refinement and development, outlines key activities that need to be completed and shows linkages between them. A five-page version of the workplan provided gives a highlights view, which shows the key tasks and deliverables, and their targeted start and completion dates. The complete workplan is available upon request from the IMG.



### 3. Preliminary IPV Financing Plan

(Full document title: 3_Preliminary IPV Financing Plan.pptx)

The IMG is working to develop financing plan for the Endgame's Objective2, and particularly the investments necessary to facilitate rapid uptake of IPV in line with Endgame timelines in a cost effective manner. The IMG is working to develop an estimate of total costs for IPV introduction, with appropriate financing plans for all 124 countries, which can be incorporated into the Endgame budget for 2014-2018. The technical support line includes the IMG's estimate of the costs associated with introducing IPV intro.

| | GAVI Countries | India and China | PAHO (non-GAVI) | Other LMICs | UMICs/HICs |
|---|---|---|---|---|---|
| **Vaccine** | Full support for vaccines priced at a range encompassing $1/dose | Assumed to self-finance | Potential subsidy ranging from $0.00 to $0.75 per dose on average | Potential subsidy ranging from $0.00 to $1.00 per dose | Potential subsidy ranging from $0.00 to $0.50 per dose |
| **Introduction needs** | Introduction grants of $0.80 per child or $100K | Assumed to self-finance | N/A | N/A | N/A |
| **Technical support** | WHO, UNICEF, GAVI secretariat and/or IMG direct costs to support IPV introduction, as well as technical assistance to countries and regions based on prioritization according to tiers and need.<br>Estimates range from $40M to $60M for 2014-2018. | | | | |
| **Funding flows** | GAVI | N/A | UNICEF SD or PAHO revolving fund* | UNICEF SD* | UNICEF SD* |

Based on the plans outlined on the previous slide, the estimated total costs for IPV during the period 2014-2018 ranges from **$328M to $449M,** which equates to roughly 6 to 8% of the total Endgame budget**.** The breakdown of costs is as follows:

- Vaccine costs (GAVI countries): $230M to $294M
- Subsidies (Non-GAVI): $22M to $54M
- Introduction grants (GAVI): $36M to $41M
- Tech. support & partner costs[1]: $40M to $60M

The initial cost projection for IPV introduction in the Financial Resource Requirements (FRRs) accompanying the Polio Eradication & Endgame Strategic Plan was $322 million (including vaccine costs, introduction grants and subsidies). This is consistent with the lower end of the cost range estimate

- [1]Approximately 78% ($31M-47M) is anticipated for support to GAVI countries (through the Business Plan) according to % of total IPV doses going to GAVI countries

above. The increase to arrive at the upper end of the cost range estimate is due to a combination of the higher number of doses / more rapid uptake (as per the "ideal" demand scenario), higher vaccine price assumptions, higher subsidy assumptions, and full application of the introduction grant to GAVI-eligible and GAVI-graduating countries. The estimated requirements for technical support and partner costs can be accommodated within the "ongoing quality improvement" budget line in the FRRs.

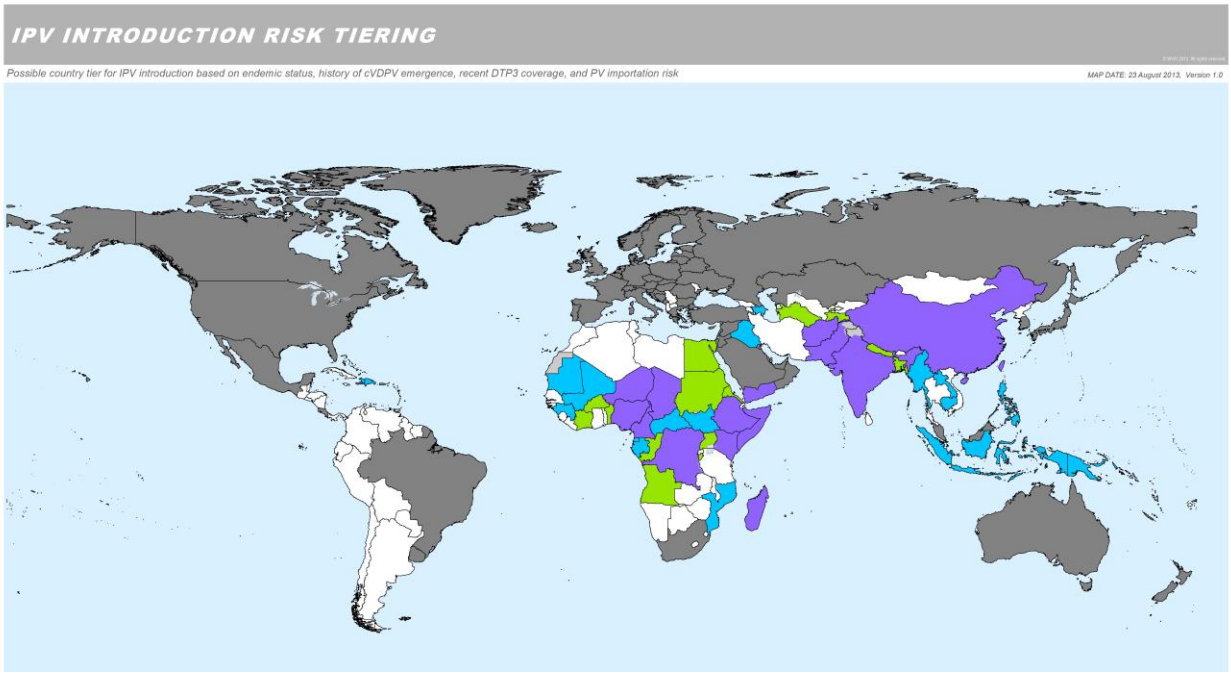
**Update Note :** At the London meeting, donors confirmed their agreement in principle to support this effort. They have requested more details on the budget- the IMG is in the process of providing these details

### 4. Country Tiering

(Full document titles: 4a_Risk Tiers for IPV Introduction.pdf and 4b_Map of Risk Tiers for IPV introduction.jpg)

In November 2012, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended that all countries should introduce at least 1 dose of IPV in their routine immunization program to mitigate the risks following the withdrawal of OPV2. Because IPV introduction is a risk mitigation strategy, the IMG has established criteria to identify countries at the highest risk of a cVDPV2 outbreak and importations following OPV2 cessation. In order to highlight countries where the risk is greatest, and prioritize efforts and focus, the 124 OPV-only using countries have been grouped into four tiers, with Tier 1 countries being at the greatest risk, and Tier 4 countries at the lowest risk level. These are depicted on the map and defined below.

**Update Note:** The Tiering will be used by the IMG and the implementing partners to guide the level of technical assistance, communication and advocacy efforts required to support IPV introduction. However all four tiers countries are encouraged to introduce IPV by the end of 2015.

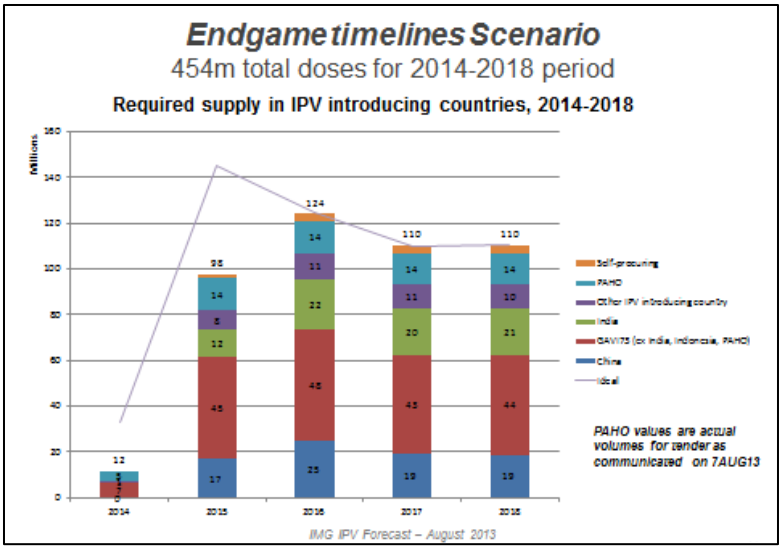


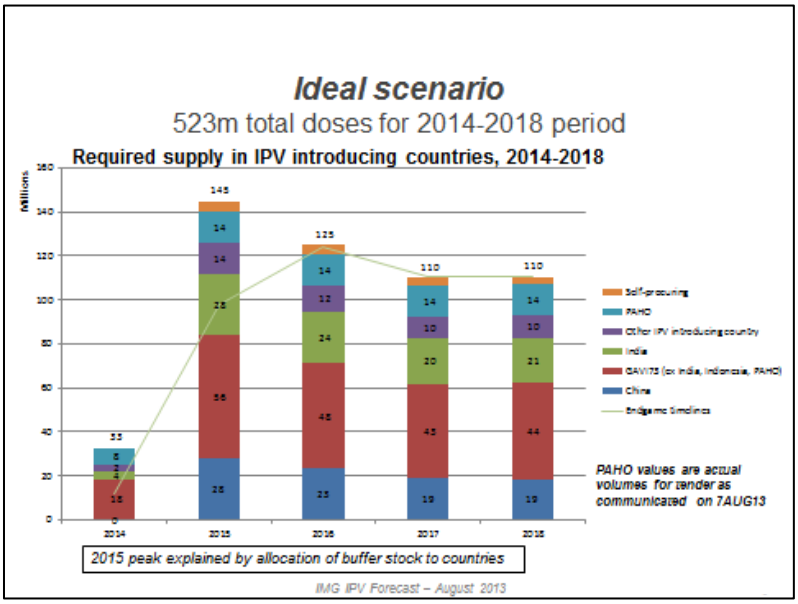

| Tier Definitions: | | |
|---|---|---|
| **Tier 1** | | WPV endemic countries OR countries that have reported a cVDPV2 since 2000[1] |
| **Tier 2** | | Countries who have reported a cVDPV1/cVDPV3 since 2000[1]<br>OR large/medium[2] sized countries with DTP3 coverage <80% in 2009, 2010, 2011 as per WUNIC |
| **Tier 3** | | Large/medium[2] countries adjacent to Tier 1 countries that reported WPV since 2003<br>OR countries that have experienced a WPV Importation since 2011 |
| **Tier 4** | | All other OPV only using countries |

## 5. DRAFT Strategic Demand Forecast; IPV Supply and Procurement

(Full document title: 5_IPV DRAFT Strategic Demand Forecast.pdf)

The IMG IPV Strategic Demand Forecast scenarios- which covers all 124 OPV using countries - was developed jointly by GAVI and GPEI through the IMG. It represents an initial view into demand to inform financial resource requirements, supply and procurement Roadmap development and IPV tender strategy. Forecasts were generated only through global-level discussions with partners; future iterations will be refined with country input. Two scenarios are described—the Endgame timelines scenario, which requires 454 million doses of IPV by 2018, and the Ideal scenario, which requires 523 million doses of IPV by 2018. The difference between them is the rate of uptake/introduction by countries. Both scenarios, however, are highly ambitious, representing an unprecedented scaling-up requiring effective and clear communications with countries, streamlined financing, technical assistance and procurement processes. These scenarios are described below:



GAVI and GPEI are also working closely together to anticipate supply and procurement-related aspects of IPV introduction. Work is underway to ensure appropriate supply availability for the coming years, inform procurement activities in Q3/Q4 2013, obtain acceptable price conditions for IPV, and strengthen the development of a long-term sustainable market adaptable to Endgame requirements. Further materials are anticipated to be available on IPV supply and procurement in the coming weeks. **Update**

**Update Notes:**

- The forecast will continue to be refined as more clarity is received on the intent of countries, on the vaccine presentations available (and therefore the expected levels of wastage)
- On 4 October, UNICEF issued a tender for IPV on the basis of the above demand forecast. It will close on 15 November and awards will be made in early 2014.

### 6. DRAFT GAVI policy considerations for support to IPV

(6_GAVI policy considerations for support to IPV DRAFT.pdf)

The GAVI Board has indicated its support to "the GAVI Alliance playing a lead role in the introduction of IPV into routine immunisation services in 73 GAVI countries as part of the Polio Eradication Endgame Strategy and Plan in collaboration with GPEI. Consistent with previous Board decisions, the GAVI Alliance should work with countries using GAVI's structures, policies and processes where possible."[2]

This document provides an overview of GAVI's policy objectives and issues related to its support for the introduction of inactivated polio vaccine (IPV). It recommends where exceptions to current policies may be required given the unique nature of the activities and challenges represented by the Endgame. Finally, it outlines policy-related risks to GAVI associated with its participation in IPV introduction as well as risks to the Endgame from GAVI's policy choices. The document is a working draft, which will be provided to the GAVI Executive Committee on 27 September 2013 for guidance, to GAVI's Programme and Policy Committee in October, and to the GAVI Board for decision in November.

An analysis is also underway by the GAVI Secretariat in consultation with partners, considering the design of processes such as country application and review mechanisms. The purpose is to plan for opening a window of support for GAVI-eligible countries, depending on the GAVI Board decision in November, in late Q4 2013.

### 7. DRAFT IPV Financing strategy for non-GAVI countries

(Full document title: 7_Draft IPV Financing Strategy for non-GAVI countries.pdf)

Work is in the early stages in order to address the following: (1) which countries would receive a subsidy and/or introductory grant for IPV adoption, (2) the appropriate subsidy and/or introductory grant amount by type of country, and (3) given those subsidy and introductory grant levels, the likelihood of non-GAVI country adoption of IPV.

[2] GAVI Alliance Board, "Review of Decisions", 11-12 June 2013.

The current thinking is that non-GAVI countries should be grouped by a combination of World Bank income level (e.g., LMIC, UMIC, etc., as determined by 2012 GNI per capita) and IPV pricing/procurement mechanism (i.e., PAHO countries).

Work is ongoing on a number of key assumptions to establish a range of potential costs for the introduction of IPV in non-GAVI countries. Current thinking is as follows:

### 8. Technical Rationale for IPV introduction

(Full document title: 8_Technical Rationale for IPV introduction.pdf)

This document highlights the technical and scientific rationale for introducing a dose of IPV in all OPV using countries. Key points include:

1. IPV by inducing immunity to type 2 will facilitate outbreak control with mOPV2 should type 2 viruses be reintroduced.
2. IPV in conjunction with withdrawal of type 2 virus from tOPV will boost immunity to types 1 & 3 which should hasten eradication of types 1 and 3 wild polioviruses and reduce polio disease caused by types 1 and 3 cVDPVs.
3. IPV induces immunity in a proportion of children which will protect them against polio caused by vaccine viruses and polio caused by wild poliovirus
4. IPV in conjunction with bOPV will decrease the number of cases of VAPP caused by types 1 & 3.
5. While the higher the IPV coverage the better, even low coverage will provide direct benefit to those vaccinated and greatly facilitate building population immunity in an emergency response.

### 9. DRAFT FAQs on IPV introduction

(Full document titles: 9a_General FAQ on IPV Introduction.docx; 9b_Technical FAQ for countries on IPV introduction.docx)

A set of two documents, the FAQ sheets provide answers to common questions around IPV introduction and the tOPV/bOPV switch. The first document is a more general FAQ, while the second answers country specific questions on introduction, such as the types of vaccine presentation available, anticipated schedule and avenues for financial and technical support. These FAQs are still under development and are presented as DRAFT documents.

7 - 8 Oct | 2013

# 7th Meeting of the SAGE Polio Working Group

## Note for the Record

World Health Organization

**DRAFT AS OF 10/21/13**

# Executive Summary

The seventh meeting of the SAGE Polio Working Group (WG) was held on 7-8 October 2013. The WG reviewed the plans to rapidly introduce IPV and prepare for potential cVDPV type 2 outbreaks following OPV2 cessation. The major conclusions of the WG are briefly outlined in this summary. A full review of the evidence and rationale for each decision are explained in this report.

**The WG recommendation for the IPV schedule is:**

- That all OPV-only using countries should introduce at least one dose of IPV into their immunization schedules by the third quarter of 2015.
- That IPV should be administered in addition to the 3-4 doses of OPV in the primary series. The dose should be administered during an immunization contact at or after 14 weeks.
- Example timing of the IPV dose is as follows:
    - 6, 10, 14 weeks or 2, 3, 4 months schedule: add IPV dose at the DPT3/OPV3 contact; or
    - 2, 4, 6 months schedule: add IPV dose at the DPT3-OPV3 contact (although the DPT2-OPV2 can be considered).
- For children starting the routine immunization schedule late (age > 3 months) the IPV dose should be administered at the first immunization contact.
- When communicating this recommendation, the following should be highlighted:
    - IPV is an additional dose to OPV and not a replacement (the combined schedule gives the optimal immunity);
    - The *primary* :purpose of IPV introduction is to mitigate the cVDPV type 2 following OPV2 withdrawal (it will also prevent VAPP due to OPV types 1 and 3.);
    - The immunization visit in which DTP3 and OPV3 (OPV4 if there is a birth dose) are administered was selected over DTP1/OPV1 because of the gains in immunogenicity of IPV at 14 weeks compared to earlier administration. The later visit gives time to allow decrease in the levels of maternally-derived transplacental polio antibodies in the infant, which can interfere with an immune response to IPV; and
    - The potential risk of an IPV only schedule should be explained to any country considering such a change (including the evidence from Israel, an IPV only using country, of prolonged transmission of wild poliovirus type 1 probably related to the inferior intestinal immunity IPV induces compared to OPV)

**In regards to the global IPV supply, financing and introduction strategy:**

- The WG applauds the collaboration between WHO, UNICEF, GAVI, and partners to create a comprehensive plan for the introduction of IPV. The WG is particularly encouraged by:
    - The commitment from GAVI to support rapid IPV introduction by adapting their policies to align with the timeline of the Polio Endgame.
    - The commitment from donors to allocate funds specifically for IPV; and
    - The extensive work done by the GPEI Immunization Systems Management Group (IMG) and its subgroups on country prioritization, demand forecast, financing, readiness for introduction, and planning.
- The WG recommends GPEI to continue the research to assess the feasibility of innovative and cost-saving IPV approaches (intradermal delivery, adjuvant, and product optimization) to ensure access to affordable IPV in the mid- to long-term, given the continuing concern over the price of IPV.
- The WG endorses the methodology of tiering countries, based on VDPV and wild virus importation risks, for focusing urgent technical support, but reinforces that introduction by the end of 2015 is essential in all four tiers (see annex 1).
- Recommends that all Tier 1 and 2 countries should have a detailed plan for IPV introduction by mid-2014 to facilitate global IPV supply and risk management; furthermore, all remaining countries should have such a plan for IPV introduction by end-2014.
- The WG encourages early IPV introduction in the remaining wild poliovirus endemic countries as part of the broader contingency planning for the accelerated interruption of wild poliovirus.

- The WG encourages a WHA resolution in 2014 on accelerated IPV introduction due to the tight timelines for global IPV introduction; this resolution is supported by evidence for sufficient global IPV supply and a financing strategy for introduction and use through 2018.

**In regards to the global bOPV access strategy**

- The WG endorses the strategy that has been developed to ensure sufficient quantities of bOPV. This strategy includes:
  (i) Label-change of bOPV products to allow for use in routine immunization (currently bOPV is for campaign use only) from all OPV suppliers
  (ii) Assuring that international suppliers are able to produce sufficient bOPV supply to meet the global demand
  (iii) Supporting countries that rely on domestic producers to rapidly develop, license and produce sufficient bOPV
  (iv) Registering bOPV in all OPV-using countries (for routine immunization use)
- The WG notes the continued importance of conducting mass campaigns with tOPV to increase type-2 population immunity prior to the switch from tOPV to bOPV for routine immunization globally.
- The WG supports a WHA resolution in 2015 on type-2 cessation (target date is 2016).

**On the development of a post-cessation type 2 virus response strategy**

- The WG recommends that the draft protocol for responding to a type 2 poliovirus detection and/or outbreak in the post-OPV2 era should consist of the following 5 major components: notification requirements for all type 2 viruses (including Sabin viruses), enhanced poliovirus surveillance activities (including expanded environmental surveillance), an mOPV2 stockpile and IPV emergency reserve capacity, outbreak/virus response protocols, and provisions for the vaccination of travelers into and out of any type 2-infected area**.**

**Criteria for assessment and the trigger for OPV cessation**

- To facilitate communications on OPV2 withdrawal with countries, the WG recommends that the programme differentiates between the criteria to determine global readiness for OPV2 withdrawal and the 'trigger' for initiating globally synchronized OPV2 withdrawal.
- The WG recommends the criteria for judging OPV2 withdrawal readiness globally include: the status of introduction of at least 1 dose of IPV into all OPV-using countries, access by all OPV-using countries to a bOPV licensed for routine immunization, implementation of surveillance and response protocols for type 2 poliovirus, completion of global Phase 1 containment activities for all wild poliovirus infectious materials and provisions for the appropriate handling of type 2 residual materials and production sites under GAP3, and GCC affirmation of wild poliovirus type 2 global eradication.
- The WG recommends that the trigger for OPV2 withdrawal would be the evidence for absence of all 'persistent' cVDPV2s for at least 6 months globally.

## Annex 1: IPV Introduction Tier Definitions and Rationale

**Tier 1**: Countries with evidence of ongoing cVDPV2 transmission or cVDPV2 reported since 2000 OR WPV endemic countries

**Rationale**:

→cVDPV2 outbreak is the primary risk following OPV2 cessation

→Potential for IPV to accelerate wild poliovirus eradication by boosting immunity to wild poliovirus types 1 and 3.

**Tier 2:** Countries with any history of cVDPVs (types 1 and 3) since 2000 OR Countries that have repeatedly reported routine immunization coverage estimates of less than 80% over the past three years

**Rationale**:

→Risk factors for VDPV outbreaks are similar for all VDPV serotypes

→Persistent low routine immunization coverage is the most important predictor of VDPV emergence

**Tier 3**: Countries sharing a border with Tier 1 countries that have reported WPV since 2003 OR Countries that have experienced a WPV importation since 2011.

**Rationale**:

→Predicted future risk of cVDPV2 importations, based on trends for importation of wild virus

→Any WPV importation since 2011 (when India eradicated polio) reflects current risk of importation from remaining endemic countries.

**Tier 4**: All other remaining countries using only OPV

Draft: 10/21/2013

# Summary of the Response Strategy to Type 2 Poliovirus in the Post OPV2 Cessation Period

## INTRODUCTION

Detection of poliovirus type 2, whether Sabin, vaccine-derived or wild strain, following cessation of oral polio vaccine type 2 (OPV2), requires a rapid response. In April 2013, SAGE recommended that GPEI work on the perquisites for OPV2 withdrawal, including drafting a protocol to facilitate prompt detection of a type-2 poliovirus from environmental sources or circulating in the population, post-cessation use of live attenuated type-2 poliovirus vaccines and a rapid outbreak response.

This document summarizes the main elements of the strategy to respond to detection of type 2 poliovirus following global cessation of OPV2.

## Post-cessation type II virus response strategy

The basic objectives of the response would be:

1. Prompt detection and notification of all type 2 poliovirus strains;
2. Rapid cessation of poliovirus circulation
3. Limiting exposure of populations to Sabin 2 poliovirus from mOPV 2 used in the outbreak response to prevent emergence of a new cVDPV type 2
4. Validating the absence of poliovirus type 2 in the population and the environment following the outbreak response.
5. Using established mOPV2 and IPV stockpiles for outbreak response under a strict release protocol endorsed by WHA.

The response strategy will comprise the following 5 major components:

- **Detection:**
  Sensitive surveillance will be vital for the programme to rapidly detect any circulating poliovirus and initiate an immediate response.

  Acute flaccid paralysis (AFP) surveillance will remain the primary mechanism for the detection of poliovirus after OPV2 withdrawal. AFP systems are likely to remain strong until global certification (2018).

  In addition, environmental surveillance will be further scaled up as a complement to AFP surveillance for detecting the presence of poliovirus in infected areas and populations. This will facilitate the more rapid identification of outbreaks in high-risk areas, provide additional information to validate the interruption of transmission and help document the elimination of vaccine-related strains after OPV cessation. Recent persistent circulation of wild poliovirus in Israel[1] suggests that WPV transmission can be sustained for several months without being detected in areas with high IPV coverage and local factors that facilitate transmission (e.g., hygiene, temperature, living conditions). This underscores the importance of strengthening environmental surveillance, especially in areas at high risk for cVDPV emergence (e.g., low routine coverage and historical cVDPV cases), and areas where there is risk of silent

[1] Anis E, Kopel E, Singer SR, et al. Insidious reintroduction of wild poliovirus into Israel, 2013. Euro Surveill 2013 Sep 19;18(38):pii=20586

transmission and circulation of poliovirus, including areas in close proximity to vaccine production facilities.

After an outbreak has been stopped, all enhanced surveillance activities will need to be maintained for a minimum of 12 months following the last virus detection.

- **Notification:**
  After withdrawal of OPV2, detection of any type-2 poliovirus (Sabin, vaccine-derived, or wild) will be an urgent notifiable event under the IHR. Notification will trigger an immediate assessment and decision regarding the outbreak response. According to the regulation, any detection of poliovirus type-2 (wild, vaccine-derived or Sabin) in any sample of any provenance should be notified after global cessation of OPV2.

- **Response:** the type and extent of response will be determined by 1) the time since OPV2 withdrawal, 2) the nature of the virus (e.g. wild vs. Sabin virus), 3) geographic location and proximity to high risk communities with immunity gaps and 4) the population characteristics (e.g., underserved, mobile, conflict-affected, history of virus importation).

  **The scale of the response** will be determined by the amount of time passed since OPV2 withdrawal and location (see annex 1). These characteristics will determine the size of the target population and the age of the target population.

  - **The time after OPV2 withdrawal** is important because it is known that mucosal immunity starts to wane 2-3 years after oral polio immunization[23]. While the risk of outbreak declines over time, immunity of the population will also decline after the OPV2 withdrawal (young infants will not have the same level of intestinal immunity to type 2, despite IPV vaccination and older children's intestinal immunity will wane). Therefore, the longer the elapsed time since OPV2 cessation, the larger the scale of response will need to be.

  - **The location of outbreak** will influence the scale of response. Countries with a high risk of poliovirus circulation and importation, such as those with a clear history of sustained WPV and cVDPV transmission ("Zone 1"), or those with consistently low immunization coverage or a history of WPV or cVDPV importation ("Zone 2") will mandate larger responses.

  The outbreak response should utilize both mOPV2 and IPV vaccination to rapidly boost and establish population immunity around the outbreak response zone to prevent the emergence of cVDPV.

  The use of mOPV2 is needed to induce the intestinal immunity among those who have not been vaccinated against type-2 previously. Recent studies have confirmed that IPV can rapidly induce serological immunity[45] and boost intestinal immunity in children previously

[2] Grassly NC, Jafari H, Bahl S, et al. Waning intestinal immunity following vaccination with oral poliovirus vaccines in India. *J Infect Dis. 2012;* 205: 1554-1561.
[3] Estívariz CF, Jafari H, Sutter RW, et al. Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6-9 months in Moradabad, India: a community-based, randomised controlled trial. Lancet Infect Dis. 2012 Feb;12(2):128-35
[4] Moriniere BJ, van Loon FP, Rhodes PH, et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet. 1993 Jun 19;341(8860):1545-50.
[5] Hanlon P, Hanlon L, Marsh V, et al.Serological comparisons of approaches to polio vaccination in the Gambia. Lancet. 1987 Apr 4;1(8536):800-1.

vaccinated with OPV. Therefore, in an outbreak response, IPV will be important adjunct to OPV in limiting transmission.

- **Travelers:**
  Humans are the only reservoir for polioviruses. Therefore, travel and migration patterns have significant impact on the risk and the extent of poliovirus circulation. During a type-2 outbreak, therefore, travel in and out of infected areas will need to be restricted to the largest degree possible; people undertaking essential travel in or out of an infected area should be vaccinated to prevent further spread of poliovirus. Especially, vaccination of travelers out of the infected area with IPV is critical for the risk they pose to the new population.

- **Stockpile**
  GPEI is establishing a 500 million dose stockpile of mOPV2 to be available specifically for outbreak response after OPV2 withdrawal. Use of the stockpile will be regulated by an established release protocol which will be endorsed by the WHA. The release protocol will include criteria and procedures for release of the stockpile (e.g., decision by DG WHO on advice by an expert panel within 48 hours of assessment and recommendation).

  The mOPV2 stockpile will be complemented by an IPV stockpile to facilitate population immunity in infected and surrounding areas and to provide an alternative to mOPV2 as appropriate.

  After OPV2 withdrawal, most OPV suppliers are expected to cease the production of Sabin 2 virus due to the stringent containment requirements for Sabin type 2 and absence of constant demand, so the potential for requesting Sabin-IPV production sites to produce extra mOPV2 stockpile should be explored.

## Next steps

After the discussion at the November 2013 SAGE, GPEI proposes to develop this into a full response protocol for review by the SAGE WG and SAGE in 2014.

Annex 1: Matrix for WPV/cVDPV response after OPV2 cessation (Preliminary Draft)*

| | Zone 1 | Zone 2 | Zone 3 |
|---|---|---|---|
| **Phase 1 (within 3 years of OPV2 withdrawal)** | - Target population (TP) dependent on time & situation<br>- Age group up to 10 years if needed | - TP dependent on situation<br>- Age group up to 5 yrs minimum | - TP dependent on situation<br>- Age group dependent on situation |
| **Phase 2 (within 3-5 years of OPV2 withdrawal)** | - TP minimum 1 million<br>- Age group up to 10 years minimum | - TP dependent on time & situation<br>- Age group up to 10 years if needed | - TP dependent on situation<br>- Age group dependent on situation |
| **Phase 3 (after 5 years of OPV2 withdrawal)** | - TP minimum several millions<br>- Age group up to 15 yrs minimum<br>- Min 5 rounds with mOPV2 (monovalent type-2 Oral Polio Vaccine) | - TP minimum 1 million<br>- Age group up to 10 years minimum | - TP minimum 1 million<br>- Age group up to 10 years minimum |

Zone 1: Countries/areas with a clear history of sustained transmission of wild poliovirus or the development of circulating vaccine derived poliovirus

Zone 2: Countries/areas with consistently low immunization coverage or history of importation of WPV or cVDPV type 1 or 3

Zone 3: Countries/areas with consistently higher coverage and few risk factors for sustained transmission of poliovirus

* Specifics will be further discussed at WG and finalized for April 2014 SAGE


DECADE OF VACCINES
GLOBAL VACCINE ACTION PLAN
STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION
2013 ASSESSMENT REPORT

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# LIST OF ABBREVIATONS

| | |
|---|---|
| CRS | Congenital Rubella Syndrome |
| CTC | Controlled-Temperature Chain |
| DoV | Decade of Vaccines |
| DTP vaccine | Diphtheria-Tetanus-Pertussis vaccine |
| GAPPD | Global Action Plan for Pneumonia and Diarrhoea |
| GVAP | Global Vaccine Action Plan |
| IMB | Independent Monitoring Board |
| IPV | Inactivated Poliovirus Vaccine |
| MDG | Millennium Development Goal |
| MS | Member States |
| NITAG | National Immunization Technical Advisory Group |
| OPV | Oral Poliovirus Vaccine |
| SAGE | Strategic Advisory Group of Experts (WHO) |
| UNICEF | United Nations Children's Fund |
| WHO | World Health Organization |
| WUENIC | WHO and UNICEF Estimates of National Immunization Coverage |

# EXECUTIVE SUMMARY

Vaccines have created a healthier world. Childhood mortality has dropped, smallpox has been eradicated, progress is being made towards polio eradication and measles deaths are on the decline. 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 do much more to meet the Decade of Vaccines' (DoV) ambitious goals.**

The Strategic Advisory Group of Experts on Immunization (SAGE) created a Decade of Vaccines Global Vaccine Action Plan Working Group (list of members in Annex) to review the annual reports provided by the GVAP Secretariat, based on country reports, on progress of the GVAP implementation and independent submissions from several stakeholders.

Based on this review, the working group has made both overarching recommendations and more specific recommendations that specifically target stakeholder groups. The SAGE endorsed these recommendations during the meeting held 5-7 November 2013.

In this executive summary, the four overarching recommendations and a summary of the related specific recommendations for the countries (in boxes) are presented.

In the report itself, more detailed recommendations are provided to countries, development partners, technical agencies and the DoV GVAP Working Group Secretariat.

## *IMPROVE DATA QUALITY*

Accurate data are critical for governments to make better programmatic decisions, monitor progress and meet immunization targets. In many countries, the quality of currently available data are too poor to inform the proper management of the immunization programmes and thus to hold governments accountable. **Governments must take the responsibility for resolving this issue.**

**To improve data quality, countries should:**

- Make the improvement of data a top national priority
- Use high quality data in decision making at all administrative levels.
- Conduct annual reviews of data, including data quality, to monitor programme performance. Actively involve National Immunization Technical Advisory Groups (NITAGs) in this review process.
- Use available data to consider resource requirements and plan for future vaccine introductions.
- Establish and/or strengthen NITAGs and utilize them to advise on policy recommendations and provide independent monitoring of progress with programme implementation and immunization data quality at the national level.

**Improving data quality is the highest priority for all stakeholders.** Particular priority should be placed on immunization coverage data and surveillance data. They must collaborate to establish a step-by-step, country tailored approach to strengthen data quality at all administrative levels. This approach should include monitoring information at district level, with consideration of using new approaches and technologies. NITAGs have a clear role to independently monitor progress and data quality at the national level.

### *ACCELERATE EFFORTS FOR DISEASE ERADICATION AND ELIMINATION*

As the world nears the end of the polio eradication effort, the challenges have increased and it is imperative that all partners now redouble their efforts to complete the job, as failure would represent a failure not only for the immunization community but for public health in general. Efforts toward meeting this goal should also strengthen immunization programmes and health systems, as well as improve routine immunization coverage.

Measles and rubella/congenital rubella syndrome (CRS) elimination, while long accomplished in the Region of the Americas, is a new challenge for other regions. All stakeholders will need to make a concerted effort to generate political will and secure the investments required to achieve measles and rubella/CRS elimination. Political support will help secure the necessary investments required to achieve measles elimination and rubella control or elimination. It is now estimated that 95% coverage is required in all districts and nationally to achieve measles elimination so it is essential that measles and rubella surveillance is increased to meet verification standards, monitor progress and take timely action. National programmes should develop and implement action plans to achieve these high-coverage levels so that measles and rubella elimination can be achieved by the targeted years.

**To accelerate eradication and elimination, countries should:**

- Establish national action plans to introduce inactivated polio vaccine and switch from the use of tOPV to bOPV.
- View neonatal tetanus elimination as part of a larger effort to strengthen maternal and child health (Equity indicator).
- Establish strategies and action plans to achieve measles and rubella/CRS elimination. These should include details on strengthening overall health and immunization systems.
- Establish case-based surveillance systems for measles and rubella to ensure timely and complete reporting.
- Strengthen rubella surveillance by building on the polio and measles surveillance platform and establish a surveillance platform for CRS.

## *REDOUBLE EFFORTS IN POOR-PERFORMING COUNTRIES FOR IMPROVING ROUTINE AND NEW VACCINES COVERAGE LEVELS*

At the current pace, many countries—mainly in the African, Eastern Mediterranean and South-East Asia Regions—will not meet routine immunizations coverage targets: to achieve coverage with routine immunization of 90% or greater at the national level and 80% or greater in every district. More worrying is that immunization coverage has remained low, stagnant or even decreasing in several of these countries.

Countries with low and stagnant coverage for routine immunization must urgently intensify efforts to improve programme performance, utilizing administrative data and surveys 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 accepted and 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.

**To improve vaccine coverage, countries should:**

- *For Countries falling short of reaching coverage targets:* urgently identify barriers and bottlenecks and implement targeted approaches to increase and sustain coverage based on systematic review of local data.
- Advocate for immunization and for efforts to further improve equity because immunizations are one of the most equitably distributed health services.
- *For Countries with a DTP1-DTP3 dropout rate of more than 10%:* review programme policies and performance and urgently implement measures to reduce dropout.
- Establish or strengthen capacity for pharmacovigilance to detect and respond to adverse effects following immunization and to strengthen confidence in immunization.

## *USE IMMUNIZATION AS A MAJOR STRATEGY TO ACHIEVE MILLENIUM DEVELOPMENT GOALS AND PROMOTE THE ROLE OF IMMUNIZATION IN THE POST-MDG CONTEXT*

In many countries, it is very likely that the Millennium Development Goal (MDG) 4 target (reduce under-five mortality by two-thirds in 2015 compared to 1990) will not be achieved. Pneumonia and diarrhoea remain important causes of child mortality and the introduction of new vaccines could contribute to reducing mortality from these two conditions. The effect of the new vaccines could be further amplified by the use of coordinated approaches and the scale up of complementary interventions, as outlined in the Global Action Plan for Pneumonia and Diarrhoea (GAPPD).

The contribution of immunization activities to achieve MDGs and to improve life-course health should be recognized and better documented. The possible contribution of immunization activities to achieve

post-MDGs objectives should be quantified (using modelling) to allow countries and partners to provide adequate resources.

**To achieve MDGs, countries should:**

- Use the opportunity of immunization visits and the introduction of vaccines against pneumonia and diarrhoea to scale up the use of other proven cost-effective interventions to reduce child mortality.
- Use prenatal care appointments and postnatal contacts with mothers to promote knowledge and change attitudes about vaccination.

# INTRODUCTION

The DoV and the associated GVAP is unprecedented in scope and aim. The vision: a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases. The mission: by 2020 and beyond, ensure that all people receive the full benefits of immunization, regardless of where they are born, who they are, or where they live.

Endorsed by the 194 Member States (MS) of the World Health Assembly in 2012, the GVAP provides the roadmap to a future in which millions of lives are saved, worldwide productivity is boosted through reduction in morbidity and disability, and access to existing vaccines for people in all communities is more equitable.

This ambitious goal has brought together the efforts of civil society, governments, donors, industry, philanthropy and academia. It has placed a strong emphasis on evidence-based, country-led prioritization and planning.

It is this emphasis on evidence that strongly informs the recommendations to national governments, international organizations and development partners. While immunizations have had a great effect on public health, much more work is required to meet the DoV' ambitious goals.

If the goals of the DoV are achieved, hundreds of millions of cases of vaccine preventable diseases and as many as 26 million deaths from these diseases will be averted. The mortality rate of children under the age of five will drop, life expectancy will increase and economies will gain billions of dollars of productivity. The prospect of a healthier, more prosperous future can be achieved—but MS, development partners, international agencies and other stakeholders must make the proper investments and remain focused to make these aspirations a reality.

Timely and high-quality data are essential for countries to be able to properly manage their immunization programs. Without high-quality data, it is not possible to take timely action to improve programme performance, to prevent outbreaks of vaccine-preventable diseases or limit their spread.

The need for improved data quality is the most pressing issue that needs to be addressed at this time so that effective monitoring and evaluation of the DoV GVAP can be undertaken.

It is crucial that national governments, development partners and international organizations take urgent action, including with available innovative tools and technologies, to tackle this key issue.

In this report, SAGE presents a review of the GVAP's indicators and makes recommendations for actions required to meet the goals and objectives of the plan. These observations and recommendations are based on reports provided by the DoV GVAP Secretariat (Bill & Melinda Gates Foundation, GAVI Alliance, United States National Institute of Allergy and Infectious Diseases, United Nations Children's Fund and

World Health Organization (WHO)) and some stakeholders.[1] The GVAP secretariat report used information provided by Member States through the WHO and UNICEF Joint Reporting Form and the surveillance reports as well as numerous other sources of information such as household surveys and other WHO databases.

## PROVIDE THE CORNERSTONE FOR ACCOUNTABILITY

High-quality data allow governments to ensure that their immunization programmes are efficient and reach their national targets. Without good data, there can be no accountability and immunization programmes will continue to perform poorly in many countries.

The SAGE noted that while all countries have national data sets, they are frequently of low-quality or out-of-date, thus undermining efforts to monitor programmes. Only good quality contemporary data can be used if progress towards national indicators is to be usefully monitored.

The SAGE noted with concern that the currently available data are of insufficient quality to reliably monitor progress. At the beginning of the decade, the improvement of data quality must be made a high priority by MS.

**The responsibility of collecting and reporting quality data in a timely fashion falls to national governments.**

It is not enough to simply collect statistics. National governments and other stakeholders should collect, monitor, analyse and use data to inform decision-making. The increasing availability of and access to new information and communications technology offers an opportunity to make data recording, reporting and analysis more accurate, timely and efficient. However, in many settings, a significant change in mind-set is needed in order to make use of the data that are available.

An essential component in increasing data quality is an improvement in recording and reporting data through administrative health information systems. Household surveys may also be used to validate administrative coverage data, provide supplemental data required to monitor programme performance and identify important determinants of un- or under-vaccination. However, surveys cannot be used to manage an immunization programme on a day-to-day basis. Innovative rapid assessment methods can help address specific issues instead of the more expensive and labour-intensive household surveys.

While the availability of high quality coverage data is key to proper management, it is also essential that countries invest in strengthening their surveillance systems to be able to document that the programme is having its desired impact in controlling the targeted diseases.

[1] The reports are available for review at the SAGE SharePoint site. Following review by SAGE and final editing, the report will be made publicly available at the WHO website at:
http://www.who.int/immunization/global_vaccine_action_plan/en/

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- Make the improvement of data quality a high priority.
- Use high-quality data in decision making at all administrative levels.
- Conduct annual reviews of data, including data quality, to monitor programme performance. Actively NITAGs in this review process.
- Promote (and consider providing incentives for) reporting accurate immunization data from private service providers and professional organizations to make the data more complete and provide a clearer and broader picture of coverage levels.
- Use all available national and subnational household surveys to collect immunization data and validate administrative coverage data.
- Ensure there are designated, well-trained and supervised professionals for data management.

**FOR NATIONAL PROGRAMMES and DEVELOPMENT PARTNERS**

- Increase investments in existing monitoring systems with the aim of improving data quality with the ultimate aim being to inform evidence-based decisions and take actions in a timely manner.
- Establish clear mechanisms for data collection, analysis, management and sharing.
- Train programme staff in the importance and utility of utilizing data at national, district and sub-district level.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Promote and provide guidance on new information and communication technologies to improve the recording and reporting of data.
- Review, revise and standardize the methodology for collection and analysis of survey data, including the use of serosurveys. The methods should provide explicit guidance on choice of sample size and the use of clinic records as a source of immunization data when immunization cards are not available.
- Channel immunization data reporting through only one institution, not both WHO and UNICEF.
- The agencies in countries and regional offices must take responsibility for assessing quality and completeness of country reports before they transmit the data to the global level.

## MAINTAIN FOCUS ON ELIMINATION AND ERADICATION TARGETS

The DoV's first major goal is the interruption of wild poliovirus transmission, and the plan presents ambitious goals for the elimination or control of measles, neonatal tetanus, rubella and Congenital Rubella Syndrome (CRS). These goals are possible, but requisite political and financial support is not guaranteed and regional progress has been uneven.

Polio eradication remains an urgent health priority and would represent a major milestone in public health. However, it is unlikely that the same levels of external funding that were raised for polio eradication will be available for the elimination or control of other diseases—so it is critical that countries invest adequate resources and use appropriate strategies to be able to tackle these other diseases.

Three WHO regions—Africa, Europe and the Eastern Mediterranean—are not on track to meet their regional measles elimination goals. Several countries in these regions are also at risk to miss the interim global targets for 2015 to increase coverage of routine immunization to greater than 90% at the national level and 80% in every district, reduce measles incidence to fewer than 5 cases per million and reduce measles mortality by 95% (compared to 2000). Efforts to control rubella and CRS are also not getting the required attention in many regions and countries.

While the DoV 2012 milestone for neonatal tetanus elimination was met (10 countries eliminated NT by 2012, with elimination being defined as less than one case per 1,000 live births in each district and maintenance of elimination based on annual WHO and UNICEF District Data spread sheet), the goal of neonatal tetanus elimination is one that has been long delayed. Since this is a relatively easy goal to achieve, it is critical that all future milestones are met and the verification of elimination in all remaining countries is achieved by 2015.

**RECOMMENDATIONS FOR POLIO**

**FOR NATIONAL PROGRAMMES**

- Implement the recommendations of SAGE and the polio Independent Monitoring Board (IMB) to establish national action plans to introduce inactivated polio vaccine and switch from the use of tOPV to bOPV.
- Implement the recommendations of SAGE and the IMB to create a polio virus containment policy and timetable by 2018.

**FOR DoV GVAP TECHNICAL AGENCIES, DEVELOPMENT PARTNERS**

- Document and adopt best practices—including dashboard, accountability, micro planning, risk assessment and outbreak preparedness and response —to improve other elimination efforts and routine immunization.
- Support countries in their transition from tOPV to bOPV/IPV, including assistance in securing an adequate vaccine supply.

**RECOMMENDATIONS FOR NEONATAL TETANUS ELIMINATION**

**FOR NATIONAL PROGRAMMES**

- View neonatal tetanus elimination as part of a larger effort to strengthen maternal and child health.
- Establish targeted approaches to reach socially disadvantaged people. These approaches should include civil society as partners.
- *For countries that have eliminated neonatal tetanus:* Establish action plans to sustain elimination. These plans should include details on strengthening surveillance and reporting.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Give priority support to countries that have not achieved elimination.
- Help countries improve surveillance as part of a comprehensive vaccine-preventable disease surveillance programme, including the development of guidelines to document the maintenance of elimination status.
- Encourage the introduction of appropriate technologies to help deliver vaccines, especially to marginalized and disadvantaged people.
- Use multiple strategies for neonatal tetanus elimination, including access to clean delivery.

**RECOMMENDATIONS FOR MEASLES ELIMINATION**

**FOR NATIONAL PROGRAMMES**

- Garner domestic political support to ensure adequate funding of measles elimination and surveillance programmes.
- Establish strategies and action plans that include details on strengthening overall health and immunization systems, identifying ways to reach disadvantaged populations, identifying and responding to outbreaks, improving case-based surveillance, encouraging the use of micro-planning and using supplementary immunization activities to help fill immunity gaps.
- Monitor the timely administration of measles vaccines as an indicator for tracking progress toward elimination.
- Take proactive measures to address vaccine hesitancy.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Promote measles elimination and increase its prominence in the global health agenda.
- Support country efforts with advocacy, outbreak investigation, outbreak response and response to vaccine hesitancy.
- Establish strategies for strengthening surveillance for measles that builds upon the acute flaccid paralysis surveillance platform.
- Promote the use of new technology and operational research in order to increase immunization coverage.

**RECOMMENDATIONS FOR RUBELLA AND CRS ELIMINATION**

**FOR NATIONAL PROGRAMMES**

- Raise and sustain political support to leverage measles elimination strategies to simultaneously control or eliminate rubella and CRS.
- Strengthen rubella surveillance by building on the polio and measles surveillance platform and establish a surveillance platform for CRS.
- *For countries that have not yet introduced rubella vaccine:* Develop action plans for introducing rubella-containing vaccine into routine immunizations, based on a review local epidemiology to determine the target age group and use of measles supplementary immunization activities to achieve timely control of rubella while minimizing the risk for paradoxical increase in CRS.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Provide advocacy support to countries.
- Support modelling to estimate disease burden of CRS where surveillance is too weak to provide the required data.
- Secure sufficient supply of rubella-containing vaccine by clearly communicating demand forecasts to the vaccine industry (with sufficient advance notice) and working to overcome existing or future barriers to sufficient supply.

## REVITALIZE EFFORTS ON 90/80

By 2015, all countries should reach 90% national immunization coverage and 80% in every district (or equivalent administrative unit) with three doses of diphtheria-tetanus-pertussis-containing vaccine (DTP3). By the end of the DoV, all countries should reach similar goals for all vaccines included in their national programmes.

Based on the current trends, only 30% of countries are likely to meet the global 2015 DTP3 coverage target. In other countries, coverage is stagnant; in some regions, warfare, civil strife and large-scale migration have resulted in sudden drops in coverage.

The immunization coverage target will be difficult to monitor and evaluate because of poor data quality, especially at the district level. Uncertainty about the size of the target population, changes in geographic boundaries and in the number of districts will make data quality issues on district level coverage hard to resolve. While Expanded Programme on Immunization managers often have great insight into country coverage and are aware of hot spots of low coverage, this knowledge may not be used when immunization strategies are planned.

Other issues that hinder progress toward this goal include poor stock management and inadequate supply of vaccines in some low-performing countries.

Monitoring coverage with all vaccines in the national programme is likely to be a challenge since the vaccines and schedules used vary by country and many countries will be adding vaccines to their national programme during the decade.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- *For countries falling short of coverage targets*: Urgently identify barriers and implement targeted approaches to increase and sustain coverage, based on systematic review of local data. Prioritize the review of policies, logistics, vaccine supply, service delivery, mapping of under- and unvaccinated populations and community demand as part of efforts to scale up coverage.
- *For countries meeting the national coverage goal but failing to reach district-level coverage*: Identify the districts with low coverage and initiate targeted action to increase coverage. Because of increasing urbanization worldwide, issues of inequity and under-immunization in peri-urban areas remain a concern. Analyse this issue and propose strategies to address these issues.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Increase support to countries with low or stagnant routine immunization coverage to help identify barriers, implement actions to increase coverage and report annually on the measures they have taken. Countries with DTP3 coverage level of less than 70% or with stagnant coverage between 70% and 80% should receive the highest priority.
- Improve coordination among departments working to strengthen health systems.
- Help secure sufficient supply of vaccines by clearly communicating demand forecasts to the vaccine industry (with sufficient advance notice) and work to overcome existing or future barriers to sufficient supply.

**FOR DoV GVAP SECRETARIAT**

- Establish an indicator for a “fully immunized infant” for Goal 3.2, including a process and timeline for collecting and reporting data.
- Establish a process to collect district-level coverage data for all vaccines, not just DTP3.

## GUARANTEE EQUITABLE ACCESS TO IMMUNIZATION TO ALL PEOPLE

In addition to monitoring geographic equity through coverage at district or similar administrative levels, the GVAP also aims to increase the proportion of MS with a difference of less than 20% in coverage between wealth quintiles to 60% by 2015 and 75% in 2020.

Monitoring progress on these two equity indicators will be extremely limited because of unavailability and poor quality of data. Data on district-level immunization coverage are often of poor quality, and few countries have survey data reflecting inequities by wealth quintile.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- Advocate for immunization and efforts to further improve equity as countries strive towards achieving universal health coverage because immunizations are one of the most equitably distributed health services.
- Collect and report district-level coverage data annually. Use these data to inform decisions at the district level. Provide incentives for innovative actions to improve quality and use data at the district level.
- Leverage other existing national and subnational surveys to collect data on equity.

**FOR DoV GVAP SECRETARIAT**

- Provide guidance to countries on validating district-level coverage data, take measures to improve reporting on district-level coverage and explore other methods to measure geographic equity in coverage (such as rural-urban disparities).
- Develop tools to facilitate district-level data analysis to inform actions at the district level.
- Develop models to estimate the added impact of equitable delivery of immunization and use this information to advocate for monitoring equity indicators and implementing efforts to achieve equity.

## CREATE STRONGER HEALTH SYSTEMS

The health systems surrounding vaccine delivery play an important role in the fight against disease as immunization is an integral part of a well-functioning health system. Hence, three indicators that offer a glimpse at the strength of a country's immunization system were examined.

The GVAP calls for a decreasing trend in the dropout rate between the first and third doses of DTP3 vaccines. Dropout rates are a useful indicator to measure service utilization and missed opportunities, but data quality is again an issue. Year-to-year changes in reported dropout rates are usually small. Given the issues with data quality, a change in dropout rates of 5% or less should be interpreted with caution. It was noted that in 2012, 36 (19%) of MS had a dropout rate ≥ 10%.

The action plan calls for all MS to sustain a DTP3 coverage level of 90% for three years by 2020. The SAGE believes there is a need to review the value of separately tracking sustained coverage over three years if the report of progress against the immunization coverage goal presents trends for several preceding years.

The action plan also calls upon all MS to have high-quality immunization coverage data by 2020. Use of the WHO and UNICEF estimates of national immunization coverage (WUENIC) Grade of Confidence as an indicator of data quality needs review, since it does not provide an indication of the quality of the national administrative coverage data. Current results are dismal: 90% of countries receive a low or medium assessment, and the measurement is qualitative and not based on empirical data.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- *For countries with a DTP1-DTP3 dropout rate of more than 10%:* Review programme policies and performance and urgently implement measures to reduce dropout. In particular, review policies that lead to missed opportunities and increased dropout rates, institute tracking mechanisms and strategies for catch-up immunization, consider incentives for immunization completion and create policies to capture all the children targeted.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Support countries with dropout rates of 10% or greater to identify causes and take corrective actions.

**FOR DoV GVAP SECRETARIAT**

- Explore means for monitoring dropout rates annually especially for countries where WUENIC is derived from survey data.
- Drop indicator 4.2 but report coverage time series as part of report on Goal 3.
- Develop and propose an alternate indicator to monitor immunization coverage data quality.

## DEVELOP AND ADOPT NEW TECHNOLOGIES

The GVAP calls for investments in research to support the development of innovations that maximize the benefits of immunizations. Such innovations include the licensing or re-licensing of vaccines for use in a controlled-temperature chain (CTC) above the traditional range of 2-8° C and new vaccine delivery technologies.

While the progress on labeling vaccines for use in a controlled-temperature chain is encouraging, the SAGE believes that more effort is required to maximize the opportunities, while cautioning that efficacy and safety should not be compromised in this effort. It also believes the report on vaccine delivery technologies should include a narrative report that includes the extent of usage and impact of innovative products, as well as the availability of the new products.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- Strengthen regulatory capacity to inform local policies and use of products that may be stored and transported in a CTC.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Consider the potential additional costs involved to get regulatory approval for products to be used in the controlled temperature chain and its impact on vaccine price.
- Consider further ways of incentivizing manufacturers to conduct the necessary studies to label their products for use in the CTC.
- Consider all the operational aspects for using this technology at the service-delivery levels.
- Work with the current vaccine vial monitor manufacturers to develop appropriate technology to ensure the proper storage and use of CTC vaccines.
- Encourage and invest in the development of innovative cost-effective technologies to facilitate delivery of vaccines and increase immunization acceptance, as well as the utilization of these new technologies at country level.
- Be mindful of the potential safety, efficacy and liability risks that could arise from use of vaccines outside recommended storage conditions.

## REACH AND EXCEED THE MDG 4 TARGET

Immunization has made a significant contribution to reducing child mortality, especially through the reduction in measles mortality. Immunization can make a further contribution through prevention of pneumonia and diarrhoea and by achieving high and equitable coverage with immunization.

The GVAP calls on countries to make optimal use of immunization to accelerate progress towards the achievement of the MDG 4 of a two-thirds reduction of childhood mortality compared to 1990 rates.

The SAGE believes that the contribution of immunization can be amplified by coordinating a scale up of complementary interventions (as recommended in the Global Action Plan for Pneumonia and Diarrhoea). While immunization itself might not play a large impact on neonatal mortality, provision of a birth dose of hepatitis B vaccine provides an excellent opportunity for delivering a package of interventions aimed at reducing neonatal mortality.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- Use the opportunity of immunization visits and the introduction of vaccines against pneumonia and diarrhoea to scale up the use of other proven cost-effective interventions to reduce child mortality.
- Use prenatal care appointments and postnatal care visits to promote knowledge and change attitudes about vaccination.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Prioritize assistance to countries not meeting the MDG 4 target—especially the 75 Countdown countries—through global and regional programs to increase coverage and reach the most vulnerable populations, including the promotion of the use of coordinated approaches and the scale up of complementary interventions, as outlined in the GAPPD.
- Recognize and better document the contribution of immunization activities to achieve MDGs. The possible contribution of immunization activities to achieve post-MDGs objectives should be quantified (modelling) to allow countries and partners to provide adequate resources.

## IMPROVE COUNTRY OWNERSHIP OF IMMUNIZATION

The GVAP calls upon countries to adequately finance their national immunization programs (on a per-person basis). However, the SAGE found that the data quality on immunization expenditures is too poor to draw conclusions about expenditure trends.

NITAGs provide an opportunity for national governments and other stakeholders to receive unbiased, critical advice on policy recommendations and for monitoring the successes and failures of the programmes. The GVAP calls upon countries to create and strengthen NITAGs as part of the efforts to strengthen national ownership of the programme. The SAGE acknowledges and appreciates that the number of NITAGs that meet the functionality criteria has increased significantly in recent years. It should be noted, however, that many countries are still lagging behind in the establishment of a NITAG mainly because of the insufficient provision of technical support from the technical partners particularly in the African and West Pacific Regions and the lack of political engagement from some national authorities. NITAGs' capacities to use evidence-based approaches should be strengthened with the support of all technical agencies and development partners. Their role in improving data quality is crucial.

**RECOMMENDATIONS FOR IMMUNIZATION FINANCING**

**FOR NATIONAL PROGRAMMES**

- Improve processes to track and report immunization expenditures.

**FOR DoV GVAP SECRETARIAT**

- Continue to report on immunization expenditures using data from the Joint Reporting Form (JRF) because it allows countries the opportunity for self-analysis; however, work to improve the quality and completeness of reporting and highlight the limitations of the data in the narrative in future reports.
- Plan to progressively transition towards using the System of Health Accounts to monitor immunization expenditures and strengthen country capacity to track their expenditures using this system.

**RECOMMENDATIONS FOR NITAGs**

**FOR NATIONAL PROGRAMMES**

- Establish and/or strengthen NITAGs and utilize them to advise on policy recommendations and to provide independent monitoring of progress with programme implementation and immunization data quality at the national level.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- *For WHO and UNICEF regional offices, regional technical advisory groups and partners:* Support countries in establishing and strengthening NITAGs. This is especially needed in the African and West Pacific Regions, which are lagging behind other regions. Support includes advocacy, technical

support and financial support.

- Promote a broader role for NITAGs beyond making recommendations for new vaccine introduction. This role includes participating in the process aiming at improving data quality.
- Sustain and further enhance the existing repository of information and tools (such as economic analysis models) to facilitate evidence-based decision making by the NITAGs.
- Communicate with NITAGS and facilitate their participation in technical meetings.
- *For the GAVI Alliance*: ensure that the existence of a functional NITAG is included in future GAVI funds applications. GAVI should consider a requirement in applications for new and underused vaccines support to have a plan to establish NITAG.

**FOR DoV GVAP SECRETARIAT**

- Improve the data quality on the NITAG indicator, with attention to missing or inconsistent data provided by MS through the JRF. This activity should be led by regional and country offices.

## BUILD GRASSROOTS SUPPORT

Community support for immunization is crucial and indeed can be the deciding factor in the eradication of a disease. The indicator included in the GVAP aims to monitor the percentage of MS that have assessed the level of vaccine confidence at a subnational level, as well as the trends in the number of people who choose not to receive vaccines because of a lack of confidence.

The SAGE found that the current indicators and report do not provide enough information to assess progress. Moreover, the idea of vaccine hesitancy is highly contextual and vaccine specific, making it difficult to create indicators that can appropriately collect, assess and interpret data on a global level.

**RECOMMENDATION**

**FOR DoV GVAP SECRETARIAT**

- Explore alternative indicators and methods for collecting data on vaccine hesitancy. Methods could include the use of coverage data and timeliness of vaccines as indicators, case studies about countering anti-vaccine messaging, human intelligence (including programme managers' views), behavioural research and meta-analysis of DHS data.

## STREGTHEN SURVEILLANCE SYSTEMS

High-quality surveillance is fundamental to assessing whether immunization is achieving its desired impact and for the verification of disease elimination and control goals. It is also essential to generate evidence to use in the decision to add vaccines to the national programme, optimize schedules and monitor the impact of vaccines.

These factors are also essential for the sustainability and optimal use of new and underutilized vaccines. The GVAP has set a target that every Member State should have measles and rubella surveillance in place by 2015.

The SAGE found the surveillance quality and timely data reporting are inadequate to meet the national programme needs or for monitoring global and regional progress with immunization. Greater investments and technical assistance are required to strengthen surveillance systems.

**RECOMMENDATIONS FOR MEASLES/RUBELLA**

**FOR NATIONAL PROGRAMMES**

- Establish case-based surveillance systems for measles and rubella to ensure timely and complete reporting. Existing polio surveillance will be useful platform to build this surveillance.
- Establish surveillance for CRS.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Provide guidance and technical support to countries and share best practices.
- Develop guidelines for conducting surveillance for CRS and support countries in establishing surveillance.

**FOR DoV GVAP SECRETARIAT**

- Identify the countries, classify the causes of low performance and inadequate reporting of vaccine-preventable diseases and propose corrective measures.

**RECOMMENDATIONS FOR SENTINEL SITE SURVEILLANCE**

**FOR NATIONAL PROGRAMMES**

- *For Low- and middle-income countries:* Invest resources to establish or strengthen sentinel site surveillance systems, including laboratory confirmation of vaccine-preventable diseases.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Provide financial and technical support to low- and middle-income countries to strengthen sentinel site surveillance.
- *For WHO:* Develop quality indicators and assist countries in monitoring surveillance quality.

## ENSURE ACCESS TO VACCINES OF ASSURED QUALITY

For effective population based protection against vaccine-preventable disease, it is essential to maintain adequate supplies of good quality vaccines. The GVAP has set a target that 100% of vaccine doses used globally are of assured quality by 2020. Currently, inadequate vaccine supplies in some countries are affecting vaccine coverage and contributing to delays with introduction of new and underutilized vaccines.

Supply shortages at the point of service delivery may have a role in low coverage (more than at the national level). However, more data are needed to document this possibility. Closer monitoring of vaccine stocks may be required to understand the reasons for supply shortages and for corrective actions.

Ensuring vaccine safety is of paramount importance. Aside from the personal harm that unsafe vaccines can cause, misplaced anxiety about vaccine safety can lead to hesitancy or refusals. Strong vaccine pharmacovigilance systems should be put in place in all countries to ensure that vaccines remain safe and that the population's trust in immunization activities over the long term is sustained. National governments, development partners and international organizations should collaborate to provide technical and financial support to countries in establishing or strengthening vaccine pharmacovigilance systems.

The WHO pre-qualification system has contributed to increasing access to vaccines of assured quality, but the WHO system is struggling to fund and respond to the increased demand for this service and this may threaten the progress achieved in the past few years. In the long term, countries need fully functional regulatory agencies to ensure sustained universal access to vaccines of assured quality.

The action plan also sets the goal of all low and middle-income countries having introduced at least one or more new or under-utilised vaccines by 2020 based on the analysis of their own needs. The SAGE makes no recommendations but notes the introduction of Hib, pneumococcal and rotavirus vaccines in low- and middle-income countries has been encouraging. However, delays with the introduction of these vaccines stemming from limited supply are concerning, especially since these vaccines could play an important role toward reaching MDG 4.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- Invest in strengthening the capacity of national regulatory authorities to ensure that all existing and future vaccines in a national programme are of assured quality.
- Establish or strengthen capacity for vaccine pharmacovigilance to detect and respond to adverse effects following immunization and to strengthen confidence in immunization.
- Forecast and resource the burden on national regulatory authorities caused by increasing the number of vaccines in an immunization programme.

**FOR DoV GVAP TECHNICAL AGENCIES and DEVELOPMENT PARTNERS**

- Continue supporting countries in strengthening regulatory capacity and vaccine pharmacovigilance.

**FOR DoV GVAP SECRETARIAT**

- Establish an indicator to monitor country capacity to conduct vaccine pharmacovigilance.
- Consider the possibility of a stock out indicator (even if stock out is more often linked to unavailability at the delivery point than on a national scale) including evaluating its usefulness for country reporting.

## IMMUNIZATION NEEDS AFFORDABLE VACCINES

While the trend in the prices of vaccines procured through the United Nations agencies was positive, the SAGE found the objectives for this indicator were not clear enough. A well-defined objective for this indicator will help to focus subsequent narrative reports on the most pertinent issues to vaccine pricing. The objective should be included in a narrative report to contextualize the data and to explain the dynamics of supply and demand as well as the determinants of the presented results.

The SAGE also believes the report was not comprehensive enough. Prices paid by self-procuring middle-income countries were not available; the relationship between price and volumes procured were not provided; the relationship between price, supply and the health of the markets was not fully addressed; there was no discussion about tier prices and pooled procurement; and there was no indication of private sector prices or prices paid by high-income countries.

**RECOMMENDATIONS**

**FOR NATIONAL PROGRAMMES**

- *For self-procuring countries:* Report public sector vaccine price information to DoV Secretariat agencies on an annual basis using the Vaccine Product, Price and Procurement Project.
- Use available data to consider resource requirements and plan for future vaccine introductions.

**FOR DoV GVAP TECHNICAL AGENCIES**

- Ensure enough resources are available to the secretariat to monitor this important objective; provide sustainable support to continue the Vaccine Product, Price and Procurement Project activities; and streamline and expand the project's activities within and outside WHO.
- Encourage broad stakeholder dialogue, including between buyers and sellers of vaccines, to achieve an optimum balance of supply security and value for money.
- Provide data and inputs to the annual GVAP vaccine price indicator report.
- *For WHO and UNICEF:* Request price information from countries through the JRF with the appropriate instructions and explanations and feedback to the countries.

**FOR DoV GVAP SECRETARIAT**

- Better define the objective for the indicator and report. Include more narrative to explore the relationship between vaccine prices, supply, demand, sources of funding and procurement volumes and mechanisms to better address the health of the vaccine market; make all possible attempts to secure information on prices in self-procuring middle-income countries, high-income countries and in the private market to get a full and comprehensive picture of the global vaccine market; and focus on processes and assess the impact of tiered pricing and pooled procurement mechanisms on vaccine prices. The report should also include case studies to highlight outliers and best practices to achieve optimal pricing.
- Focus subsequent narrative reports on key issues such as limited availability of relatively mature vaccines like measles-rubella and measles-mumps-rubella and determine how market conditions can help to improve security of supply; the link between IPV and the eradication of polio; vaccine price data and middle-income countries' access to quality and affordable vaccines; and priority vaccine of regional public health importance.

## THE NEXT FRONTIERS

Immunization continues to be one of the most essential public health interventions for all populations, and access to vaccines should be regarded as a human right. New vaccines and improved vaccine delivery technologies play a crucial role in fighting disease and saving lives.

The GVAP sets out an array of targets, including the licensure and launch of vaccines against major diseases that continue to kill millions of people in the developing world (such as HIV, tuberculosis and malaria). In addition, the on-going global impact of seasonal influenza and the threat of pandemic flu continue to drive the search for an influenza vaccine that provides broad protection against its various strains.

Since progress with immunization innovations is to be presented only every other year and no report was made available in the 2013 secretariat report, the SAGE makes no recommendations on these indicators but notes the increasing importance of operational research to improve service delivery and increase community demand to achieve all immunization goals. The SAGE also notes the recent progress on a partially effective malaria vaccine and encourages continued research toward a more effective product.

It should also be noted that the sustained use of these vaccines after external support ends will be critical to realizing full benefits. Evidence and evaluation of the economic benefits of these vaccines should be considered, and fully functional NITAGs can play an important role in this process.

## ANNEX: LIST OF SAGE DECADE OF VACCINES, GLOBAL VACCINE ACTION PLAN WORKING GROUP MEMBERS.

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***DoV GVAP WORKING GROUP SECRETARIAT***

- Bill & Melinda Gates Foundation
- GAVI Alliance
- United States National Institute of Allergy and Infectious Diseases
- United Nations Children's Fund
- World Health Organization

SAGE Working Group on Influenza Vaccines and Immunizations

**Influenza A (H5N1) Vaccine Stockpile and Inter-Pandemic Vaccine Use**

**Background Document**

## 1. Introduction

Highly pathogenic avian influenza A (H5N1) viruses remain a pandemic threat. Since its re-emergence in 2003, highly pathogenic avian influenza (HPAI) A (H5N1) viruses have become endemic in poultry in several countries and have continued to cause severe human disease in countries where poultry are infected. Vaccines against H5N1 have been recognized as an important tool in reducing illness during a possible H5N1 pandemic and for protecting persons exposed to the virus during the interpandemic period. As a result, WHO has developed policies for the establishment and use of H5N1 vaccine stockpiles during a pandemic and guidelines for the use of H5N1 vaccines during the interpandemic period, focused on persons at high-risk of H5N1 disease because of occupational exposure. Since these policies were issued by WHO, there have been developments related to H5N1 vaccines and the epidemiology of HPAI H5N1 viruses and human disease. Notably, the Pandemic Influenza Preparedness (PIP) Framework has provided a mechanism for access to pandemic influenza vaccines during a pandemic. As a result, WHO requested that previous recommendations regarding the stockpile and use of H5N1 vaccines be re-examined.

In 2013, the WHO Strategic Advisory Group of Experts (SAGE) Working Group on Influenza Vaccines and Immunizations (WGIVI) undertook a review of evidence and discussion of two questions related to H5N1 vaccines: (1) should WHO create a H5N1 vaccine stockpile; if yes, how should the vaccine stockpile be used, what is the number of doses required, and which vaccines should be included; and (2) is there a need to change the 2009 recommendations to countries on inter-pandemic use of H5N1 vaccine?

Although each of these questions has been addressed previously by SAGE, this document reviews and summarizes evidence accumulated in the intervening years and proposes revised recommendations based on available data.

## 2. Summary of SAGE WGIVI recommendations

The WHO SAGE Working Group on Influenza Vaccines recommends the following based on a review of available data.

1. *WHO should not create a stockpile of H5N1 vaccines. WHO should ensure real-time access to pandemic vaccines under the "Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits" or "PIP Framework."*

   This decision is based on the following:
   a. PIP Framework "Standard Material Transfer Agreements 2" (SMTA2) are legally binding contracts that WHO will conclude with individual vaccine manufacturers and through which

WHO will secure access, on a real-time basis, to pandemic vaccine at the time of a pandemic. The availability of a well-matched pandemic vaccine in the event of pandemic reduces the value of a pre-pandemic stockpile of vaccines, acknowledging the limitations of timely supply as a result of production and distribution timelines.

b. No significant change in the epidemiology of H5N1 viruses or disease has been observed that would change the assessment of pandemic risk. No new countries have reported cases in humans since 2009, indicating no geographic expansion of risk.

c. Vaccines produced and stockpiled before a pandemic virus strain emerges may be poorly matched antigenically to eventual pandemic strains. The relatively poor heterotypic immune responses elicited by current vaccines mean that a stockpiled vaccine that is antigenically different than a pandemic strain may result in diminished effectiveness. The continued emergence of new clades and sub-clades of HPAI H5N1 viruses (e.g., clade 2.3.2.1) increase the likelihood that, if an HPAI H5N1 virus were to cause a pandemic in the future, the pandemic virus strain would be significantly drifted antigenically compared with past strains. Decisions on selection of vaccine candidates, therefore, would be very challenging, and potentially require a stockpile containing multiple vaccines representing various clades and subclades to ensure a well-matched vaccine is available once a pandemic strain emerges.

d. The recent emergence of avian influenza A(H7N9) viruses in China, H3N2 variant viruses in the United States, and the 2009 H1N1 pandemic virus highlight the risk of non-H5N1 strains as pandemic threats. Stockpiling H5N1 vaccines would result in no benefit in the event that the next pandemic is caused by a virus other than H5N1.

e. The value of stockpiled vaccine for use early in a pandemic for containment or delaying the spread of a nascent pandemic is questionable. Based on experience with the 2009 H1N1 pandemic, the rapid spread of the pandemic viruses would likely preclude targeting vaccine to populations initially affected.

2. *The 2009 recommendations for use of licensed H5N1 vaccine during inter-pandemic periods should remain unchanged.* The 2009 recommendations[1] can be summarized as follows:

- Vaccination is *strongly recommended* for laboratory workers involved in certain high-risk activities (e.g., large-scale production or manipulation of, or work over a long period of time with, HPAI H5N1 virus strains, work with drug-resistant HPAI H5N1 viruses or viruses that have the potential for increased transmissibility to mammals).
- Vaccination is *recommended* for first responders to human or animal HPAI H5N1 cases or outbreaks.
- Vaccination is *recommended* for health-care workers who evaluate or manage patients with suspected or confirmed HPAI H5N1 virus infection in designated referral facilities.
- Vaccine is not recommended for the following: persons who may only potentially come in contact with infected animals, for essential workers in areas where HPAI H5N1 virus is enzootic, or for the general population.
- Insufficient evidence exists to recommend use of H5N1 vaccines to immunologically prime individuals.

This decision is based on the following:

a. As noted above, no clear change in the level of risk to exposed populations has been observed.

b. No changes in populations at risk for HPAI H5N1 virus infection have been observed.
c. While risk remains low, even in exposed populations, certain high risk groups may benefit from vaccination given the severity of the disease if infected.

## 3. Background

### 3.1 Epidemiology of Human Infections with Highly Pathogenic Avian Influenza A (H5N1) Viruses

Since the previous reports by the SAGE H5N1 Vaccine Work Group,[1,2] the epidemiology of human infections with HPAI (H5N1) viruses is largely unchanged. The United Nations Food and Agricultural Organization (FAO) considers six countries to be endemic for HPAI H5N1 viruses circulating among poultry (Bangladesh, China, Egypt, India, Indonesia, Vietnam) with poultry outbreaks occurring frequently in nearby countries.[3,4] Human cases of HPAI H5N1 virus infection have declined since peaking in 2006, but sporadic cases with a high case fatality proportion continue to occur and be detected, particularly in six countries (Figure 1, Bangladesh, Cambodia, China, Egypt, Indonesia, and Vietnam).[5-8] The majority of cases have been comprised of children and young adults with few cases aged older than 40 years; the median case age overall is approximately 18-20 years, but has varied from year-to-year and by country. As of October 2013, 641 HPAI H5N1 cases with 380 deaths (59% case fatality proportion) had been reported to WHO from 15 countries since November 2003.[9]

In general, no population-level immunity to H5N1 viruses has been demonstrated. Although the number of studies is limited, persons with laboratory-confirmed infection produce antibodies and more severely ill persons mount a more robust immune response for longer duration.[10] However, as of October 8, 2013, the total number of persons globally reported to have been infected since November 2003 is only 641.[9] Recent (since 2003) limited serologic surveys to detect serum antibodies identify very low prevalence (0-3%) of antibodies to H5 viruses among persons living in HPAI H5N1 areas affected (0-3%) or in persons with an occupational exposure (0-<1%).[11] Together, these data suggest that few people have any anti-H5 antibodies.

Cases in humans have been identified more frequently during cooler periods (e.g., December through March, Figure 1), suggesting seasonality associated temporally with increases in HPAI H5N1 poultry outbreaks, but sporadic cases can occur year-round in endemic countries or where HPAI H5N1 poultry outbreaks are common (e.g., Cambodia). Risk factors for human infection with HPAI H5N1 virus infection continue to be the same as reported previously for zoonotic transmission, primarily direct contact or close exposure to sick or dead poultry or environments contaminated by infected poultry (including swimming or bathing in a pond), or visiting a live poultry market.[11-16] Few cases have been attributed to occupational poultry exposures. For some cases, the source of HPAI H5N1 virus exposure and infection is unknown.

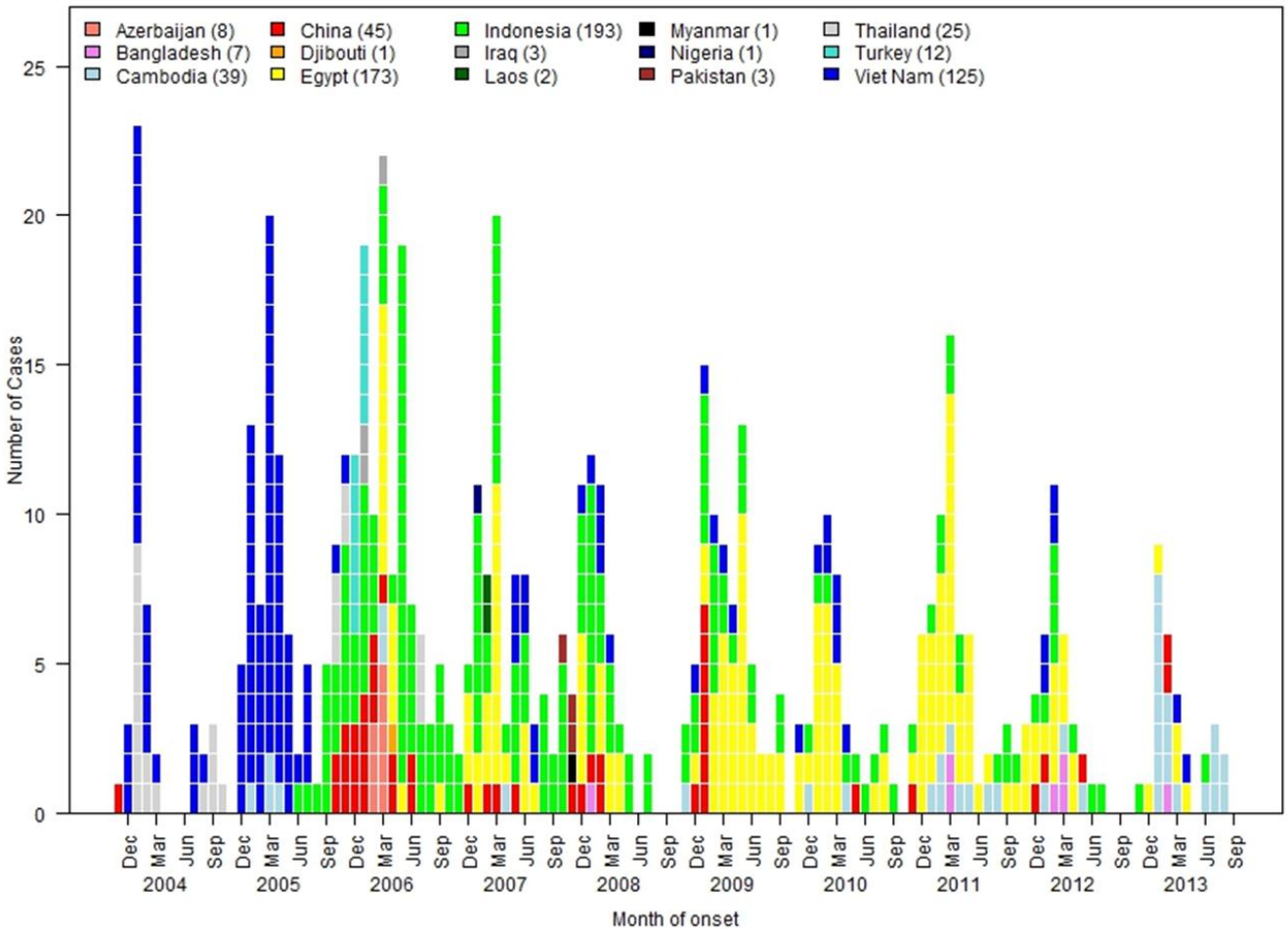
Clusters of HPAI H5N1 cases have declined, but continue to occur infrequently. The majority of such clusters are comprised of blood-related family members who shared a common exposure to poultry.[17,18] However, in some clusters, limited, non-sustained human-to-human HPAI H5N1 virus transmission occurred in a person without poultry exposure who had prolonged, close unprotected exposure to a symptomatic family member with confirmed HPAI H5N1 virus infection, in a household or hospital setting.[19-22] Only one case of limited human-to-human HPAI H5N1 virus transmission has been reported in an unrelated health care worker who had prolonged, unprotected hospital exposure to an HPAI H5N1 case-patient.[23] Limited seroprevalence studies have reported serological evidence of H5N1 virus antibodies in blood relatives.[16,24] Case clusters among blood-related family

members and not in exposed unrelated close contacts suggest the possibility of genetic susceptibility to HPAI H5N1 virus infection.[25]

The incubation period for HPAI H5N1 virus infection has been estimated to have a wide range (median approximately 3 days, range 2-9 days), which may be influenced by many factors, including the infectious dose of HPAI H5N1 virus, single versus multiple virus exposures, clade/subclade of virus, modality of transmission, host factors, and others.[19-22,26,27]

The case fatality proportion has remained consistently high at approximately 60%, with variability by country and year. Generally, but not in all countries, case fatality is lowest in young children.[28] Surveillance varies by country, but most case-finding is still focused upon hospitalized patients with severe respiratory distress who had recent poultry exposures. Few countries except for Egypt have identified HPAI H5N1 cases early in the clinical course or clinically mild, non-pneumonic disease, particularly in children.[29] The true denominator for HPAI H5N1 virus infections is unknown. A small number of asymptomatic or clinically mild HPAI H5N1 virus infections have been identified through surveillance or through limited seroprevalence studies, predominantly among children.[16,22,24,28,30-32] A case of asymptomatic HPAI H5N1 virus infection in an adult was identified through investigations of contacts of a confirmed case.[33] However, the epidemiological evidence to date does not suggest that a large number of asymptomatic or mild illnesses have occurred. Therefore, while the case fatality proportion from cases reported to WHO may be biased upward, it is unlikely that the true HPAI H5N1 case fatality is substantially lower, especially since some severe and fatal cases are undoubtedly also being missed. Mortality from HPAI H5N1 virus infection is associated with late clinical presentation, delayed diagnosis, and late antiviral treatment.[28,34-36]

Figure 1. Number of confirmed human cases of laboratory-confirmed influenza A(H5N1) by month of onset. Data are current as of September 16, 2013.



## 3.2 Clinical Manifestations of Human Infections with Highly Pathogenic Avian Influenza A (H5N1) Viruses and Treatment

The clinical characteristics of human infections with HPAI H5N1 viruses remain unchanged.[37,38] The spectrum of HPAI H5N1 virus infection includes rare asymptomatic infection, clinically mild febrile upper respiratory illness, and severe pneumonia, respiratory failure and multi-organ disease. Clinically mild febrile upper respiratory illness has been reported in children.[22,28,30] In patients with severe respiratory illness, the progression from illness onset to respiratory failure is often rapid (4-6 days). Diarrhea is more common in children than adults.[28,37,38] At hospital admission, many patients have experienced high fever, non-productive cough, shortness of breath, dyspnea, leukopenia, lymphopenia, and moderate thrombocytopenia, with clinical and radiographic evidence of pneumonia. The most common complication is viral pneumonia, progressing to respiratory failure and acute respiratory distress syndrome (ARDS), and some patients have experienced elevation of transaminases, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH), with septic shock requiring vassopressors, disseminated intravascular coagulation (DIC), hemophagocytosis, and renal failure.[37,38] A few atypical presentations of HPAI H5N1 virus infection with febrile diarrheal illness without respiratory symptoms, or with fever, diarrhea, pneumonia and encephalitis, have been reported in pediatric patients.[39,40] Although most hospitalized patients have received treatment with broad-spectrum antibiotics, very few cases of bacterial or fungal co-infection have been reported with HPAI H5N1 virus infection.[37,38] One case of HPAI H5N1 virus infection was reported in a patient with HIV infection.[41]

While emergence of oseltamivir resistance has been reported during treatment,[42,43] oral oseltamivir monotherapy remains the primary treatment for HPAI H5N1 patients. Observational studies have reported that early administration of oral or enterically administered oseltamivir treatment compared to late treatment is associated with survival, and oral oseltamivir treatment versus no treatment is associated with survival.[28,34,35,37,44-46] Inhaled or intravenous zanamivir should be considered for documented or suspected oseltamivir-resistant HPAI H5N1 virus infection.[47] Since most HPAI H5N1 viruses circulating among poultry are resistant to the adamantane antivirals, WHO does not recommend use of amantadine or rimantadine except for combination treatment when treating HPAI H5N1 virus infection with known susceptibility.[47] However, this recommendation may need revision to support the use of adamantanes in combination with oseltamivir in countries where HPAI H5N1 viruses have shown decreased resistance to this older class of drugs. Combination antiviral treatment with drugs of different mechanisms of action as well as immunotherapy with convalescent plasma have been administered to a small number of HPAI H5N1 patients, but clinical trials or larger observational studies are needed to assess efficacy and effectiveness.[38,48] Importantly, clinical management for HPAI H5N1 patients involves much more than administering antiviral treatment, and includes evidence-based management of complications and appropriate supportive care.[48,49] An extremely important component of clinical management is to follow recommended infection control guidance to prevent nosocomial HPAI H5N1 virus transmission to healthcare personnel and family members, including guidance to prevent exposure to other influenza viruses and non-influenza respiratory viruses of public health concern.[49-52]

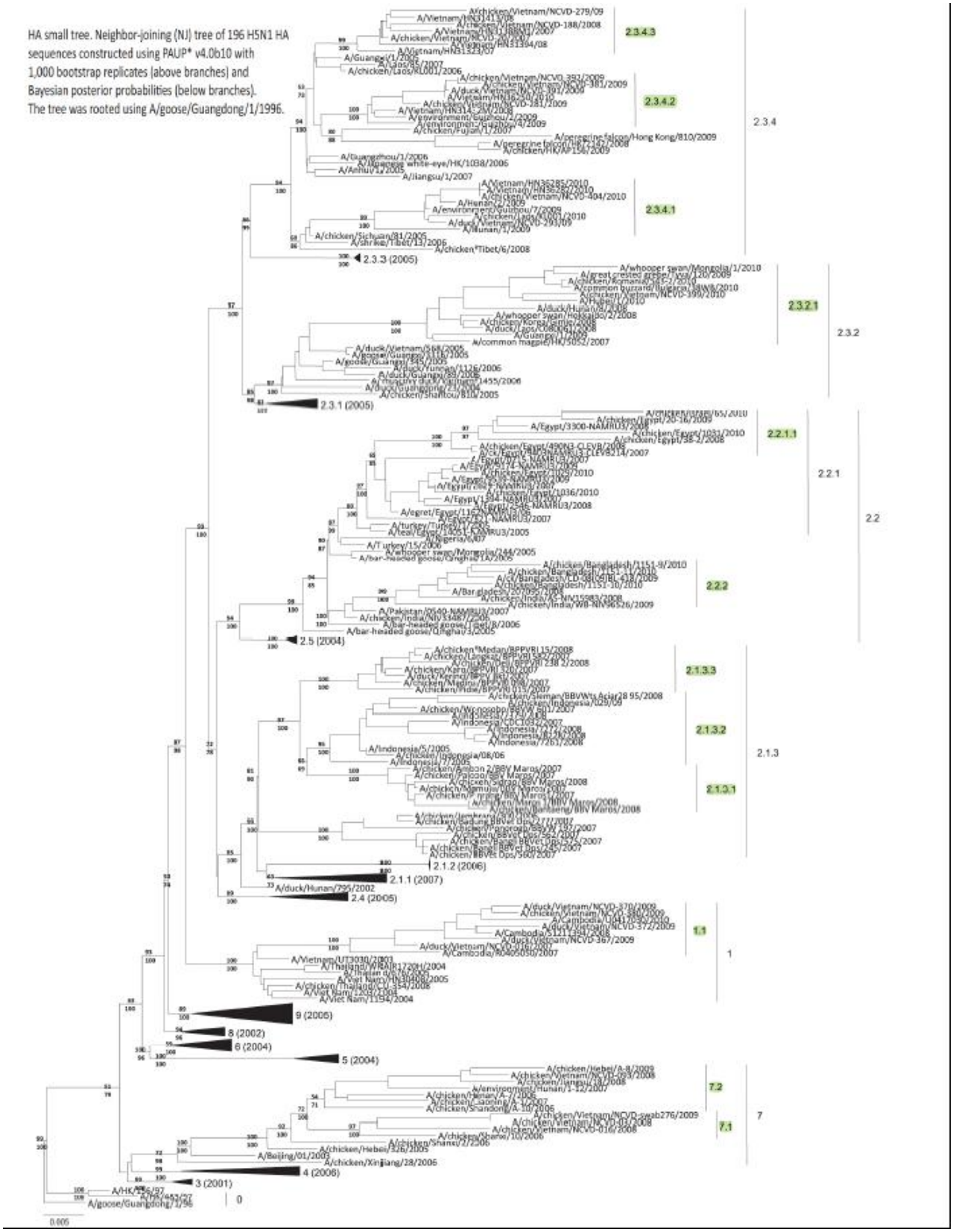
## 3.3 Virologic features of HPAI H5N1 viruses

### 3.3.1 Geographic distribution of clades

The evolution of HPAI H5N1 viruses is monitored using the sequence of the HA gene, encoding the major surface antigen. Viruses are grouped into clades based on the phylogenetic characterization and sequence homology of the HA gene. A clade is defined by three criteria: sharing of a common mode in the phylogenetic tree, monophyletic grouping with bootstrap value of $\geq$60 at the node, and average percentage pairwise distances between and within clades of >1/5% and 1.5%, respectively.[53] There have been 25 distinct clades of HPAI H5N1 viruses identified to date (Figure 2). However, 13 of these have not been detected since 2008.

HPAI H5N1 viruses have been found in poultry and wild birds in Asia, the Middle East, Europe and Africa. Clade 1 viruses have detected in poultry populations in the Mekong River Delta since 2003 and are divided now into clades 1.1.1 and 1.1.2. Clade 2.1 viruses have circulated since 2003 in Indonesia and since 2010 have evolved as a single new clade termed 2.1.3.2a. Clade 2.2.1.1 viruses were enzootic in Egypt and detected in Israel as of 2011; these viruses have evolved into a newly designated clade 2.2.1.1a, which appears to still be maintained primarily within the commercial poultry sector. Clade 2.2.2 is enzootic in Bangladesh and neighboring countries, and they have evolved as clade 2.2.2.1. Clade 2.3.2.1 has produced three newly designated clades. Clade 2.3.2.1a (provisionally designated as A/Hubei/1/2010-like) has been dominant in Vietnam since as early as 2009, and has been detected in Bangladesh and neighboring countries in recent years. Clade 2.3.2.1b (A/barn-swallow/HK/1161/2010-like) has been identified in in China, Hong Kong SAR and Vietnam. Clade 2.3.2.1c (represented by A/Hong Kong/6841/2010) has circulated broadly in domestic and wild birds in many Asian countries, most recently in Indonesia and Vietnam.

Figure 2. Phylogenetic analysis of HA sequences.



### 3.3.2 Antiviral susceptibility

There are two categories of drugs available for treating human infection with HPAI H5N1 viruses: neuraminidase inhibitors (e.g. oseltamivir, zanamivir, laninamivir and peramivir) and matrix protein 2 (M2) inhibitors (amantadine and rimantadine). Current WHO clinical management and treatment guidelines recommend oral oseltamivir as the primary antiviral treatment for persons infected with HPAI H5N1 viruses.[54] In general, resistance to the neuraminidase inhibitors is very low across all clades and resistance to the M2 inhibitors varies over time and by clade.

At the Centers for Disease Control and Prevention (CDC), the M2 gene sequences of 213 HPAI H5N1 viruses collected between January 2011 and March 2013 were analyzed for the presence of molecular markers of resistance to M2 inhibitors, amantadine and rimantadine (Table 1). Of the 231 tested viruses, 22 were isolated from human and 191 from either birds or the environment. Viruses were collected in 6 countries, with the majority (72%) from Vietnam. The majority of viruses (90%) were isolated from poultry. Among viruses isolated from humans, eight (36%) harbored markers of M2 inhibitor resistance, including three out of five (60%) clade 1.1 viruses and all five (100%) clade 2.1.3.2 viruses. Of the remaining 191 viruses, 23 (12%) viruses were resistant to M2 inhibitors, including 18 of 20 (90%) clade 1.1 viruses and five of 167 (3%) clade 2.1.3.2 viruses. Overall, M2 inhibitor resistance declined from 18% (21/117) among viruses collected in 2011, to 12% (10/83) among those collected in 2012, to 0% (0/13) in 2013. Because the number of viruses collected and tested in 2013 is rather low, additional testing of recently collected viruses representing various circulating clades needs to be done to confirm the trend of declining resistance to M2 inhibitors.

HPAI H5N1 viruses (n=173) collected from January 2011 through March 2013 and isolated in eggs were tested for susceptibility to the NA inhibitors oseltamivir and zanamivir (Table 2). Of these 173 viruses, 21 were collected from humans and 152 from either birds or the environment. None of the analyzed viruses contained known markers of resistance to NA inhibitors (see, H5N1 Genetic Changes Inventory, CDC). Of note, the V149A, NA substitution previously reported as having a modest effect of inhibition of NA activity by zanamivir was detected in 13 (62%) of the 21 clade 1.1. viruses.[55]

When compared to the respective clade median $IC_{50}$, a majority of viruses (170/173, 98%) exhibited normal inhibition by oseltamivir and zanamivir (<10-fold increase). The exception was two clade 1.1 viruses which demonstrated reduced inhibition by zanamivir (13- to 22-fold), and one virus from clade 2.3.2.1 with which showed a 10-fold reduced inhibition by oseltamivir. One of the clade 1.1 viruses, A/Cambodia/V04117301/2011, had the V149A and T466I changes in the NA, while the other virus, A/chicken/Vietnam/NCVD-780/2011, had the R430W substitution. The clade 2.3.2.1 virus, A/muscovy duck/Vietnam/NCVD-1220/2012, had the G147R substitution in the NA.

Table 1. M2 inhibitor susceptibility of HPAI H5N1 viruses tested by CDC (Collected from January 2011 to March 2013). (CDC, unpublished data)

| Clade/host | Tested | M2 inhibitor resistant/total tested | | | | M2 resistance markers (No.) |
|---|---|---|---|---|---|---|
| | | 2011 | 2012 | 2013 | Total | |
| **Human** | 22 | 4/9 | 4/7 | 0/6 | 8/22 | L26I+S31N (3), V27A (5) |
| 1.1 | 8 | 1/1 | 2/2 | 0/5 | 3/8 | L26I+S31N |
| 2.1.3.2 | 5 | 3/3 | 2/2 | 0/0 | 5/5 | V27A |
| 2.2.1 | 8 | 0/4 | 0/3 | 0/1 | 0/8 | |
| 2.3.2.1 | 1 | 0/1 | 0/0 | 0/0 | 0/1 | |
| **Non-human** | 191 | 17/108 | 6/76 | 0/7 | 23/191 | V27A (1), A30S (1),V27A+S31N (1), L26I+S31N (18), S31N (2) |
| 1.1 | 20 | 15/15 | 3/3 | 0/2 | 18/20 | L26I+S31N |
| 2.2.2 | 2 | 0/2 | 0/0 | 0/0 | 0/2 | |
| 2.3.2.1 | 167 | 2/89 | 3/73 | 0/5 | 5/167 | V27A, A30S,V27A+S31N, S31N |
| 2.3.4.2 | 2 | 0/2 | 0/0 | 0/0 | 0/2 | |
| All | 213 | 21/117 | 10/83 | 0/13 | **31/213 (14.5%)** | L26I+S31N (21), V27A (6), A30S (1), S31N (2) S31N+V27A (1) |

Table 2. Inhibition of Neuraminidase Activity of HPAI H5N1 Viruses Tested since January 2011 to March 2013[a]

| Clade | Oseltamivir | | | | Zanamivir | | | |
|---|---|---|---|---|---|---|---|---|
| | Tested (n) | Normal | Reduced | Highly Reduced | Tested (n) | Normal | Reduced | Highly Reduced |
| 1.1 | 21 | 21 | 0 | 0 | 21 | 19 | 2[b] | 0 |
| 2.1.3.2 | 5 | 5 | 0 | 0 | 5 | 5 | 0 | 0 |
| 2.2.1 | 8 | 8 | 0 | 0 | 8 | 8 | 0 | 0 |
| 2.3.2.1 | 138 | 137 | 1[c] | 0 | 138 | 138 | 0 | 0 |
| All | 172 | 171 | 1 | 0 | 172 | 170 | 2 | 0 |

[a]Viruses were tested in the fluorescent NI assay using NA-Fluor kit. NA inhibition based on fold difference in $IC_{50}$ compared to the median $IC_{50}$ value of all tested viruses by clade. [b]A/Cambodia/V04117301/2011; NA sequence (V149A, T466I); GISAID accession pending, A/chicken/Vietnam/NCVD-780/2011 (R430W) GISAID accession no. EPI425519, [c]A/muscovy duck/Vietnam/NCVD-1220/2012; NA sequence (G147R), GISAID accession no. EPI425327. The WHO AVWG criteria (ref: Meetings of the WHO working group on surveillance of influenza antiviral susceptibility - Geneva, November 2011 and June 2012. Wkly.Epidemiol.Rec. 87, 369-374.) for type A viruses – Normal inhibition: <10-fold; Reduced inhibition: 10-100-fold; Highly Reduced inhibition: >100-fold.

A recent review of antiviral resistance among HPAI H5N1 virus isolates from 2002-2012, supports the findings that resistance to neuraminidase inhibitors is low and has not really changed over time.[56] In contrast, resistance to M2 inhibitors among isolates from humans decreased from 97% in 2002-2004, to 58% in 2005-2007, and 39% in 2008-2012. [56] Resistance to M2 inhibitors among isolates from birds was lower than in humans but followed the same general decrease over time.

### 3.4 Influenza A (H5N1) vaccines

#### 3.4.1 Current status of licensed vaccines

Currently, 21 H5 vaccines have achieved regulatory licensure (Table 3). Ten are inactivated whole virion vaccines, six are inactivated split virion vaccines, three are inactivated subunit vaccines, one is inactivated surface antigen vaccine, and one is a live attenuated vaccine. In addition to these 21, three additional H5 vaccines will soon be submitted for licensure: an inactivated whole virion H5N1 vaccine by VaBiotech (Vietnam), a live attenuated H5N2 vaccine by the Government Pharmaceutical Organization (Thailand), and a recombinant H5 vaccine by Protein Sciences H5 (USA).

Table 3. Licensed H5 influenza vaccines

| Type | Producer (country) | Commercial name | Subtype | Strain | Substrate | Adjuvant | Dose (HA content in µg) |
|---|---|---|---|---|---|---|---|
| Inactivated whole virion | Baxter (Austria) | Pandemic Influenza Vaccine H5N1 Baxter | H5N1 | A/Vietnam/1203/2004 | Vero cells | None | 7.5 |
| Inactivated whole virion | Baxter Innovations GmbH (Austria) | Vepacel | H5N1 | A/Vietnam/1203/2004 | Vero cells | None | 7.5 |
| Inactivated whole virion | Biken (Japan) | Adsorbed Influenza Vaccine (H5N1) "BIKEN" | H5N1 | A/Vietnam/1194/2004 | Eggs | $Al(OH)_3$ | 3, 30 |
| Inactivated whole virion | Denka Seiken (Japan) | Adsorbed Influenza Vaccine (H5N1) "Seiken" | H5N1 | A/Vietnam/1194/2004 | Eggs | $Al(OH)_3$ | |
| Inactivated whole virion | Kitasato Institute (Japan) | Adsorbed Pandemic Influenza Vaccine (H5N1) "Hokken" | H5N1 | A/Viet Nam/1194/2004 | Eggs | $Al(OH)_3$ | 30 |
| Inactivated whole virion | Kaketsuken (Japan) | Adsorbed Pandemic Influenza Vaccine (H5N1)"Kaketsuken" | H5N1 | | Eggs | $Al(OH)_3$ | |
| Inactivated whole virion | Valneva (France), Kaketsuken (Japan) & GSK (Belgium) | | H5N1 | | EB66® cell line | $AS0_3$ | |
| Inactivated whole virion | Omninvest (Hungary) | Fluval H5N1 | H5N1 | A/Vietnam/1194/2004 | Eggs | $AlPO_4$ | 6 |
| Inactivated whole virion | Sinovac Biotech (China) | Panflu | H5N1 | A/Vietnam/1194/2003 | Eggs | $Al(OH)_3$ | 15 |
| Inactivated whole virion | RIBSP (Kazakhstan) | Kazfluvac® | H5N1 | A/Astana RG/6:2/2009 | Eggs | $Al(OH)_3$ | |
| Inactivated split virion | GSK Biologicals (Belgium) | Adjupanrix / Qpan | H5N1 | A/Vietnam/1194/2004 | Eggs | $AS0_3$ | 3.75 |
| Inactivated split virion | GSK Biologicals (Belgium) | Prepandrix | H5N1 | A/Indonesia/05/2005 | Eggs | $AS0_3$ | 3.75 |
| Inactivated split virion | GSK Biologicals (Belgium) | Pumarix | H5N1 | A/Indonesia/05/2005 | Eggs | $AS0_3$ | 3.75 |
| Inactivated split virion | CSL Ltd (Australia) | Panvax | H5N1 | A/Vietnam/1194/2004 | Eggs | $Al(OH)_3$ | 30 |
| Inactivated split virion | Sanofi Pasteur (France) | | H5N1 | | Eggs | | |
| Inactivated split virion | Sanofi Pasteur (USA) | Sanofi pasteur Influenza Virus Vaccine, H5N1 | H5N1 | A/Vietnam/1203/2004 | Eggs | None | 90 |
| Inactivated subunit | Microgen (Russia) | OrniFlu® | H5N1 | A/Vietnam/1194/2004 | Eggs | $Al(OH)_3$ | 2 x 15 |
| Inactivated subunit | Novartis V&D (Italy) | Prepandemic influenza vaccine (H5N1) | H5N1 | A/Vietnam/1194/2004 | Eggs | MF59C.1 | 7.5 |
| Inactivated subunit | Novartis V&D (Italy) | Foclivia | H5N1 | A/Vietnam/1194/2004 | Eggs | MF59C.1 | 7.5 |
| Inactivated surface antigen | Novartis V&D (Italy) | Aflunov | H5N1 | A/turkey/Turkey/1/05 | | MF59C.1 | 7.5 |
| Live-attenuated | Microgen (Russia), Institute of Experimental Medicine (Russia) | Ultragrivak® | H5N2 | A/17/Duck/Potsdam/88/92 (H5N2) x Len 17 (H2N2) | Eggs | None | $10^{8.3}TCID_{50}$ |

### 3.4.2 Current status of national H5 vaccine stockpiles

Several countries are known to have an in-country stockpile of H5 vaccines: Australia, Japan, New Zealand, Solomon Islands, Singapore, the United States, and the United Kingdom.

As an example, part of the national strategy for pandemic influenza, the United States' plan is to stockpile enough pre-pandemic influenza vaccines to cover 20 million in the critical workforce. As of 2013, the United States has stocked bulk vaccine from 4 different clades (1, 2.1.3, 2.2, and 2.3.4) of enough quantity to produce 16.61 million doses of a vaccine formulated at 90µg of HA per dose. In addition, the United States has a stockpile of bulk oil-in-water adjuvants (MF59 and $ASO_3$). Studies are currently underway to mix and match the adjuvants and the vaccines to identify antigen-sparing regimens for use during a pandemic. The United States has spent approximately $1 billion in these efforts to date.

### 3.4.3 Safety

The safety profile of the H5N1 vaccines currently available has been reviewed recently and comprehensively and has not changed since the previous reports.[1,2,57] In general, the vaccines have demonstrated a good safety profile.

Although oil-in-water adjuvanted H5N1 vaccines have shown a good safety profile in clinical trials, during the 2009 pandemic a number of studies demonstrated an increased risk of narcolepsy in persons who had received the GSK monovalent H1N1pdm09 vaccine (Pandemrix®) containing the ASO3 adjuvant, raising concerns of the possible role of the adjuvant. [58-60] No other immunological adverse effects have been identified with the AS03-containing or oil-in-water adjuvanted H1N1pdm09[61-63] vaccines. The risk of Guillain-Barre syndrome after such adjuvanted vaccines is similar to that reported for unadjuvanted trivalent seasonal vaccine.[64,65] However, the association of narcolepsy with a pandemic influenza vaccine highlights the requirement for strong systems for assessments of safety in the pre- and post-licensure periods of vaccine development.

### 3.4.4 Immunogenicity

Immune correlates of protection for influenza viruses are not well understood and it is possible that the current serologic assessment criteria may not be appropriate for H5 vaccines. However, without means to assess vaccine efficacy against laboratory-confirmed infection or clinical illness, antibody-mediated immunity remains the standard. There is some work to assess the role of cell-mediated immunity; however, the data are sparse.

Most inactivated influenza vaccines are poorly immunogenic in naïve individuals, requiring 2 doses to elicit antibody responses associated with protection in a majority of vaccines. Using current assessment methods, the avian H5 hemaggultinin (HA) appears to be less immunogenic than those of human influenza viruses. For example, the standard amount of HA that is in a non-adjuvanted inactivated seasonal influenza vaccine is 15µg. Early studies of unadjuvanted inactivated H5 vaccines suggested that multiple doses of up to 90µg each would be needed be needed to elicit antibody titers associated with protection against human influenza virus subtypes. Compared with the standard one-dose, 15µg vaccine, a two-dose 90µg vaccine translates into 12-fold fewer people that could be vaccinated with any given production, a strategy not conducive for pandemic planning.

Because of the poor immunogenicity of the H5 HA, adjuvants have been used in an effort to enhance the quantity, breadth and durability of the immunologic response. Further, the use of adjuvants allows for a dose-sparing approach which is appealing for pandemic preparedness (i.e., more people can be vaccinated with less

antigen). The three main adjuvants used in the currently licensed H5 pandemic vaccines are $Al(OH)_3$, $ASO_3$ and MF59. $Al(OH)_3$, or alum, is an aluminum salt and is the only adjuvant licensed for use in humans in the United States. In general, studies using $Al(OH)_3$ in H5 inactivated vaccines have produced variable results that are less than impressive.[57] In contrast, the two oil-in-water adjuvants, ASO3 and MF59, have demonstrated substantial improvements in the immunogenicity inactivated H5 vaccines. Although antibody response to two-dose vaccine regimens generally were reduced after 6 months and low or absent 12-17 months after primary vaccinations.[57]

In an effort to improve the durability and cross-reactivity of the antibody response to H5N1 vaccines, several studies have investigated the safety and immunogenicity of booster doses administered at different intervals after primary H5N1 vaccination. Using homologous H5N1 vaccine for the priming and boosting inoculations, both unadjuvanted and adjuvanted vaccines primed for more robust boosted responses, even when antibody responses to primary vaccination were modest.[66-68] Using adjuvanted vaccines for both priming and boosting generally elicits the most robust and cross-reactive antibody responses. H5N1 vaccination can also prime for boosting with a heterologous vaccine. Priming is associated with more rapid, more robust and more durable responses following heterologous H5N1 vaccine boosting with improved breadth of cross-clade antibody responses.[66,68-71] These findings suggest that priming with an available H5N1 pre-pandemic vaccine and boosting with a heterologous H5N1 vaccine antigenically matched to an emerging pandemic strain may be an effective and dose sparing approach to protecting populations during a pandemic.

### 3.4.5 Heterotypic (hetero-clade) immune responses

HPAI H5N1 viruses continue to evolve and produce new, distinct clades. This viral evolution highlights the need for a vaccine that confers cross-reactive immunity and cross-clade protection. A few clinical trials of H5N1 vaccines have assessed cross clade immunogenicity or the presence of anti-H5 antibodies after seasonal influenza vaccination. H5N1 vaccination strategies that include the use of oil-in-water adjuvants (MF-59 or AS03) and/or heterologous prime and boost vaccination provide the best cross-clade H5 antibody responses seen to date.[66,72,73] Priming with clade 0 adjuvanted vaccine induced memory B cell responses that are expanded following boosting with a clade 1 vaccine and resulted in high titers of neutralizing antibody against antigenically diverse clade 0, 1 and 2 viruses.[74] Similarly, clade 1 vaccine prime and clade 2 vaccine boost strategies have achieved antibody responses to both clades that were substantially higher than those achieved by primary vaccination alone.[73]

## 4. Should WHO create a stockpile of H5N1 vaccines for pandemic use?

### 4.1 Review of WHO stockpile recommendations and status of current stockpile/situation

In May 2007, the World Health Assembly adopted Resolution WHA60.28 that requested that WHO "establish, in close consultation with Member States, an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential as appropriate, for use in countries in need in a timely manner and according to sound public-health principles…"[75] In October 2007, a WHO scientific consultation reviewed options for the use of a WHO H5N1 influenza vaccine stockpile.[2] Based on the data available at that time, SAGE recommended that WHO establish a stockpile of approximately 150 million doses, including 50 million doses for use in aborting or delaying nascent pandemics and 100 million doses for distribution to low and middle-income member countries to help maintain essential services during a pandemic.[76] WHO received two manufacturer pledges totaling 110 million doses towards this goal, but did not establish a physical stockpile. In 2009, these two pledges were

partially converted into donations of H1N1 pandemic vaccines. Following the end of the H1N1 pandemic, given that many doses of H1N1 pandemic vaccine donated by both GSK and Sanofi Pasteur had not been used by WHO, both companies renewed their pledges of H5N1 vaccines towards the international stockpile.

The SAGE recommendation to create an international stockpile of H5N1 vaccines became an integral part of the PIP Framework, adopted by the 194 countries of WHO in May 2011. Among its objectives, the PIP Framework aims to ensure real-time access by developing countries to pandemic vaccines. Section 6.9 of the Framework requests the WHO Director-General to establish and maintain a stockpile of vaccines for H5N1 and other influenza viruses with human pandemic potential and specifies that the WHO stockpile will initially include 150 million doses of H5N1 vaccine for use in accordance with expert guidance."[77]

The PIP Framework also requires WHO to conclude contracts (called "Standard Material Transfer Agreement 2" or "SMTA2") with vaccine manufacturers to secure access, on a real-time basis, to pandemic vaccines. An SMTA2 was signed in December 2012 with GSK. Under its SMTA2, GSK has committed to provide to WHO access to 10% of its real-time production of pandemic vaccine. The agreement specifies that the GSK commitment to provide pandemic vaccine replaces GSK's previous pledge of H5N1 vaccine doses to the WHO stockpile. It is expected that Sanofi Pasteur will also replace its pledge towards a H5N1 stockpile, with a commitment to provide real-time access to pandemic vaccine. As a result, it is anticipated that as of 2013, there will no longer be any pledges to the WHO stockpile of H5N1 vaccine.

### 4.2 Review of options for creating a WHO H5N1 vaccine stockpile

Subsequent to the original SAGE recommendations in 2007,[2] two options were considered by SAGE WGIVI: 1) no stockpile, with reliance on donated vaccine during a pandemic; and 2) a physical stockpile of vaccines produced and stored before a pandemic. A third possible option briefly discussed included a "virtual stockpile" in which vaccine producers maintain a perennial rotating stock of H5N1 vaccines that are designated for donation to WHO in the event of a pandemic. A virtual stockpile would require that manufacturers have ongoing production of H5N1 vaccine.[78] Given that no such ongoing production exists or is planned, this option was not considered a sufficiently viable option and is not discussed further.

Option 1. *A physical stockpile of H5N1 vaccines produced and stored before a pandemic to be distributed in the event of a pandemic.* This option reflects the existing WHO recommendations and previous SAGE guidance. While the creation of a stockpile would require decisions on formulations, number of doses, location of storage, and plans of its use, the SAGE WGIVI focused its discussion on the advantages and disadvantages of creating the stockpile, rather than these details.

Advantages.

1. Timely availability of vaccine to target populations following the emergence of a pandemic. Because of the timeline of influenza vaccine production and distribution, having vaccine already produced and ready to ship (or be filled and finished if stored in bulk) would maximize the opportunity to protect target populations. Because stockpiled vaccine could arrive in the first few weeks

following pandemic emergence, persons might be vaccinated before exposure. This option produces the possibility of using a vaccine for early mitigation or slowing spread of a pandemic in its early phases. This option also could be used in a containment strategy during the very beginning of a pandemic.[2]

2. Early vaccination of target populations could be used to prime high-risk persons for more rapid and robust immunity when pandemic vaccine is available.

Disadvantages.

1. Because of the continuing evolution of HPAI H5N1 viruses, a stockpiled vaccine may be a less effective vaccine should a pandemic virus be antigenically dissimilar to stockpiled vaccine virus strains.
2. Should a non-H5N1 influenza A virus cause the next pandemic, an H5N1 vaccine stockpile would be ineffective.
3. Due to the presence of circulating viruses representing multiple antigenic clades, a stockpile of H5N1 vaccines may require multiple H5N1 vaccines to best ensure an antigenically well-matched vaccine is available at the time of a pandemic.
4. Because H5N1 vaccines are currently not in production, supply of vaccines for a stockpile may not be available.
5. The costs of a stockpile are likely to be substantial. Creation of a stockpile requires purchase, maintenance and scheduled rotation of stocks. It is estimated that a "pay-as-you-go" physical stockpile of 150 million donated doses would cost around $85 million but would need replenishing every 3-5 years.[78] If donations are not available, the cost of purchasing the vaccine was estimated at $450 million. The cost to have a "committed replenishment" of a physical stockpile was estimated to range from $360 to $880 million depending upon the replenishment cycle.[78]
6. The high cost of creating and maintaining a physical stockpile would produce opportunity costs. For instance, efforts to continue to enhance routine preparedness efforts (e.g., surveillance, rapid response capabilities) might be compromised if investing in vaccine stockpiles was prioritized.

The WGIVI did discuss a variant of Option 1 – the creation of a small stockpile (fewer than 100,000 doses) for rapid deployment to populations initially affected. The advantages and disadvantages were qualitatively the same as those of the large stockpile initially recommended by SAGE, while costs concerns would be relatively reduced (even so, the absence of donated vaccine, would result in substantial costs for this option). The group determined that one additional, important disadvantage to this option was the lack of data to support early intervention with vaccine as a tool to contain or slow the spread of an early pandemic. Additionally, the small supply would likely be only enough for one country, so if multiple outbreaks were identified simultaneously, decisions on allocations would be challenging. The

experience with the rapid early spread of 2009 H1N1 virus highlighted the challenges in early detection and rapid deployment for the purpose of containment.

Option 2. No stockpile, with reliance on negotiated agreements regarding access to vaccine during a pandemic (PIP Framework SMTA2s).

Advantages

1. Best ensures antigenically well-matched vaccines to the pandemic virus strain, thereby maximizing vaccine effectiveness.
2. Supply is assured under the PIP Framework. Agreements for real-time access to pandemic vaccine can be negotiated in advance of a pandemic.
3. Costs are lower to WHO and are mainly related to transport of vaccine at the time of a pandemic. No costs are incurred for maintenance and replenishment of vaccine stockpiles.
4. Logistically simpler if vaccine distribution is managed by vaccine manufacturers, rather than requiring agreements to ship from vaccine stockpile locations.
5. Is not reliant on interpandemic vaccine production schedules of manufacturers.

Disadvantages

1. Vaccine availability in the event of an H5N1 pandemic would be delayed compared with Option 1, assuming that the stockpiled vaccine is determined to be appropriate for prevention of infection with the pandemic strain (that is, they are reasonable matched antigenically). Because of the time required for vaccine production, reliance on development of pandemic vaccines that are produced using the pandemic virus H5N1 strain would mean that vaccine would likely not be widely available during the initial waves of a pandemic. In addition, use of vaccine in attempts to slow the early spread of a pandemic would have to rely on other methods of control (e.g., antiviral use or nonpharmaceutical methods such as social distancing).
2. Communication challenges should the lack of a stockpile be interpreted as poor planning by WHO.

The SAGE WGIVI recommended Option 2 as the preferred option.

## 5. Should the 2009 recommendations for the use of licensed H5N1 vaccines during the interpandemic period be changed?

5.1 Review of 2009 recommendations and rationale for the recommendations

In April 2009, the SAGE H5N1 Working Group reported on the use of licensed H5N1 influenza vaccines in the interpandemic period.[1] Based on available data from five licensed vaccines and several others in the licensure process, the following vaccine recommendations were made:

Vaccination was *strongly recommended* for laboratory workers involved in certain high-risk activities (e.g., large-scale production or manipulation of, or work over a long period of time with, HPAI H5N1 virus strains, work with drug-resistant HPAI H5N1 viruses or viruses that have the potential for increased transmissibility to mammals). Vaccination was *recommended* for first responders to human or animal HPAI H5N1 cases or outbreaks, and for health-care workers who evaluate or manage patients with suspected or confirmed HPAI H5N1 virus infection in designated referral facilities. However, vaccination was not recommended for persons who may only potentially come in contact with infected animals, for essential workers in areas where HPAI H5N1 virus is enzootic, or for the general population. The group noted in several cases that the risks and benefits to specific populations should be weighed carefully and that the persons themselves be involved in the decisions regarding vaccinations. While discussion about the use of H5N1 vaccines to immunize against future pandemic virus exposure was undertaken, the group determined that too few data were available to recommend H5N1 vaccines for this purpose. Finally, the group highlighted the need to gather more data on several issues and stressed that vaccines currently stockpiled could be used to fill gaps in knowledge.

The full text of the discussion and the data reviewed are available.[2]

5.2 Rationale for maintaining current WHO recommendations

a. No significant change in the epidemiology of HPAI H5N1 viruses or disease has been observed that would change the assessment of risk to the general population, nor to persons potentially exposed in affected countries. Between 2010 and 2013, relatively few cases of HPAI H5N1 virus infection in humans were reported [mean of 42 cases and 24 (57%) deaths in humans each year[79]]. Furthermore, no new countries reported cases in humans since 2009, indicating no geographic expansion of risk.
b. No changes in populations at risk for HPAI H5N1 virus infection have been observed. That is, the group could not identify additional risk groups for which vaccine might be recommended, nor has additional data been developed to identify a change in risk among persons in previously known risk groups.
c. While risk remains low, even in exposed populations, certain high risk groups may benefit from vaccination given the severity of the disease if infected.
d. In persons exposed during laboratory work, it is possible to immunize them using an antigenically well-matched vaccine.

The WG acknowledged that, lacking ongoing production of new H5N1 vaccines, the recommendations for the use of H5N1 vaccine during the interpandemic period might be relevant only to populations that have access to existing stockpiled vaccines. Countries without existing stockpiles, but who wish to vaccinate the risk groups above would be encouraged to discuss methods to obtain vaccine with manufacturers or countries where stockpiles currently exist.

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Status Report on Progress Towards Measles and Rubella Elimination

# SAGE Working Group on Measles and Rubella (17 October 2013)

## *Contents*

# I. Introduction

The updated WHO position papers on use of measles vaccines (2009) and rubella vaccines (2011) both made significant policy advances. Since 2011, 9 countries have introduced rubella vaccine in their national immunization programme and 13 countries are planning introduction in 2014 or 2015. As the world moves towards universal use of combined measles-rubella (MR) and measles-mumps-rubella (MMR) vaccines, there is need to integrate the existing recommendations on use of measles and rubella vaccines and address policy gaps that have been raised by countries. In addition, with the changing epidemiology of measles and rubella, there is a need to provide more specific guidance on appropriate target age range for supplementary immunization activities (SIAs) using MR vaccine or single-antigen measles (M) vaccine. This report provides an update on progress towards global control and regional elimination targets, the evidence to support draft policy recommendations on the use of MR vaccine for both doses in the routine immunization schedule, criteria for when to expand the target age range for SIAs using M and MR vaccines, draft recommendations for vaccination of health workers, and a prioritized list of research topics to address barriers to measles and rubella elimination.

SAGE is being asked to review this report, provide guidance on how to get back on track to achieving global and regional targets, decide whether the available evidence supports more specific recommendations on both the use of MR and M vaccines and on vaccination of health care workers, and discuss the prioritized list of research topics.

# II. Current global and regional targets

## Global targets

Millennium Development Goal 4 aims to reduce deaths among children overall by two thirds by 2015 compared with the level in 1990. Worldwide, the mortality rate for children under five dropped by 41% - from 87 deaths per 1,000 live births in 1990 to 51 in 2011.[1] Accelerated measles control activities have contributed an estimated 23% of the overall reduction in <5 year child mortality between 1990 and 2008.[2] Despite these enormous accomplishments, if current trends continue, the 2015 MDG4 target will not be met and 19 countries[3] are experiencing no decline, or an increase in <5 year child mortality.[4]

[1] The Millennium Development Goals Report 2013, accessed on 9 October 2013 at: http://www.un.org/millenniumgoals/pdf/report-2013/mdg-report-2013-english.pdf

[2] Van den Ent, M, et al. Measles mortality reduction contributes substantially to reduction in all-cause mortality among children less than 5 years of age, 1990-2008. J Infect Dis 2011,204:S18-S23

[3] Afghanistan, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, the Democratic Republic of the Congo (DRC), Equatorial Guinea, Gabon, Guinea-Bissau, Iraq, Kenya , Lesotho, Mali, Mauritania, Papua New Guinea, Somalia, Swaziland

[4] The Second Report of the independent Expert Review Group (iERG) on Information and Accountability for Women's and Children's Health, accessed on 9 October 2013 at http://www.who.int/woman_child_accountability/ierg/news/ierg_2013_report_launch/en/index3.html

In May 2010, Member States at the World Health Assembly (WHA) established the following measles control targets to be achieved by 2015 as milestones towards the future eradication of measles:

- achieve ≥90% coverage with the first dose of measles-containing vaccine nationally and ≥80% vaccination coverage in every district or equivalent administrative unit
- reduce annual measles incidence to less than five cases per million and maintain that level
- reduce measles mortality by 95% or more in comparison with 2000 estimates.

At the WHA in May 2012, the Global Vaccine Action Plan (GVAP) of the Decade of Vaccines was endorsed. One of the four high level goals in GVAP is meeting global and regional elimination targets and the target for measles and rubella is to achieve elimination in at least 5 WHO Regions by 2020. These GVAP measles and rubella elimination targets are closely aligned with the targets in the Global Measles and Rubella Strategic Plan, 2012-2020 which was endorsed by SAGE at their November 2012 meeting. The Global Measles and Rubella Strategic Plan includes a five-pronged strategy to: 1) achieve and maintain high levels of population immunity by achieving ≥95% vaccination coverage in all districts with two doses of measles- and rubella-containing vaccines; 2) monitor disease using effective surveillance, and evaluate programmatic efforts; 3) develop outbreak preparedness and respond rapidly to outbreaks; 4) communicate and engage to build public confidence and demand for immunization; and 5) perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

## Regional targets

On 13 September 2013, the 11 Member States of the South East Asian Region (SEAR) of WHO endorsed a resolution to eliminate measles and accelerate control of rubella/CRS by 2020. With this decision, all six WHO regions now have measles elimination targets. The Region of the Americas (AMR) achieved its target in 2002. The target dates for the other Regions are Western Pacific Region (WPR) (2012), European (EUR) and Eastern Mediterranean Regions (EMR) (2015) and the African (AFR) and South East Asian Regions (2020).

Four of the six WHO regions have set control or elimination targets for rubella. The Americas targeted rubella and congenital rubella syndrome (CRS) elimination by 2010 and achieved this in 2009, one year ahead of schedule. The European Region aims to eliminate rubella by 2015. The Western Pacific and South East Asian Regions aim to have significantly accelerated rubella control and CRS prevention by 2015 and 2020, respectively. The African and Eastern Mediterranean Regions have yet to establish rubella control or elimination goals.

While the GVAP goals for measles and rubella elimination match the WHO Regional targets for 2015, that is measles elimination in 4 Regions (AMR, EUR, EMR and WPR) and rubella elimination in 2 Regions (AMR and EUR), there is a lack of specificity with respect to the 2020 GVAP goals. Four Regions still need to establish target dates for rubella elimination and it is not explicit as to which Region is not included in the 2020 target date for elimination of measles and rubella.

# III. Progress Towards Global Targets

- Good progress towards the global 2015 targets has been made with coverage with the first dose of measles-containing vaccine (MCV1) increasing from 73% in 2000 to 84% in 2012. However MCV1 coverage has remained at 84% for the past 4 years and 34% of Member States are yet to reach at least 90% MCV1 coverage. 74% of Member States have a second dose of measles-containing vaccine (MCV2) offered through routine services reaching 56% coverage in target-aged children in 2012. SIAs reached 112 million children in 2012.
- Since 2000, after setbacks in 2010 and 2011, reported measles incidence decreased by 77% to 33 cases per million population in 2012. 63% of Member States have achieved the 2015 global incidence target of measles incidence <5 per million population. From 2000–2011, estimated measles deaths decreased by 71% globally.
- 69% of Member States provide at least one dose of rubella-containing vaccine (RCV) in their national immunization programme and reported rubella cases have decreased by 83% since 2000.
- In November 2012, SAGE concluded that despite this progress, based on current trends and programme performance, the 2015 global targets as well as regional elimination targets in 4 out of 6 WHO Regions will *not* be achieved on time.

## Immunization Activities

During 2000–2009, estimated global MCV1 coverage increased from 73% to 84% and has leveled off at 84% from 2009 to 2012. By 2012, 3 of the 6 WHO regions (AMR, EUR, and WPR) had achieved ≥90% estimated MCV1 coverage (Table).

The proportion of all Member States with ≥90% MCV1 coverage increased from 43% in 2000 to 66% in 2012. Since 2010, notable progress was seen in the Western Pacific, the American and European Regions. However, both African and the Eastern Mediterranean Regions have shown a decline in the proportion of Member States with ≥90% MCV1 coverage from 2010 to 2012 (see Figure below)

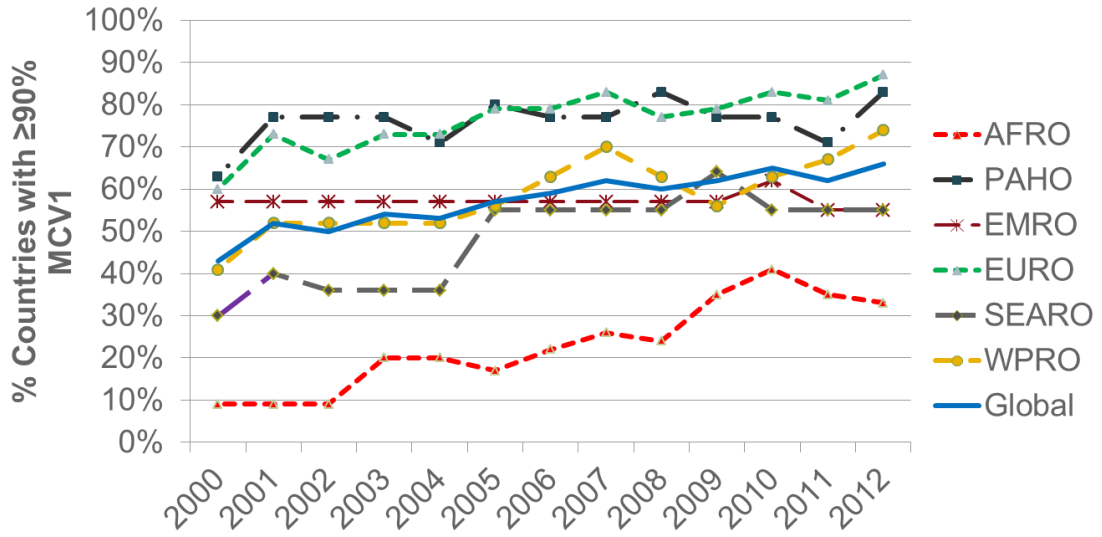



**Figure: Proportion of countries with ≥ 90% MCV1 coverage by WHO Region and Globally, 2000-2012**

In 2012 based on country administrative data, only (58 countries) 37% of all Member States achieved the target of exceeding 80% MCV1 coverage in every district showing a slow but steady increase over the past 10 years. Progress can be seen for Western Pacific, the South East Asia and European Regions with only modest improvements in the African and American Regions. However, the Eastern Mediterranean Region has been declining since 2009.

Of the estimated 21 million children who never received MCV1 in 2012, 13.5 million (64%) were in just 6 Member States: India (6.4 million), Nigeria (3.8 million), Ethiopia (1 million), Indonesia (0.9 million) Pakistan (0.7 million) and the Democratic Republic of the Congo (DRC) (0.7 million).

By 2012 MCV2 was offered through routine services in 147 (75%) Member States, ranging from 12 (26%) of 46 countries in the African Region to 53 (100%) of the countries in the European Region.

By 2012 coverage with MCV2 in target-aged children, based on administrative records, was reported to WHO and UNICEF by 137 (92%) Member States with coverage of 56%, up from 13% in 2000.

During 2000–2012, over one billion children received a measles vaccination through SIAs. During 2012, based on reports by Member States to WHO, 32 measles SIAs reached >112 million children. Reported coverage was >95% for 20 (63%) of SIAs with 14 (44%) Member States conducting coverage surveys to validate coverage. Of the 32 SIAs, 7 were MR SIAs and 26 have integrated at least one other child health intervention (e.g. OPV, bed nets, de worming and Vitamin A).

By 2012, 132 (68%) Member States were providing at least one dose of RCV, up from 99 (52%) in 2000. Though rubella coverage is almost identical to that of measles, as all Member States provide rubella vaccine combined with measles or measles and mumps vaccines, regional and global coverage is much lower as not all Member States use the vaccine.

The proportion of Member States having introduced rubella vaccine by 2012 ranged from 7% in the African Region to 100% of Member States in the American and European Regions.

## Disease Surveillance

The number of Member States annually reporting measles surveillance data to WHO and UNICEF increased from 169 (88%) in 2000 to 187 (93%) in 2012 and for rubella from 102 (53%) in 2000 to 174 (90%) in 2012. Effective measles and rubella surveillance includes establishing case-based surveillance with laboratory testing of persons with suspected measles, rubella or the syndrome of acute rash and fever to confirm cases and outbreaks and to identify measles and rubella virus genotypes. By 2012, 183 (94%) Member States had implemented case-based surveillance, up from 120 (62%) in 2004. In addition, the number of Member States supported with standardized quality-controlled measles and rubella testing by the WHO Measles and Rubella Laboratory Network had increased to 184 (95%) from 71 (37%) in 2000. Though 128 (66%) of Member States reported data on congenital rubella syndrome (CRS) in 2012, up from 75 (39%) Member States in 2000, few cases of CRS are reported, as described below.

During 2000–2012, the number of global reported measles cases reached its lowest levels ever decreasing by 75% from 853,480 to 227,335 cases and measles incidence decreased 77% from 146 to 33 cases per million population, with all WHO regions reporting decreases in case numbers and incidence (see Figure and Table).

From 2000-2008, the number of global reported measles cases decreased; however, from 2008 to 2009, overall global reported measles cases remained stable, with increases in the African Region (AFR) from 37,012 to 83,479 and in the EMR from 12,120 to 36,605 balanced by a decrease in the WPR from 147,987 to 66,609.

From 2009 to 2010, global reported measles cases increased to 342,107. Decreases in WPR to 49,460, in EMR to 10,072, and in the SEAR from 84,356 to 52,529 were offset by increases in AFR to 199,174 and in the EUR from 7,499 to 30,625.

From 2010 to 2011, global reported measles cases increased to 354,882. Further decreases in WPR to 21,050 were offset by increases in the other regions: EMR to 35,923, SEAR to 65,161, AFR to 194,364 and EUR to 37,073 (Figure).

From 2011 to 2012 the global number of cases of measles decreased to 227,335 with a decrease in all regions but EMR. Globally, the percentage of Member States with reported measles incidence <5 cases per million population increased from 38% in 2000 to 63% in 2012.

Table. Estimates of coverage with the first dose of measles-containing vaccine administered through routine immunization services among children aged 1 year, reported measles cases and incidence by WHO region, 2000 & 2012. Estimated measles deaths globally and by WHO Region for 2000 & 2011.

| | 2000 | | | | | 2012 | | | | | | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WHO region** | **% coverage with the first dose of measles-containing vaccine [a]** | **Number of reported measles cases [b]** | **Measles incidence (cases per million population) [c d]** | **% Member States with incidence <5 per million [d]** | **Estimated Measles Deaths (95% CI)** | **% coverage with the first dose of measles-containing vaccine [a]** | **Number of reported measles cases [b]** | **% decline from 2000** | **Measles incidence (cases per million population) [c d]** | **% decline from 2000** | **% Member States with incidence <5 per million [d]** | **Estimated Measles Deaths (95% CI) and [ % decrease since 2000]** |
| African | 53 | 520,102 | 841 | 8 | 338,500 (216,300-736,100) | 73 | 106,052 | 80 | 124.94 | 85 | 39 | 55,200 (22,600-338,400) [84%] |
| Americas | 93 | 1,755 | 2 | 89 | <100 | 94 | 88 | 95 | 0.09 | 96 | 100 | <100 |
| Eastern Mediterranean | 72 | 38,592 | 90 | 17 | 59,600 (31,600-100,500) | 83 | 36,456 | 6 | 59.53 | 34 | 41 | 30,200 (19,000-55,800) [49%] |
| European | 91 | 37,421 | 50 | 48 | 400 (140-2,400) | 94 | 27,030 | 28 | 36.92 | 26 | 74 | 140 (16-1,800)[62%] |
| South-East Asia | 65 | 78,558 | 51 | 0 | 137,100 (94,800-205,300) | 78 | 46,945 | 40 | 25.61 | 50 | 36 | 70,700 (51,800-100,400)[48%] |
| South-East Asia (excluding India) | 77 | 39,723 | 80 | 0 | 48,800 (23,700-97,300) | 88 | 28,277 | 29 | 47.39 | 41 | 40 | 14,500 (8,000-30,000) [70%] |
| India | 59 | 38,835 | 37 | 0 | 88,300 (71,100-108,000) | 74 | 18,668 | 52 | 15.1 | 59 | 0 | 56,200 (43,800-70,300)[36%] |
| Western Pacific | 85 | 177,052 | 105 | 30 | 12,800 (4,200-64,600) | 97 | 10,764 | 94 | 5.86 | 94 | 70 | 1,300 (180-43,900)[90%] |
| **Total** | **73** | **853,480** | **146** | **38** | **548,300 (347,000-1,108,900)** | **84** | **227,335** | **75** | **33.33** | **77** | **63** | **157,700 (93,600-540,300)[71%]** |

**a** Coverage data: WHO/UNICEF estimates of national immunization coverage. Geneva, World Health Organization, 2013 (update of 13 July 2013).
**b** Reported case data: Measles reported cases. Geneva, World Health Organization, 2012 (update of 13 July 2013) Americas data for 2012 from Measles/rubella/congenital rubella syndrome surveillance data final classification, 2012. (update 25 September 2013) (http://ais.paho.org/phip/viz/im_vaccinepreventablediseases.asp, accessed 8 October 2013).Kenya data for 2013 from WHO / AFRO"
**c** Population data: United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision, CD-ROM Edition
**d** Any Member State not reporting data on measles cases for that year were removed from the denominator

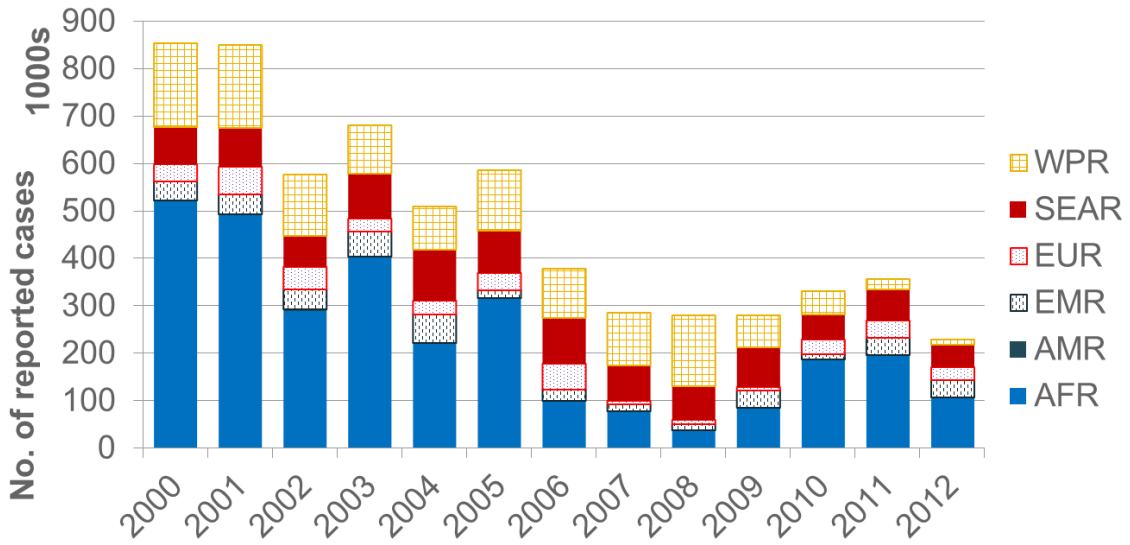



**Figure: Reported measles cases by WHO Region, 2000-2012**

In 2012, a number of Member States experienced large measles outbreaks which in some cases have been ongoing since 2011 or before. These include: DRC (134,042 cases in 2011 and 73,794 in 2012), Nigeria (8,491 cases in 2010; 18,843 in 2011; and 19,062 in 2012), India (18,668 in 2012), Pakistan (14, 984 in 2012), Ukraine (12, 744 in 2012); Somalia (17,298 cases in 2011 and 9,983 in 2012), Indonesia (9,429 in 2012), China (6,183 in 2012), Sudan (8,523 in 2012), Angola (4,442 in 2012), Ethiopia (4,235 cases in 2010; 3,255 in 2011 and 4,347 in 2012) and Romania (4,271 in 2012). The outbreaks were primarily due to low MCV1 coverage or due to suboptimal or delayed SIAs. In areas of high reported coverage, outbreak investigations found that susceptible individuals had accumulated over several years among adolescents and adults who had missed vaccination, thus high reported national routine or SIA coverage had masked subnational immunity gaps.

During 2000–2012, global reported rubella cases decreased 83% from 670,894 to 93,990. However, these numbers should be interpreted with caution because rubella is grossly under-reported particularly in Member States not using rubella vaccine. The greatest decrease in reported rubella cases was a 95% decrease in the European Region, from 804,567 to 30,509, and a 99.9% decrease in the Americas, from 39,228 in 2000 to only 5 cases in 2012. In other regions the number of cases increased during this period in parallel with the increase in the number of Member States reporting rubella cases. Compared to rubella fewer Member States report CRS cases, though the number increased from 75 (39%) in 2000 to 128 (66%) in 2012. The number of reported CRS case is very low, with 297 reported CRS cases in 2012 which is a reflection of poor or no CRS surveillance and low reporting.

## Disease Burden Estimates

During 2000–2011, estimated measles deaths decreased by 71% from 548 300 to 157 700, and all Regions plus India had substantial reductions in estimated measles mortality ranging from 36% to 90%.

In 2011, estimated global measles mortality increased from the 2010 estimate and 99% of the measles mortality burden was in AFR, EMR, and SEAR. In India, the 36% decrease in estimated measles mortality during 2001–2011 was mainly due to the National Measles Catch-up Programme to provide MCV2, beginning in 2010 with MCV2 introduction in routine services in states with reported MCV1 coverage ≥80%, and with SIAs followed by MCV2 introduction in routine services in states with reported MCV1 coverage <80%.

While surveillance for rubella has improved over the past decade, only a small proportion of CRS cases are reported. Disease modelling studies suggest that the burden of CRS has been stable from 1996 to 2008, dropping slightly from 120,342 estimated cases in 1996 to 111,888 in 2008.

### Draft Recommendations

- For elimination, Member States need to achieve ≥95% coverage nationally and in every district with 2 doses of MCV either through routine services and/or SIAs. The elimination effort should continue to be used as a mechanism for strengthening routine coverage in every district.
- In order to align regional goals with the GVAP goal of achieving measles and rubella elimination in at least five WHO regions by 2020, encourage Regions that have not yet established rubella elimination goals (AFR, EMR, SEAR, WPR) to do so using the unique opportunity offered by the Global Alliance for Vaccines and Immunization (GAVI) support.
- Regional TAGs to review country plans for measles and rubella elimination, including planned dates for introduction of RCV for countries not yet using rubella vaccine.

# IV. Progress Towards Regional Targets

## African Region

- Countries in the African Region have established the goal to eliminate measles by 2020.
- As of 2012, only 3 countries were using rubella vaccine in their childhood immunization programme and the Region has not yet established a rubella control or elimination goal.
- Between the years 2001 and 2012, the African Region improved its MCV1 coverage from 56% to 73%.
- In 2012, 20,935 cases of measles were confirmed by lab and epidemiological linkage (incidence rate of 27 per million); As of August 2013, 35,558 confirmed measles cases have been reported (incidence rate of 41 per million)
- As of end 2012, 15 countries out of 46 (32%) are on track to meet the measles elimination target. On the other hand, 16 countries (35%) are clearly at risk of failing to reach the 2020 elimination goal, unless programmatic measures are taken to ensure that the implementation of the strategies in strengthened.
- Weak immunization systems particularly in some large countries (Nigeria, DRC, Ethiopia) remain the major challenge to achieving elimination targets.

The African Region of the WHO is comprised of 46 Member States with a total population estimated at 850 million in 2012. The African Region adopted the measles mortality reduction goal since 2001, and has been implementing the WHO/UNICEF recommended strategies ever since. In September 2011, the 60$^{th}$ Regional Committee of the WHO adopted a goal of measles elimination for the African Region by the year 2020, which includes the following targets:

- Achieve 90% coverage with the first dose of measles vaccine nationally (WHO/UNICEF estimates) AND exceed 80% vaccination coverage in every district or equivalent administrative unit in all countries.
- Achieve at least 95% coverage with measles vaccines during SIAs in at least 80% of districts.
- Achieve a measles incidence of less than one confirmed measles case reported per million population per year (excluding imported cases).
- Achieve the surveillance performance targets

WHO/AFRO does not yet have a goal for CRS/rubella elimination. However, countries are being encouraged to determine the local burden of disease and to introduce rubella vaccine according to the recommendations provided in the most recent WHO rubella vaccine position paper.

### Progress

**Routine Immunization:** Between 2001 and 2012, the African Region has improved its MCV1 coverage from 56% to 73% (according to the WHO/UNICEF estimates), with an average improvement of 1.5 – 2

percentage points per year. (Figure) In 2012, nine of the 46 member states achieved measles vaccination coverage of 95% or more[5], while 15 had coverage of 90% or more. On the other hand, 5 countries[6] had coverage of less than 60%, down from 19 countries in 2000.

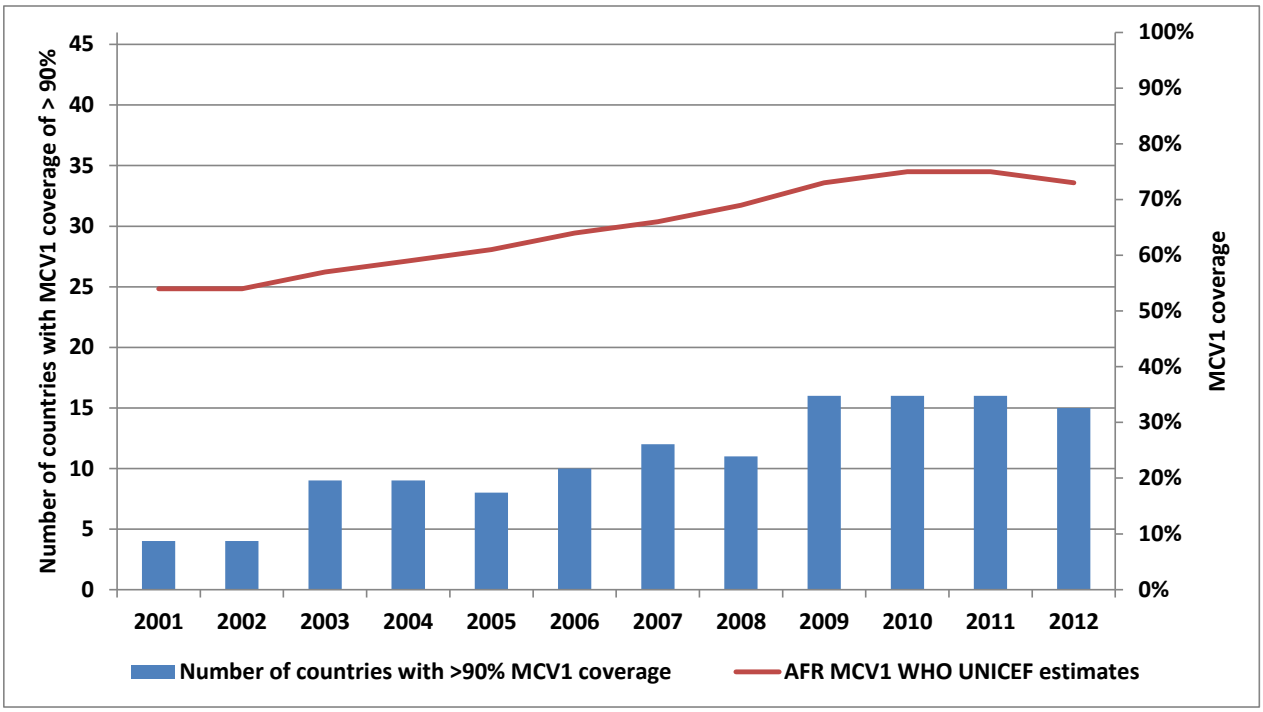



**Figure. Regional MCV1 coverage (WHO/UNICEF estimates) and countries with >90% coverage. 2001 – 2012.**

As of October 2013, 6 countries[7] have received GAVI approval and have introduced/ or are in the process of introducing MCV2. In 2014, four more eligible countries[8] are expected to apply for support from the GAVI to introduce MCV2 in the second year of life. As of August 2013, MCV2 is provided as part of the routine immunisation doses in a total of 13 countries.[9]

As of 2012, 3 countries in the African Region (Cape Verde, Mauritius and Seychelles) have introduced RCV in their national childhood immunization programme. In addition, 3 countries (Ghana, Rwanda, and Senegal) have been approved to receive funding from GAVI to introduce RCV in 2013/2014. Furthermore Burkina Faso and the United Republic of Tanzania have submitted an application to GAVI to introduce RCV in 2014/2015.

[5] Algeria, Angola, Cap vert, Eritrea, Gambia, Mauritius, Rwanda, Seychelles, Tanzania.
[6] Central African Republic, Eq Guinea, , Guinea, , Mali, Nigeria
[7] Burundi, Zambia, Eritrea, Ghana, the Gambia, Sao Tome and Principe
[8] Malawi, Mozambique, Senegal, Sierra Leone.
[9] Algeria, Botswana, Burundi, Cape Verde, Ghana, Lesotho, Mauritius, Seychelles, South Africa, Swaziland, Eritrea, the Gambia, Zambia.

**Supplemental Immunization Activities (SIAs):** Between 2001 and May 2013, a total of 596.2 million children were vaccinated through SIAs in 43 Member States.[10] Out of the 167 SIAs conducted over that period, 110 SIAs have attained administrative coverage of 95% or more, while 33 SIAs had reported coverage of less than 90%. From 2010 to October 2013, in 11 of the 40 countries which conducted follow-up measles SIAs, and for which we have detailed district level administrative coverage data, at least 90% of the districts achieved administrative coverage levels of 95% or more. Both Ghana and Rwanda have conducted MR SIAs in 2013, while Cape Verde and Senegal are expected to do so by the end of 2013.

**Measles case-based surveillance:** As of October 2013, 43 countries in the Region have established case-based surveillance for measles[11], supported with a network of 44 national measles serological laboratories, of which three also serve as regional reference laboratories[12].

In 2012, 55,717 suspected cases were reported from the countries in the Region, of which 91% benefited from appropriate investigation, and 20,935 cases of measles were confirmed by lab and epidemiological linkage. Twenty-seven countries have met the target of 80% or more districts reporting, with Regional average of 84%. At regional level, the non-measles febrile rash illness rate is 3.7 per 100,000, with 29 of 43 countries having met the target of at least 2 per 100,000 population. The Regional incidence of confirmed measles is 4.2 per 100,000 population in 2011 and 2.7 in 2012.

In 2013, between January and end-July a total of 58,657 suspected cases were reported of which 35,558 were confirmed by laboratory and epidemiological linkage. At regional level, the non-measles febrile rash illness rate is 2.9 per 100,000, and 77% of the districts have already reported at least one suspected case of measles with a blood specimen. The Regional incidence of confirmed measles is 4.1 per 100,000 population as of August 2013. (Table)

[10] All countries in the African Region except Algeria, Mauritius and Seychelles.
[11] These 43 countries include all Member States in the African Region except Mauritius, Sao Tome & Principe and Seychelles.
[12] The three Regional Reference Laboratories are located in Johannesburg (South Africa), Kampala (Uganda), and Abidjan (Cote d'Ivoire).

**Table. Key Measles Surveillance Performance Indicators, African Region 2007 – end July 2013.**

| Performance indicators | 2010 | 2011 | 2012 | 2013[13] |
|---|---|---|---|---|
| Number of reporting countries (out of 46) | 42 | 43 | 43 | 43 |
| Number of suspected measles cases reported | 163,575 | 74,896 | 55,717 | 58,657 |
| Number of confirmed measles cases | 127,422 | 32,323 | 20,935 | 35,558 |
| Percentage of confirmed measles cases (%) | 78% | 43% | 38% | 60.6% |
| % of cases investigated appropriately including with the collection of blood samples (target >80%) | 96% | 82% | 91% | 78% |
| Non-measles febrile rash illness (target >2/ 100,000 population ) | 3.7 | 4.4 | 3.7 | 2.9 |
| % districts reporting at least 1 case with blood sample (target >80%) | 84% | 81% | 84% | 77% |
| Incidence of confirmed measles per 100,000 population | 16.5 | 4.2 | 2.7 | 4.1 |

## Challenges

The MCV1 coverage across the Region, which has been increasing steadily between 2002 and 2010, has shown a levelling off in the last three years. Some of the countries with large populations still have major infrastructure and systemic challenges to raise and maintain high coverage levels. The countries with the largest number of children who did not receive first dose measles vaccine include Nigeria, Ethiopia and DRC.

Large scale measles outbreaks have continued in DRC, due to the gaps in national and subnational level routine immunization coverage, as well as the delays in conducting follow-up measles SIAs in 2010, (linked to delays in mobilizing resources for scheduled follow-up measles SIAs). The situation is compounded by the increasing shift in epidemiological susceptibility involving older children, and thus requiring a widening of the target age group for follow-up and outbreak response immunization activities.

There is a need to foster stronger country ownership and leadership in the implementation of strategies towards the attainment of the measles elimination targets.

## Summary

Countries in the African Region continue to implement strategies to meet the specific programmatic targets for Regional measles elimination to be met by end 2020. As of end 2012, fifteen countries[14] are on track to meet these targets. On the other hand, 16 of the 46 countries have missed most of the targets, and are at risk of failing to reach the 2020 elimination goal, unless programmatic measures are taken to ensure that the implementation of the strategies in strengthened.

[13] Data for January – end July 2013.

[14] Algeria, Botswana, Cape Verde, Eritrea, the Gambia, Ghana, Mauritius, Mozambique, Rwanda, Sao Tome and Principe, Seychelles, Swaziland, Tanzania and Zimbabwe

## American Region

- Member States have approved a plan of action for maintaining the elimination of measles, rubella and CRS in the Region of the Americas
- Continued circulation of the measles and rubella in other regions of the world has a profound economic impact on the Americas in responding to outbreaks.
- The public health implications of mass gatherings are becoming more pronounced; as such events draw ever-larger international crowds. This raises the possibility of the importation of measles and rubella viruses from other regions of the world.
- Technical Advisory Group (TAG) recommended administration of the second dose of MMR vaccine (MMR2) at 15-18 months with a note that it can be given simultaneously with other vaccines.
- Follow up campaigns are still maintained to guarantee high population immunity against measles besides maintaining high routine immunization coverage.
- Recent outbreaks also suggest that spatial heterogeneity in coverage should be a particular focus of programme activities.
- Advocacy strategies have been used for keeping the measles and rubella elimination in the political agenda. International Expert Committee (IEC) Members for the verification process have held a key role as advocates for maintaining the elimination.
- Major on-going challenges include funding constraints due to competing health priorities in the Member States, and among donor agencies.
- The Americas is at the final stage in the process to verify the region free of endemic measles, rubella and CRS.

### Background

Since 2002, the Region of the Americas has achieved and maintained elimination of measles and the last case of endemic transmission of rubella was reported in 2009. However, continued circulation of the measles virus in other regions of the world has had an impact on the epidemiology of measles in the region.

All of the reported measles cases (N=146) in 2012 and 2013 (N=318) have been linked to imported viruses. In 2012, the most common genotype was B3, mainly due to several secondary cases reported from the outbreak in Ecuador. In 2013, the most common circulating genotype has been D8, which has been mostly related to outbreaks in USA and Brazil. There were 166 cases of measles reported in the United States by the 34th epidemiological week. Also, Brazil has confirmed 114 cases by the week 38: vast majority from an outbreak from Pernambuco (85%) (see Figure).

In 2012, 16 people were reported to have rubella. In 2013, as of October 3, 7 rubella cases have been reported; majority linked to a rubella outbreak in Japan. While rubella remains endemic elsewhere in the

world, imported CRS will continue to be a public health concern in the Americas. In 2012, 3 cases of CRS were detected in the United States in infants whose mothers were infected during their pregnancy in Africa. CRS cases have not been reported on this year.

## Strategies for Maintaining the Regional Elimination of Measles and Rubella

### *Political commitment*

Due to virus importation and consequent risk for reintroduction of viruses in the Americas, at the Pan American Sanitary Conference in 2012, the Member States approved a plan of action for maintaining the elimination of measles, rubella and CRS in the Region of the Americas (resolution CSP28.R14. annexed). According to the Plan of Action countries are called upon to strengthen active surveillance of measles, rubella and CRS and to ensure measures for responding in a timely manner to imported outbreaks.

### *Surveillance*

All countries have a sensitive and timely case based measles and rubella/CRS surveillance system, but the quality of active epidemiological surveillance is not always homogenous at the sub-national and local levels. There are also some gaps in the surveillance of CRS; where they exist, countries use alternative and complementary lines of evidence such as conducting retrospective studies. Integrated epidemiological surveillance of measles/rubella met nearly all of the performance indicators for 2012, over 80%, and high performance has been continued in 2013. Virologic surveillance has been sufficient to document the interruption of transmission of measles and rubella for verification of elimination and detect virus importations.

PAHO has developed and validated the research protocol and instruments for external assessments of the surveillance systems and implemented first evaluations in 2013. Also for the purpose of analysing the performance and challenges of Measles and Rubella Laboratory Network, a meeting was held in May 2013 with the participation of experts from regional reference laboratories for measles and rubella for the Region of the Americas as well as PAHO immunization professionals.

### *Outbreak response*

Over-all countries have responded well to reported cases of measles and rubella, carrying out outbreak response activities such as searching for cases, tracing contacts, and evaluating risk. PAHO has also enhanced outbreak investigation and response at local, national, and regional levels by developing a standardized guideline for post-elimination setting; outbreak investigation workshop to familiarize this guideline at the regional level is taking place is December 2013. The costs associated with control of outbreaks can be substantial, and rapid containment of the first cases is crucial. In Ecuador, the public health response to the outbreak in 2011-2012 was estimated to cost over eight million dollars. The government is currently conducting an economic study, to understand better the amount of indirect costs associated with containing the outbreak.

### *Mass gatherings*

The public health implications of mass gatherings are becoming more pronounced; as such events draw ever-larger international crowds. This raises the possibility of the importation of measles and rubella viruses from other regions of the world, which could lead to outbreaks, and at a high cost in terms of health, placing the maintenance of the elimination of these diseases at risk. PAHO has cooperated with

Member States in hosting mass gatherings, and released health alerts on measles and rubella. In this year, the Region of the Americas was the venue of two large-scale international events, including the 28th World Youth Day 2013 in Rio de Janeiro Brazil and the 9th World Games 2013 in Cali, Colombia. As part of preparation, countries carried out supplementary immunization activities and intensified surveillance both before and after events. In the coming years, the Americas host the 2014 FIFA World Cup and the 31st Summer Olympic Games in 2016, both in Brazil. As always, PAHO stands ready to support countries seeking technical advice as part of preparedness for mass gatherings.

***Vaccination and coverage monitoring***

Most of the countries in the region report a very high immunization coverage (>95%). During 2012, countries and territories reported higher coverage for the first dose (MMR1) of 94%, recommended at one year of age, however, for MMR2 it is 77%. With the goal of achieving the highest MMR2 coverage possible, the TAG recommended administration of the MMR2 vaccine at 15-18 months with a note that it can be given simultaneously with other vaccines, such as the first DPT booster. However, follow-up campaigns are still maintained to guarantee high population immunity against measles in addition to maintaining high routine immunization coverage. The countries analyse vaccination coverage by age cohorts to target population groups with concentrations of unvaccinated individuals. Last year four countries implemented national follow-up campaigns: Bolivia, Haiti, Honduras and Nicaragua. Recent outbreaks also suggest that spatial heterogeneity in coverage should also be a focus of concern. The countries have conducted rapid monitoring of vaccinated in high risk areas and implement mop-up campaigns or intensified vaccination activities in areas with lower vaccination coverage. As per SAGE and TAG recommendation, PAHO is initiating research on efficacy on administrating MMR vaccine and yellow fever vaccine together.

***Advocacy and Communications***

Communication approaches have been variously used for promoting routine immunization, and campaigns through social communications. Vaccination Week was held in April 2013 to raise population awareness and to keep the topic on the forefront of social and political agendas; the next one is planned to take place in 2014. A large scale promotion campaign for FIFA is planned in 2014 to disseminate messages on the importance of being vaccinated against measles and rubella.

Strategies for advocacy have been also used for keeping the measles and rubella elimination in the political agenda. An important goal of this advocacy and fundraising work is to secure continuity of technical cooperation for the Member States in order to maintain the achieved results. International Expert Committee Members for the verification process have held a key role as advocates for maintaining the elimination. At the regional level PAHO is currently developing an advocacy book showing the impact of the different elimination strategies in the Americas. Testimonies are included from people who worked in member states, as well as from those involved in elimination efforts at the regional level.

***Resource mobilization***

Major on-going challenges include funding constraints; due competing health priorities in the Member States, and among donor agencies.

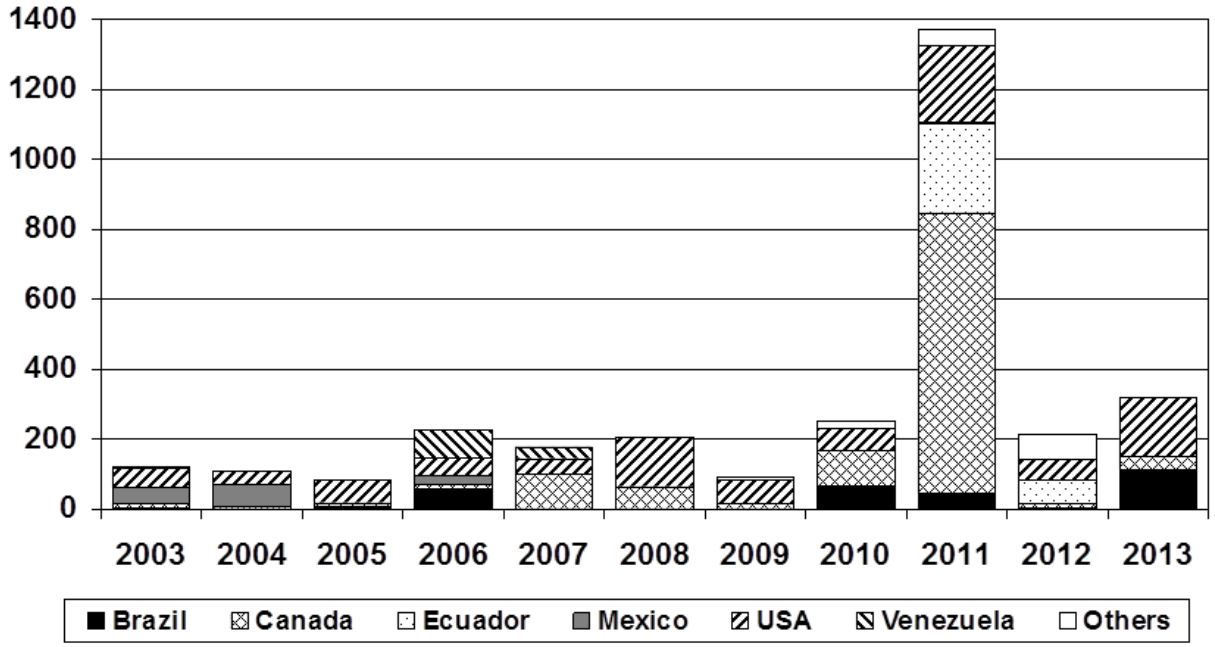
## Verification of the elimination of measles, rubella and CRS

The American Region is at the final stage in the process to verify the region free of endemic measles, rubella and CRS. In May 2013, the fourth meeting of the IEC was held jointly with the 23 national commissions and a sub-regional commission from the English Speaking Caribbean in order to:

1. follow-up on progress made on the documentation and verification of elimination, know the results of IEC members' country visits and the status of the national documents presented by the countries,
2. identify obstacles and challenges to maintaining the elimination of measles, rubella and CRS in the Region, and
3. discuss the implementation of the Regional Plan of Action for maintaining the elimination of measles, rubella and CRS and the work plan for 2013-2014.

The recommendations from the meeting, endorsed by TAG, include general and specific recommendations for countries and the PAHO Secretariat. According to the recommendations the final national elimination reports should be submitted to the IEC by the end of the year. The countries should also implement their national plan of actions to maintain the elimination including follow-up campaigns. IEC conducted field visits to Haiti, Colombia, Argentina, Peru, Ecuador and Brazil in 2012-2013. IEC members will continue making visits to countries where maintaining elimination remains a significant challenge in 2014. Moreover, the IEC is planning to present the progress report on the verification process for the PAHO's Executive Committee in 2014 and held a regional meeting with the National Commissions in April 2014.

**Figure: Distribution of Confirmed Measles Cases Following the Interruption of Endemic Transmission, the Americas, 2003-2013***




*** Data as of epidemiological week 39/2013**

## Eastern Mediterranean Region

- EMR has made significant progress towards measles elimination both in terms of improving MCV1 coverage and decreasing numbers of reported cases from 2000 to 2010.
- Since 2010 the Region has gone through many challenges including political changes, conflicts, floods, and famine. These have led to a decrease in the regional MCV1 coverage and increase in outbreaks and reported measles cases. Outbreaks occurred in Afghanistan, Pakistan, Somalia, Sudan and Yemen, Syria and neighboring countries.
- Although there is no regional rubella elimination target, 13 countries have adopted a rubella elimination target and are making good progress towards achieving that target. Most of the regional rubella burden is among GAVI eligible countries that have not yet introduced RCV.
- Both routine coverage data and SIA quality are key challenges to be addressed.

### Introduction

In 1997, the 22 countries in the Eastern Mediterranean Region (EMR) resolved to eliminate measles from their region by 2010 (EM/RC44/R.6). Despite significant progress, in terms of morbidity and mortality reduction in all countries, the region did not achieve measles elimination by the target date of 2010. Accordingly, in 2011, the Regional Committee of the Eastern Mediterranean resolved to revise the target date of measles elimination to 2015 (EM/RC58/R.5)

Several EMR countries are suffering from complex emergencies, internal conflict and financial constraints which constitute major challenges facing measles elimination. Endemicity of poliovirus in Afghanistan and Pakistan and early 2013 re-emergency of polio cases in Somalia add to these challenges.

Countries of the EMR are at different stages of measles endemicity and have variable capacity of measles elimination. EMR countries are categorized in 3 groups, based on incidence of measles in 2011:

Countries **at elimination** and ready for validating elimination (reporting 0 cases for ≥2 years or more in presence of a nationwide measles case-based surveillance and high measles coverage for both MCV1 and MCV2): Bahrain, Jordan, Syria, Palestine. However in 2012 crisis started in Syria that has disrupted the proper implementation of routine immunization and measles cases appear late 2012 after two consecutive years with no laboratory confirmed case. Then measles cases appear neighboring countries hosting Syria refugee one of them is Jordan which also had reported zero cases for ≥2 years. Bahrain and Palestine maintained zero reporting of confirmed case.

Countries **close to Elimination**: (incidence < 5 cases/1,000,000 with a nationwide measles case-based surveillance and high measles coverage for both MCV1 and MCV2): Egypt, Iran, Oman, Tunisia, maintained their status except Iraq and Lebanon which have experienced measles outbreaks since early 2013 to date.

Countries with **high burden of disease**: Afghanistan, Djibouti, Kuwait, Libya, Morocco, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, South Sudan, United Arab Emirates and Yemen. These countries still present the highest number of cases in the EMR, but there are on-going activities such as SIAs and implementation of RED and technical supports to advice how to close the immunity gaps.

## Measles and Rubella Epidemiology

### *Measles*

The implementation of elimination strategies in Member States has led to a rapid decrease in measles and rubella incidence in the region. In 2012 six countries (26%) have reported measles incidence of <1 case per million persons in the presence of a sensitive and well-functioning nationwide surveillance system: Bahrain, Iraq, Jordan, Oman, Palestine and Syria. In spite of this progress, there has been a resurgence of measles cases in several countries from late 2009 which has continued to 2013. The total confirmed measles cases reported in 2012 and January-July 2013 are 23,451 and 11,312 cases respectively, 79% of these cases are reported from Afghanistan, Pakistan, Sudan and Yemen. Pakistan and Sudan alone accounts for 70% of cases in 2012 and 74% in 2013, despite implementing of follow up SIAs in 2010-2011.

This resurgence has occurred in some countries that have been reporting high routine and SIAs vaccination coverage however, a substantial proportion of the measles cases reported during these outbreaks were unvaccinated, which raises the concern about the quality of the reported routine coverage data as well as the quality of implemented SIAs.

Table. Countries Reporting High Number of Confirmed Measles Cases, 2009- 2013 (July)

| Countries | 2009 | 2010 | 2011 | 2012 | Jul-13 |
|---|---|---|---|---|---|
| Afghanistan | 2158 | 1528 | 1357 | 2797 | 315 |
| Pakistan | 267 | 1008 | 2675 | 8046 | 5994 |
| Sudan | 27 | 568 | 5581 | 8461 | 2338 |
| Yemen | 77 | 352 | 2411 | 2159 | 298 |
| Total | 2529 | 3456 | 12024 | 21463 | 8945 |

### *Rubella*

Currently, 16 of the 22 countries in EMR are using rubella vaccine in their EPI program with high coverage ≥90% coverage of RCV1 and as of 2012 15 countries using a 2 dose of MMR and one country using MR schedule. Thirteen countries (60 %) have established a national target for rubella/CRS elimination. Ten countries now are implementing CRS surveillance as well. In addition, rubella case-based surveillance is integrated with measles surveillance in all countries in the Region. In 2012, 1606 rubella confirmed cases were reported by the EMR countries. Tunisia used to provide rubella vaccine for girls only, a strategy that created an immunity gap among males resulting in a huge rubella outbreak in 2011 and 2012 with reported cases of 1072 and 155, respectively. This has been reverted in 2013 by conducting MR campaign and introducing rubella vaccine in the routine immunization.

The new GAVI window for supporting MR catch up campaign is an excellent opportunity to intensify measles/rubella control and elimination activities. In January 2012, the EMRO organized a Regional

consultation on Rubella and CRS to discuss the regional situation and the possibility of establishing regional rubella and CRS control or elimination target.

Table. Countries Reporting High Number of Confirmed Rubella Cases (with the exception of Tunisia, these countries have not yet introduced rubella vaccine), 2009 to 2013 (July)

| Countries | 2009 | 2010 | 2011 | 2012 | Jul-13 |
|---|---|---|---|---|---|
| Afghanistan | 34 | 45 | 87 | 89 | 7 |
| Pakistan | 84 | 206 | 211 | 178 | 495 |
| Sudan | 343 | 302 | 237 | 173 | 238 |
| Yemen | 173 | 154 | 153 | 134 | 423 |
| Tunisia | 4 | 155 | 1072 | 483 | 8 |
| Total | 634 | 707 | 688 | 574 | 1163 |

The above four countries excluding Tunisia as well as two more countries (Djibouti and Somalia) are all eligible for GAVI support to introduce rubella vaccine. So far only Yemen has applied to GAVI for MR introduction campaign and was approved with condition on implementation of effective vaccine management which was implemented in during September 2013.

## Progress Towards the Current Goal

### *Achieving high population immunity*

Based WHO/UNICEF estimates, routine MCV1 coverage improved during the past decade from 72% in 2000 to 84% in 2011. However, estimates for 2012 indicated a decrease in MCV1 regional coverage to 83% due, mainly, to the drop in MCV1 coverage in Pakistan and the slight decrease in Morocco, Syria, and Yemen. 12 countries maintained reporting of 95% or more for MCV1 in 2011 and 2012. In addition, the coverage of routine immunization has impressively increased in priority countries. For example, MCV1 coverage estimate was 64% in South Sudan in 2012.

Despite the progress in the Region, countries including Afghanistan, Pakistan, Somalia, Sudan and Yemen have experienced several outbreaks in late 2010 through 2013. These outbreaks occurred due to delay in implementation of the follow-up SIAs, a deteriorating security situation, and/or inadequate funds.

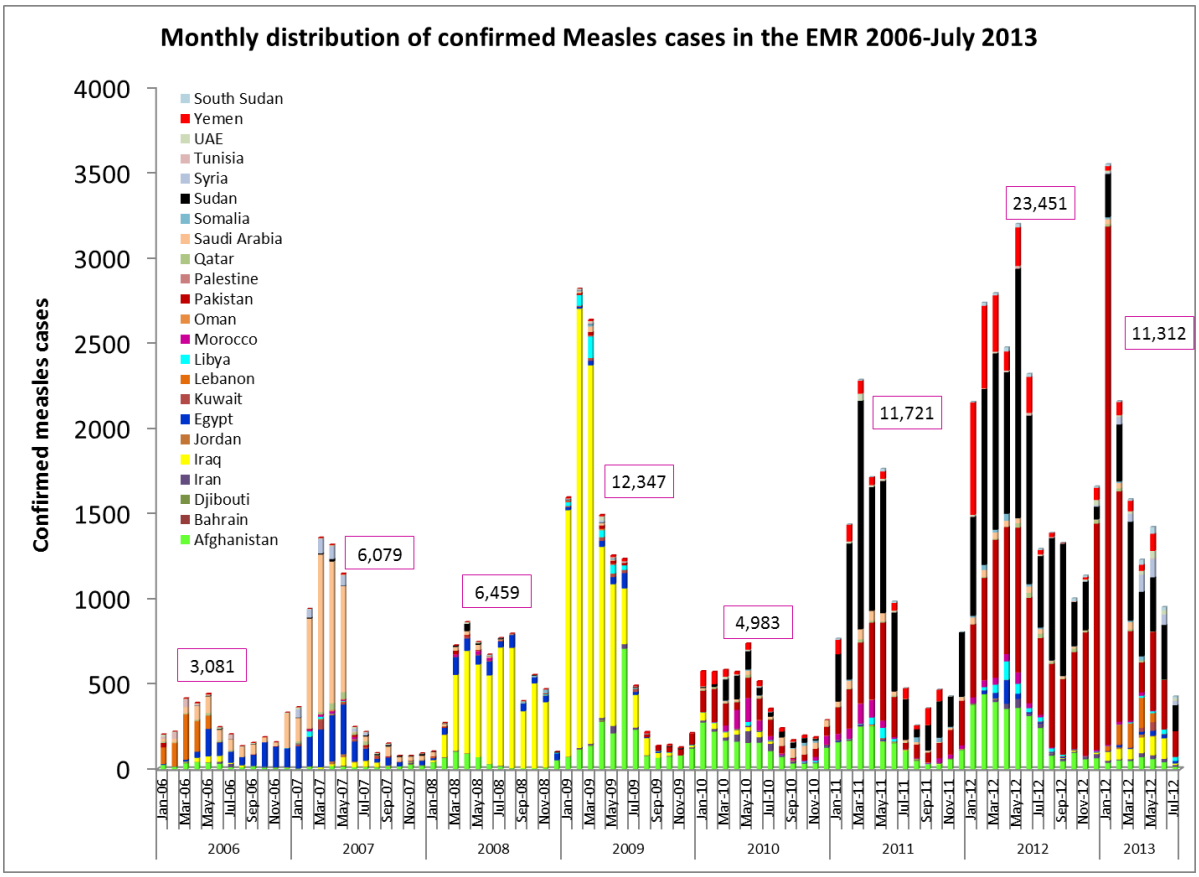
As of 2012, twenty one member states are implementing a 2$^{nd}$ dose of measles vaccine through routine services. Eleven of these countries have reached the 95% coverage with 2 doses of MCV at national level based on national reporting in 2011 and 2012.

Follow-up measles campaigns are being conducted in countries that have not reached the target 95% coverage with 2 doses of measles vaccine. During 2012 up to September 2013, around 55 million children have been vaccinated through measles supplementary immunization activities (SIAs) in Afghanistan, Djibouti, Pakistan, Somalia, S. Sudan and Yemen. A new initiative for the implementation of synchronized MCV campaigns in Syria and Jordan will be conducted in November 2013.

### *Case-based and laboratory surveillance*

All EMR countries have moved to measles case-base surveillance with laboratory confirmation, 21 (95%) of these countries are implementing nationwide, and two countries Somalia and South Sudan are

performing surveillance in identified sentinel sites. In 2009, 13,892 samples were tested in the EMR Lab Net for measles IgM; this increased to 15,074 serum samples tested in 2012. Countries report monthly to EMRO measles cases and surveillance indicators. There is a significant improvement in the performance of measles case-based surveillance in most of the countries in the region, as reflected by the status of measles surveillance performance indicators.




Also much progress has been made towards collecting genotype information from measles cases, 21 (91%) EMR countries have characterized circulating measles virus as a result of the increased capacity of the laboratory network. From 2000-2009 the major genotypes detected were D4 (47%) and B3 (38%), but since 2011 to date genotype B3 is increasingly being detected accounting for 81% of the reported genotypes in 2012, other genotypes detected were D5, D8, D9 and H1.

## Enabling Factors

- Commitment of EMR countries towards measles elimination renewed, RC58/R.5
- Partners' support to low income countries (e.g., The Measles and Rubella Initiative)
- Accumulating experience from other disease elimination/eradication efforts and successful implementation of measles catch–up and follow up campaigns.
- Current activities and initiatives to strengthen health systems and routine immunization in priority countries which resulted in improved reported vaccination coverage and measles surveillance being expanded and strengthened.

- GAVI windows of support for MCV2 introduction, RCV and measles SIAs in priority countries.

### Challenges

The Region is still facing challenges to reach the measles elimination goal. From 2010 to date the Region is going through many challenges: political changes, conflicts, floods, famine as well as shortage of funds from partners. Routine vaccination coverage in many countries in the Region didn't reach at least 95% coverage with both MCV1 and MCV2 in all districts, the level that supports reaching measles elimination. Therefore, maintaining very high levels of population immunity throughout the population is a significant challenge in this context.

Measles epidemiological and molecular surveillance is not up to the standard that supports validating measles elimination, even in most of the countries with established nationwide surveillance. Some countries of the region are experiencing measles outbreaks even among the age groups that have been vaccinated during SIAs with reported high coverage. Pockets of susceptible populations still exist in some countries in the form of hard to reach populations in low income countries and in countries with big expatriate populations. All this has had an adverse effect on measles elimination activities and increased risk of outbreaks, as seen in Afghanistan, Pakistan Somalia, Sudan and Yemen. Funding for follow up campaigns and competing priorities are continuing challenges for these countries.

### Addressing the challenges

- Renewed commitment by member states (EM/RC58/R.5)
- Strengthening capacities at country level in regard to micro-planning and use of innovative approaches to reach unreached and hard to reach populations (e.g. RED/ CHD)
- Technical support to priority countries in surveillance and outbreak investigation
- Efficient use of available funding and encourage countries to maximize benefits from all GAVI windows of support especially new vaccine introduction, MR campaign, outbreak response and HSS
- Increasing the coordination/communication between Member States and EMRO with development partners in the region

## European Region

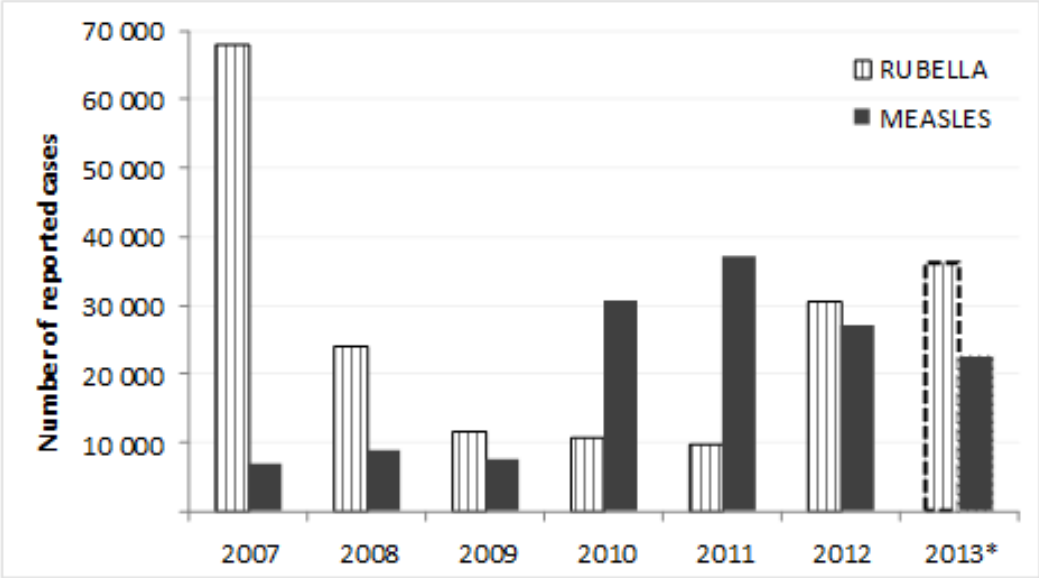
- Measles and rubella outbreaks are still occurring in the Region and are not always responded to with timely and appropriate control measures.
- The *Measles and Rubella Elimination 2015 - Package for Accelerated Action* has been launched in order to guide WHO Europe and Member States to reach the goal by 2015.
- Renewed political commitment and urgent need to close immunity gaps in the population are the main priorities for Member States.

### Progress towards the current goals

Following an all-time low in the number of reported measles cases in 2007 with just 6936 cases, the period 2008-2012 has seen an increased level of measles transmission with over 110,000 cases. The majority of cases were reported from countries that experienced large-scale outbreaks including Bulgaria,

France and Ukraine. Most cases occurred in the general population although outbreaks were also reported related to susceptible subpopulations (ethnic minorities, religious and philosophical groups).

**Figure. Number of reported measles and rubella cases in the WHO European Region, 2007 through first eight months of 2013.**




Data source: 2007-2012 data: WHO/UNICEF Joint Reporting Form.
*Data for the first eight months of 2013: Monthly measles and rubella reports to WHO Regional Office

For 2013, a large number of cases similar to that reported for 2012, is expected. For the first eight months of 2013, 24 023 measles cases have been reported. Large outbreaks have occurred in Georgia and Turkey with 7423 cases and 7018 cases, respectively. Other countries such as Germany and the United Kingdom have also experienced resurgences. In 2013, outbreaks have also affected susceptible subpopulations such as the orthodox protestant community in the Netherlands and the Orthodox Jewish Community in the UK (London). Unlike 2012, when no measles-related deaths were reported, six deaths (age range 4 months-31 years) were reported to date for the first eight months 2013.

For 2012 and the first eight months of 2013, the majority of cases were among unimmunized individuals and were mostly reported in infants and children. However, older age-groups were also affected. During these consecutive time periods, 26% and 34% of the total cases, respectively, occurred among adults aged 20 years and older. The observed age pattern of cases reflects the persistent gaps in population immunity. Such gaps can be explained by historical immunization programme weaknesses, late introduction of vaccine and gaps in service delivery. Nevertheless, taking into consideration that MCV has been routinely used for more than 20 years the majority of cases could have been prevented.

The number of reported rubella cases decreased from 804 567 in 1999, to 9672 cases in 2011. However, in 2012 a few countries reported high incidence and outbreaks. During that year, out of 30 509 cases of rubella, 88% were reported from Romania and Poland with 20 812 cases and 6263 cases, respectively. The outbreak in Romania in 2011-2012 with over 24 000 cases resulted in 55 confirmed CRS cases, nine

of whom were fatal. As for 2012, a large number of rubella cases is expected for 2013, as 36,871 rubella cases, almost all from Poland, have been reported for the first eight months of 2013. The annual reported number of reported measles and rubella cases since 2007 is shown in the figure above.

## Successes and Challenges

The epidemiology of measles and rubella in recent years mirrors differences of population immunity between Member States in the European Region. Some countries do not face significant increase of incidence after the importation of measles or rubella viruses. However, with the large number of measles and rubella cases reported in 2012, and so far in 2013, it is becoming increasingly apparent that the routine childhood immunization programmes and activities may not be sufficient to reach the 2015 target without renewed political commitment, accelerated action and innovative ways of reaching susceptible populations. Closing immunity gaps in the population whilst maintaining high routine vaccination coverage with two doses of MMR vaccine presents challenges for immunization programmes to increase overall population immunity. In July 2013, Armenia, Azerbaijan and Georgia agreed on comprehensive efforts for the coming year to close immunity gaps in the population and prevent further spread of the disease within and across their borders. The major activities should be completed by mid–2014.

Rubella surveillance is still a challenge in the WHO European Region. Until 2012, four countries (Belgium, Denmark, France and Germany) did not have national surveillance for rubella. There is also a need for improving the laboratory capacity for rubella surveillance. Different surveillance systems for congenital rubella syndrome, congenital rubella infection and/or rubella in pregnancy, exist in the Member States. The Regional office receives annual reports on the case count; however, the available information is not sufficient and adequate for detailed analyses. Under-reporting is likely, as rubella still persists in a few Member States and only 276 CRS cases were reported in the European Region during 2000–2012.

## Actions taken

To support the documentation of the elimination effort, a verification process is on-going. The Regional Verification Commission for Measles and Rubella Elimination (established in January 2012) serves as the foundation for this effort, which is further guided by a *Framework for the verification process in the WHO European Region.*[15] The Regional Office has also assisted Member States in establishing national verification committees (NVC). To date, 38 of the 53 Member States in the Region have established a NVC. Four sub-regional meetings of the RVC with NVCs and representatives of national health systems were held in late 2012 and 2013. A standardized assessment for verifying the interruption of endemic measles and rubella virus transmission will be based on detailed information on a number of components. These include: measles and rubella epidemiology, virological surveillance, analysis of vaccinated population cohorts, the quality of surveillance and the sustainability of the National Immunization Programme.

To meet the 2015 target, the Regional Office recognizes the need for greater political commitment and accelerated actions by Member States as well as scaled up support from WHO and other partners. A

[15] World Health Organization 2012. Eliminating measles and rubella. Framework for the verification process in the WHO European Region. www.euro.who.int/__data/assets/pdf_file/0005/156776/e96153-Eng-final-version.pdf

*Package for accelerated action 2013–2015*[16] has been developed through a consultative process and endorsed by the European Technical Advisory Group of Experts on Immunization (ETAGE). It identifies priority areas in which the Regional Office will strengthen technical support to Member States as they seek to eliminate measles and rubella, and sets indicators and milestones by which progress resulting from the efforts of all stakeholders can be measured.

Alongside traditionally tried and tested methods to boost demand for vaccines and provide equitable access, the Package considers innovative ways to change current approaches, acknowledging that "business as usual" may not be sufficient to reach the elimination target. The Package for accelerated action groups recommended activities in the following six categories:

- Vaccination and immunization system strengthening
- Surveillance
- Outbreak prevention and response
- Communications, information and advocacy
- Resource mobilization and partnerships
- Verification of measles and rubella elimination.

Renewed attention, and commitment and innovative tools are required to overcome the many challenges of maintaining strong immunization programmes. For this reason a *Guide to Tailoring Immunization Programmes (TIP)* [17] was developed to provide proven methods and tools to assist national immunization programmes design targeted strategies that increase uptake of infant and childhood vaccinations. The Guide provides tools to identify susceptible populations to identify the barriers to vaccination and implement evidence-based interventions. The Guide is intended for use by healthcare professionals, public health authorities and decision makers. After successful pilot-testing in Bulgaria in 2012, the Guide was launched in April 2013 as part of the Package for accelerated action and is to be rolled out in several countries across the Region. Sweden has already implemented it to improve vaccination coverage among an ethnic minority group, immigrants and an anthroposophic community.

Vaccination concerns among a significant minority of healthcare workers results in lack of strong provider recommendation for vaccination during patient encounters. To address these concerns there are also plans to adapt TIP to specific healthcare worker networks each year as part of the Package, and to engage the academic and practicing network of paediatricians at the national level to enhance support for measles and rubella elimination activities.

The Regional Office has also developed a manual to assist immunization programme managers to respond to communications issues caused by real or perceived vaccine-related events (VRE). The manual *Vaccine*

[16] World Health Organization 2013. Measles and rubella elimination 2015. Package for accelerated action: 2013–2015. www.euro.who.int/__data/assets/pdf_file/0020/215480/PACKAGE-FOR-ACCELERATED-ACTION-20132015.pdf

[17] World Health Organization 2013.The Guide to Tailoring Immunization Programmes. Increasing coverage of infant and child vaccination in the WHO European Region www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf

*safety events: managing the communications response*[18] provides practical, informative strategies and tools to help plan and manage a communications response following a VRE in a local community, at a national level, or beyond. The aim of the manual is to increase public trust and confidence in vaccines, and to minimize the negative impact of VREs.

### Summary

The occurrence of widespread outbreaks or indigenous transmission of measles in a few countries persisted in 2013. While most countries of the Region have controlled rubella, a small number still reported a high incidence and outbreaks. Sub-optimal rates of vaccination coverage and immunity gaps in the population remain at the core of the problem of continued measles or rubella transmission in the Region. Moreover, outbreaks of measles and rubella have also repeatedly occurred among certain subpopulations underlying their persistent vulnerability to these diseases.

Political and public complacency about the value of immunization and the lack of perceived threat of vaccine preventable diseases has contributed to suboptimal vaccination coverage. This, together with persisting immunity gaps in the population calls for a renewed political commitment, improved risk communication by health authorities and accelerated action by Member States and partners to eliminate measles and rubella in the WHO European Region. The process of verifying the elimination of measles and rubella in the Region that began in 2011 will provide an opportunity for each country to evaluate the sensitivity of measles and rubella surveillance and identify areas where more efforts are needed to achieve the goal of eliminating these diseases

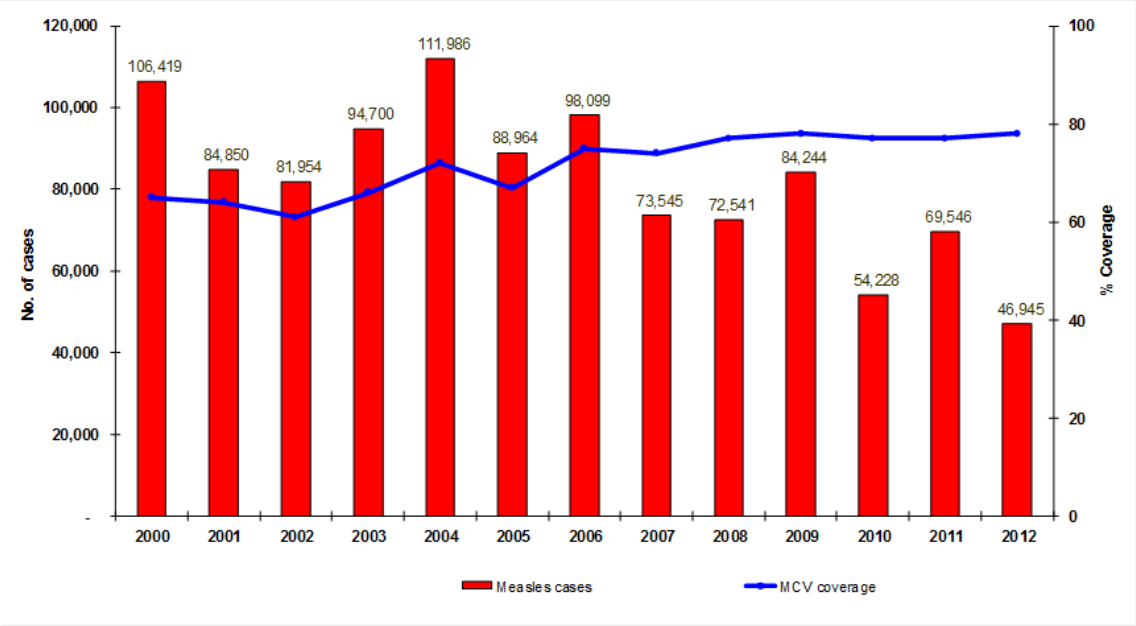
## South-East Asia Region

- In September 2013, all Member States unanimously adopted the resolution to eliminate measles and control rubella/CRS by 2020.
- Regional routine MCV1 coverage has significantly increased from 65% in 2000 to 78% in 2012; however, MCV1 coverage remains below 80% in both India and Indonesia.
- All countries provide two doses of MCV with India completing a measles catch-up SIAs targeting 139 million children.
- Six out of 11 countries have introduced nationwide RCV into their national immunization program with one wide age range MR SIA conducted in Nepal in 2013.
- Funding remains a key challenge to achieving the regional measles and rubella targets in addition to the introduction of RCV in a few large countries and scaling up the use of MCV2.

[18] World Health Organization 2013.Vaccine Safety Events: managing the communications response. A Guide for Ministry of Health EPI Managers and Health Promotion Units. www.euro.who.int/__data/assets/pdf_file/0007/187171/Vaccine-Safety-Events-managing-the-communications-response-final.pdf

In the South East Asia Region (SEAR), MCV1 coverage has increased from 65% in 2000 to 78% in 2012 along with a decline in total number of reported measles cases in this same period (See Figure). In SEAR, only five countries remain to introduce rubella into their national immunization programmes (NIP). They are DPR Korea, Myanmar, Indonesia and Timor-Leste; in India four states (Delhi, Goa, Pondicherry and Sikkim) have already introduced MMR in their routine immunization, and the Government of India is currently discussing the roll out of rubella nationwide. Only Nepal and Timor-Leste remain to add a second dose of measles into their NIP.

**Figure: Reported Measles Cases* and MCV1 Coverage+, SEAR, 2000–2012**




* source: WHO/UNICEF JRF; + WHO/UNICEF coverage estimates, 2013

A total of 17,402 suspected cases of measles were reported from the countries of SEA Region in 2013, as of September 30th; of these 2,934 were laboratory confirmed measles and epidemiologically linked cases, and 3,219 laboratory confirmed and epidemiologically-linked rubella cases. There were a total of 189 measles outbreaks reported resulting in the report of 5,182 suspected cases of measles. A total of 1165 laboratory & epidemiology linked confirmed cases of measles and 2,717 cases of rubella were reported from these outbreaks.

The total measles catch up campaign target for India was 139 million (spanning 2010-2013), out of which 33.4 million were vaccinated during 2013. Further, India had initiated WHO-NPSP assisted laboratory based measles surveillance on the AFP surveillance platform in two southern states in 2005, which now has been expanded to 15 states covering 90% of the country population with laboratory strength of 11 across the country. As part of this surveillance expansion plan, in 2013, three more states (Maharashtra, Odisha and Uttar Pradesh) have been added to this measles surveillance network, with a plan to expand further to cover 24 states and 95% of the county population by the end of 2013.

In Nepal, the third phase of the MR campaign started on 14 December 2012 and finished on 14 January 2013 in 35 districts. The target was 5,580,281 and coverage was reported at 5,638,149 (100%). One dose of OPV was integrated during the MR campaign. Bangladesh had planned a massive SIA for November 2013 targeting children from 1 to 15 years of age for a total target of 52 million. Unfortunately, due to unavoidable circumstances, the SIA is now postponed to February 2014.

In February 2013, a Regional Consultation on the Feasibility of Measles Elimination and Rubella/CRS Control was held in Kathmandu, Nepal, where participants from all countries of the Region met. Supported by international technical partners as well as the WHO's Headquarters and the SEA Regional Office, the countries agreed that measles elimination and rubella control was both programmatically and technically feasible and recommended 2020 as the target year. This issue was further discussed at the meeting of the SEA Immunization Technical Advisory Group (SEA-ITAG) in April 2013 which also reaffirmed the feasibility of measles elimination and rubella/CRS control by the year 2020. Finally, in early July, at the High Level Preparatory Meeting for the 66th Regional Committee of SEA Region, the proposal to set 2020 as the target year was accepted and a draft resolution prepared accordingly. At the 66th SEA RC meeting, the Member States unanimously adopted the proposed resolution to eliminate measles and control rubella/CRS by 2020 in the SEA Region.

In September 2013, at the 66$^{th}$ Meeting of the SEA Regional Committee, a resolution was passed setting 2020 as the target year for the Region to eliminate measles and control rubella/CRS. There were several events that led up to the passage of this important resolution for the SEA Region.

Immediately following the passage of the RC resolution, SEARO organized from 23-27 September 2013 a Regional Surveillance Standards Workshop on measles and rubella/CRS. The workshop was to achieve consensus on the indicators to monitor progress towards the 2020 goal and agreement on the quality indicators for measles and rubella/CRS surveillance in the Region.

SEA Region countries are committed to the elimination of measles and rubella/CRS control by 2020. However, there are many challenges to the achievement of the measles elimination and rubella/CRS control goals for this Region. Some of these are:

- A preliminary estimate projects the cost to be in excess of US $ 800 million for the SEAR to achieve the measles and rubella goals. Major efforts will be needed to mobilize the required resources;
- Expansion of the laboratory network will be needed in almost all countries to strengthen the quality of measles/rubella surveillance;
- Several large population countries still need to introduce rubella vaccine and scale up second dose of measles vaccine;
- Countries will need both additional financial resources as well technical support to move from the current outbreak surveillance to that of a case-based surveillance for measles and rubella.

## Western Pacific Region

- All countries in the Region have made tremendous efforts to achieve and sustain measles elimination with significant decrease in measles incidence since 2008 and a high regional MCV1 coverage of 98%.
- The Measles Regional Verification Commission is now established and will monitor progress towards measles elimination annually.
- There has been a measles resurgence in 2013 in China. Endemic transmission continues only in China, Malaysia and the Philippines.
- In 2013, the Regional TAG recommended the region establish a rubella elimination target. Rubella vaccine is provided in all but four WPR countries and areas.
- Intensified efforts are needed to identify and close gaps in population immunity by conducting high-quality SIAs in countries with sustained measles virus transmission and improve routine MCV1 and MCV2 coverage

### Background

The Western Pacific Region consists of 37 Member States (including 27 countries and 10 areas). For surveillance and verification purposes, the 21 Pacific islands are considered as one epidemiological block. In 2003, the Regional Committee for the Western Pacific (RC) resolved to eliminate measles. A target year of 2012 was established in 2005, and reaffirmed in 2010. In 2012, the Regional Committee urged member states to interrupt all residual endemic measles virus transmission as rapidly as possible. These RC resolutions emphasize accelerating rubella control and CRS prevention by combining them with measles elimination activities. In June 2013, the Technical Advisory Group on Immunization and Vaccine Preventable Diseases in the Western Pacific Region recommended that the Region establish a rubella elimination goal.

### Regional update

Annual data on MCV coverage are reported from 36 of the 37 WPR countries and areas to WHO and UNICEF through the joint reporting form (JRF); overall, MCV1 coverage in WPR was 98% in 2012. In 2012, 15 (42%) countries and areas achieved $\geq$95% MCV1 coverage; MCV1 was administered at 8 months in one (3%), at age 9 months in six (17%), at age 10 months in one (3%), at age 12 months in 24 (67%), and at age >12 months in four (11%).

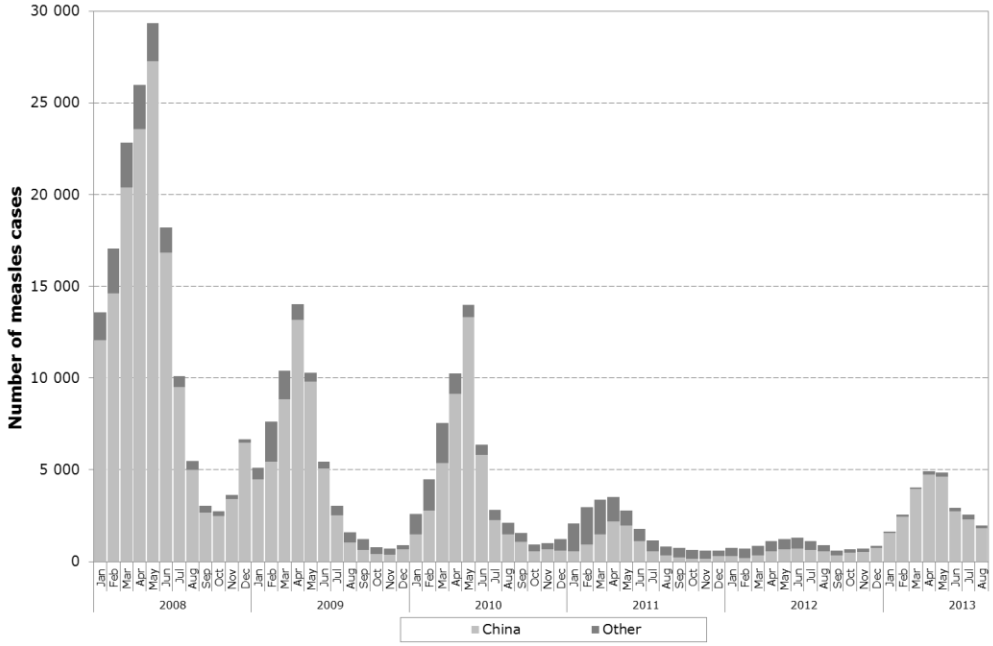
Thirty-three countries and areas provide routine MCV2, with 11 (31%) reporting $\geq$95% MCV2 coverage in 2012. Among the 33 countries and areas reporting MCV2 coverage in 2012, the scheduled age of MCV2 administration ranged from 12 months to 7 years. In 2012, more than 1.1 million children were targeted for vaccination in measles SIAs in Papua New Guinea and MR SIAs in Mongolia and Solomon Islands.

Measles case-based surveillance is conducted in all 37 WPR countries and areas. As of August 2013, nine (64%) of 14 countries and areas met the target of ≥2 suspected cases discarded as non-measles per 100,000 population; 96% of suspected cases were adequately investigated; 92% of suspected cases had adequate specimens collected for laboratory testing; and 96% of blood specimens received by the laboratory had results available within 7 days.

## Progress to achieve elimination

By end of 2012, measles incidence reached an historic low, decreasing to 5.9 cases per million population. In 2013, only three countries in the Region report on-going endemic transmission: China (incidence 28.1 per million), Malaysia (8.1 per million), and the Philippines (7.2 per million). The only other countries reporting measles incidence rates above 5 per million population are Lao People's Democratic Republic (18.0 per million) and Macao (5.9 per million). In 2013, the predominant measles virus genotype detected in WPR is H1, with a few cases reported as B3, D8, D9, and G3.

**Figure: Measles cases by month of onset, Western Pacific Region, 2008-2013**




The WPR Guidelines on Verification of Measles Elimination were finalized in March 2013; progress toward measles elimination in WPR will be monitored by the Regional Verification Commission through annual progress reports from each country or area and from the Pacific islands countries and areas reporting as one epidemiologic block. The first annual progress reports from National Verification Committees were due on 1 October 2013.

Rubella-containing vaccine is not provided in four WPR countries and areas; three of these countries (Cambodia, Papua New Guinea, and Viet Nam) are eligible for financial support offered by the GAVI Alliance to conduct a wide-age-range SIA using combined measles-rubella vaccine followed by the introduction of rubella vaccine in their national routine immunization programs. In addition to contributing to rubella elimination, these SIAs provide a unique opportunity to boost population immunity to measles and contribute momentum to achieve and sustain measles elimination in WPR.

## Challenges and opportunities

To achieve measles elimination in the Western Pacific Region, intensified efforts are needed to identify and close gaps in population immunity and by conducting high-quality SIAs in countries with sustained measles virus transmission (e.g., China, Malaysia, and the Philippines). Although China represents 75% of the regional population, in 2013, 96% of all confirmed measles cases were reported from China. In response to the relative measles resurgence, China hosted a National and International Consultation on Measles Elimination and EPI Strengthening in June 2013. Recommendations from the consultation included that provincial (or smaller) SIAs were needed to fill immunity gap; population coverage surveys should be considered among young children at national and subnational levels; to develop stronger immunization practice standards to reduce missed opportunities; and to reduce nosocomial transmission of measles by reducing admissions, isolating cases, and vaccinating health workers

Additional efforts are needed to strengthen routine immunization services in countries and areas with <95% coverage with the routine MCV1 or MCV2, to introduce a MCV2 dose in the four remaining countries and areas that do not yet have a routine 2-dose MCV schedule, and to use SIAs to close immunity gaps among measles-susceptible populations in countries and areas that have ongoing measles virus transmission.

High-quality case-based measles surveillance is critical to the verification process. Despite overall improvement in measles surveillance performance, gaps persist, as reflected by the low proportion of second-level administrative units with one or more non-measles discarded case per 100,000 population. Additionally, incomplete investigations of suspected measles cases in some countries challenge efforts to rapidly identify and respond to outbreaks and to measure and document progress towards elimination. The sensitivity of the measles surveillance system in other countries with discarded non-measles reporting rates of <2 per 100,000 population might be insufficient to rapidly detect and respond to outbreaks or to meet verification criteria.

Important progress has been made towards accelerating rubella control in recent years, including an increased number of countries using combination measles-rubella vaccine and an increased number of countries integrating measles and rubella surveillance. As a way forward, countries are encouraged to integrate measles and rubella elimination activities whenever possible; build rubella case-based surveillance, ideally integrating with measles surveillance; and gain understanding of rubella epidemiology and population immunity profiles to help develop effective and feasible immunization strategies to achieve rubella elimination.

# V. Use of Rubella Vaccine in the Routine Vaccination Schedule

- Recommendations in the current rubella position paper are either unclear or weak with regards to the timing of administration of the 1st dose of RCV and to the choice of RCV formulation when two doses of measles containing vaccine are used by countries. This lack of clarity has led to suboptimal timing and usage of RCV in some countries.
- This section highlights the current practices and provides the rationale for the following draft recommendations:
  - For countries introducing or using rubella vaccine, it is strongly recommended that this be given in combination with the first dose of MCV (as MR or MMR).
  - In countries using RCV and a two-dose schedule of MCV, both doses should be the same formulation of MR or MMR. That is the same vaccine should be used for both doses.

## Current policy guidance

The current position paper on rubella (http://www.who.int/wer/2011/wer8629.pdf) recommends that countries take the opportunity offered by accelerated measles control and elimination activities to introduce RCVs. In addition, it states that

> *"The first dose of an RCV can be delivered at 9 months or 12 months, depending on the level of measles virus transmission.*
>
> *"However, when combined with measles vaccination, it may be easier to implement a second dose of RCVs using the same combined MR vaccine or MMR vaccine for both doses"*

However, the position paper does not provide clear guidance as to the optimal timing for the administration of the RCV and it does not clearly explain the statement on the practicality of using the same formulation of RCV for both routine doses.

This section describes two issues that have arisen from unclear or weak policy guidance regarding the use of RCV as part of national routine immunization programmes. It proposes strengthening the recommendations and provides the rationale for them.

## The timing of administration of the 1st dose of rubella containing vaccine

By 2012, 132 of 194 (68%) WHO member states have introduced RCV either as MR or MMR through their national immunization programmes. Of these, 117 (60%) have RCV included in both routinely administered doses of measles-containing vaccine (MCV). However, 9 member states with two routine doses of MCV have only one dose of RCV in their schedule -- 8 countries (Cape Verde, Iraq, Jordan, Lebanon, Maldives, Philippines, Saudi Arabia, and Tunisia) include the RCV only with MCV2 and the 9$^{th}$ country (Bangladesh) includes RCV with MCV1 but not with MCV2. Sixty two countries are yet to introduce a RCV (see table).

Table: The vaccine formulation and number of member states using measles and rubella containing vaccines in their routine national programmes

| Vaccine used for first dose | Vaccine used for second dose | Number of countries |
|---|---|---|
| M | none | 42 |
| M | M | 20 |
| M | MR or MMR | 8 |
| MR or MMR | none | 6 |
| MR or MMR | M | 1 |
| MR or MMR | MR or MMR | 117 |
| Total | | 194 |

### The problem

Given that global MCV1 coverage is considerably higher than MCV2 coverage (84% vs 36% for 2 year old cohorts in 2012), countries providing RCV with MCV2 rather than with MCV1 miss the opportunity of the higher coverage achieved with MCV1. In addition, as the second dose is given to older children than the first dose, this will delay the protection of children against rubella in some countries until children are 7 years of age. For example, for the 8 countries that have RCV only with MCV2, both the Philippines and Lebanon can gain 47% and 10% points in coverage by including the RCV with MCV1. In addition, children in Tunisia can be protected against rubella by 12 months of age rather than at age 6 years.

Therefore, there is a need to provide stronger recommendations on the timing of the first dose of RCV for the 8 countries that have already introduced RCV and give it with MCV2 only as well as for the 62 countries that are yet to introduce RCV.

### Recommendation

- For countries introducing or using rubella vaccine, it is strongly recommended that this be given in combination with the first dose of MCV (as MR or MMR).

## Using the same vaccine formulation for both routine doses

In 2012, of the 194 WHO member States, 146 administer a second dose of MCV through their routine national immunization programmes with 48 countries yet to introduce the routine second dose of MCV. Among the 146 countries using two routine doses of MCV, 117 include RCV with both doses, 9 use only 1 dose of RCV and the remaining 20 countries do not include RCV at all.

### The problem

As stated above the current recommendation is not strongly in favour of using the same measles- and rubella-containing vaccine formulation for both doses. In addition, it does not mention that when the formulation contains mumps vaccine (MMR), then at least two doses must be given.

There are clear programmatic disadvantages of not including RCV with both MCV1 and MCV2. These include:

1. Complexities in vaccine procurement, logistics, recording, and reporting. There are inherent problems associated with ordering, procurement and downstream supply of different vaccine

formulations (e.g., M and MR or MMR) as well as recording and reporting which vaccine has been administered to an individual child. There is also the potential for programmatic error, for example administering M when MR or MMR is indicated in the schedule.

2. Higher wastage. With different vaccine formulations aimed at different target age groups, there is the potential for increased wastage resulting from unused vaccine in an opened vial at the end of the vaccination session. The actual wastage depends on the session size (i.e., the number of children attending and requiring a specific vaccine formulation), session frequency, and the nature of the vaccination post (fixed site, school-based immunization, vs. an outreach session).
3. Lower coverage. Providing RCV only once may lead to lower coverage levels than if it is provided at two different opportunities. Using RCV for both routine doses with result in more children being protected against rubella.

In addition to the disadvantages above, there are a number of programmatic considerations that need to be taken into consideration:

***Cost***

The cost of single-antigen measles vaccine at UNICEF 2013 procurement prices (for a 10-dose vial) is between 21.5 to 42.5 US cents per dose compared to 52.4 US cents per dose for MR vaccine.[19] Hence, the cost increase will be between 10 to 30 US cents per dose. However, there will be no added administration costs as one preparation will be replaced by another. In addition, due to larger volumes, the price of MR vaccine is very likely to come down from its current levels.

***Safety***

The safety of RCV in pregnant women has been established[20]; hence it can be used not only in routine immunization of children but also in mass immunization campaign settings targeting adolescents and adults without safety concerns[21].

***Global vaccine supply***

Currently there are 3 manufacturers supplying measles vaccine in 10-dose vials to UNICEF (P.T. Bio Farma, Sanofi Pasteur and Serum Institute of India Ltd). MR in 10-dose vials is supplied to UNICEF by Serum Institute of India Ltd and it is expected that their capacity for the manufacture of MR vaccine will increase directly in proportion to the decrease in demand for measles only vaccine. Recommendations to countries to use two RCV doses instead of one would have some additional supply requirements. For example, if all the 20 countries (no RCV) added 1 additional dose of RCV; and the 8+1 countries (1 RCV dose) made the switch to 2 doses of RCV, the requirement for MR vaccine (assuming a 15% wastage) is just over 59 million doses. This quantity of MR is already available with ease, e.g. the MR campaign in Bangladesh targeting <15 year olds will require approx. 60 million doses of MR vaccine. This has been fully met in addition to other needs from across the world. Hence a global shortage, at least in the

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[19] http://www.unicef.org/supply/files/Measles.pdf; http://www.unicef.org/supply/files/MR.pdf

[20] Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001-2008**.** Castillo-Solórzano C; Reef SE; Morice A; Vascones N; Chevez AE; Castalia-Soares R; Torres C; Vizzotti C; Ruiz Matus C.
*J Infect Dis; 204 Suppl 2: S713-7, 2011 Sep.*

[21] Congenital rubella syndrome after rubella vaccination in 1-4 weeks periconceptional period.
Nasiri R; Yoseffi J; Khajedaloe M; Sarafraz Yazdi M; Delgoshaei F. Indian J Pediatr; 76(3): 279-82, 2009 Mar.

medium term, is not expected and can be entirely avoided by prior planning of the phasing in of MR and phasing out of measles only vaccine.

***Cold chain capacity***

Since measles only vaccine will be replaced by MR vaccine, for the same presentation (1 dose or 10 dose vials) there will be no additional demand on cold chain capacity and existing cold chain capacities in countries will be adequate to deal with the change in formulation.

Based on the disadvantages and considerations listed above, there is need for a stronger recommendation to use the same formulation of measles- and rubella-containing vaccine for both routine doses in the childhood immunization schedule.

## Recommendation

- In countries using RCV and a two-dose schedule of MCV, both doses should be the same formulation of MR or MMR. In other words, the same vaccine should be used for both doses.

## VI. Target Age Range for Measles Follow-up SIAs and for Measles - Rubella Catch- up SIAs

- Country experience and preliminary results from mathematical modelling were reviewed to address the question: *What criteria should be used to guide countries on when to expand the target age range for follow-up measles (M) SIAs beyond 5 years and catch-up measles-rubella (MR) SIAs beyond 15 years?*
- Measles and rubella elimination has been achieved and maintained in countries using a range of different vaccine delivery approaches (2 routine doses only, 2 routine doses and a single catch-up SIA, 2 routine doses and regular SIAs, and 1 routine dose and regular SIAs). These countries have all achieved and maintained elimination by reaching and sustaining vaccination coverage ≥95% in routine services and/or SIAs for all cohorts born since the introduction of vaccination and in all or nearly all districts.
- Factors affecting the magnitude and duration of impact from M, or MR SIAs, include the pre-existing population immunity (from routine vaccination, previous SIAs, and natural infection), the target age range for the SIA, the coverage achieved in the SIA, and the interval between SIAs. The final impact of M or MR SIAs is determined by how well the choice of target age range and the coverage achieved fill existing gaps in population immunity.
- Poor quality coverage and surveillance data hamper the ability to accurately assess age-specific susceptibility to measles and rubella and hence identify the appropriate target age and interval between SIAs. Where better quality coverage and surveillance (including serosurveillance) data are available, this provides more valuable local evidence to guide programme planning than mathematical modelling that is currently available. The priority should be on improving this data in every country.
- The following sections on M and MR SIAs provide the rationale for the following draft recommendations:

  o No magic formula exists to determine the appropriate target age range for M or MR SIAs. Current rules of thumb are pragmatic and not based on specific evidence.

  o The analysis of immunity should be triangulated with measles and (if applicable) rubella surveillance data. Age groups with high incidence rates should correspond to age cohorts with lower levels of immunity. Data from high-quality serological surveys should also be used when available.

  o The target age range of M SIAs should be extended beyond 5 years based on a comprehensive review of the country situation, focusing on the age pattern of susceptibility to measles based on routine and SIA coverage results, the age-specific incidence of measles, the age distribution of measles cases, available seroprevalence data, population characteristics, and the programme capacity to achieve high (>95%) coverage.

  o Catch-up MR SIAs should be extended beyond 15 years either to accelerate the progress toward established rubella/CRS elimination goals or to fill gaps in population immunity based on similar epidemiologic and programmatic considerations as for M SIAs. Additional information to consider for

MR SIAs include levels of rubella immunity among women of child bearing age, epidemiology of rubella and CRS, and population characteristics – e.g., age-specific fertility rates and age of mothers of CRS affected infants or to accelerate progress towards established rubella/CRS elimination goals.

o Consideration should be given to the trade-offs between strengthening routine delivery versus conducting poor quality wide age range SIAs especially in countries where systems are weak.

## Target age range for M follow-up SIAs

### Current Practice and description of the issue

The current Measles Position Paper recommends all programmes provide two doses of measles vaccine and achieve high coverage in order to raise population immunity to ≥95% and prevent epidemics. Delivery of the second dose may occur at a scheduled age through routine services or periodically through mass campaigns depending on which strategy achieves the higher coverage. Countries may add a second dose to the routine immunization schedule when first dose coverage is ≥80% at the national level for three consecutive years as determined by the most accurate means available (for example, a well conducted population-based survey or WHO/UNICEF estimates). SIAs should start with a wide age-range catch-up SIA targeting children 9 months to 14 years of age, followed by regular follow-up SIAs targeting children born since the last SIA, generally 9 to 59 months of age. Follow-up SIAs should occur every 2-4 years so that an SIA is conducted before the number of susceptible pre-school age children reaches the size of a birth cohort.

In AFR countries accelerated measles control in the 1990s by testing ideas that SIAs targeting the age groups at highest risk of adverse outcomes from measles (those <5 years of age) or SIAs targeting urban areas would reduce measles incidence and deaths. At the time the limited data on the age distribution of cases suggested that 25-50% of cases were older than 5 years. These SIAs had limited impact on both cases and deaths, as reviewed by Otten in 2003[22]. In response countries were urged and supported financially to conduct SIAs targeting children up to 15 years of age. For follow-up SIAs the regional TAG recommended in 2005 the following guidelines that have been informally adopted by other regions:

- "After measles SIAs that achieve relatively homogeneous coverage rates of >90%
    - If routine measles coverage ≥80% - an interval of 4 years is recommended targeting children 9-59 months of age.
    - If routine measles coverage >60%-79% - an interval of 3 years is recommended targeting children aged 9-47 months.
    - If routine measles coverage <60% - an interval of 2 years is recommended targeting children 9-35 months of age
- After measles SIAs that achieve relatively homogeneous coverage rates <90%
    - If routine measles coverage ≥80% - an interval of 3 years is recommended.
    - If routine measles coverage <80% - an interval of 2 years is recommended."

[22] Otten MW Jr, Okwo-Bele JM, Kezaala R, Biellik R, Eggers R, Nshimirimana D. Impact of alternative approaches to accelerated measles control: experience in the African region, 1996-2002. J Infect Dis. 2003 May 15;187 Suppl 1:S36-43.

Countries have generally followed these guidelines for follow-up SIAs, except that most have targeted children 9-59 months of age regardless of the interval between SIAs. Countries that have followed the above recommendations include several countries in AFRO conducting SIAs in a 3 year cycle that targeted children 9-47 months of age (Central African Republic, Comoros, Eritrea, Madagascar, Niger, Swaziland, Togo, Uganda, and Zambia). Two countries in WPR also followed these guidelines: the Philippines in 2007 targeted children 9-47 months of age in an SIA held 3 years after the previous one and in 2010 Papua New Guinea also targeted children 6-35 months of age in an SIA held two years after the previous one.

Countries have also used a "90% rule" for the target age range of a catch-up or follow-up SIA. Under this rule of thumb, the SIA should target an age range that includes 90% of the age distribution of reported cases. Though this rule of thumb has worked well in many situations, it can be misleading in some situations, for example where overall incidence is low. Work is underway to use dynamic models of disease transmission to better define the rule. Catch-up SIAs in large countries in Asia (Bangladesh, China, India, and Pakistan) targeted from 9 months to 10 or 12 years based on the age range of reported cases. For example, in Bangladesh 86% of reported cases in 2003 were under 10 years of age, prompting the choice of 9 months to 9 years for the catch-up SIA in 2005-2006. Catch-up SIAs in other countries (e.g. Egypt, Kyrgyzstan, Republic of Korea, Sri Lanka) chose target age ranges targeting older children and adolescents based on the age distribution of cases and/or serosurveys, e.g., from 8 to 16 years in the Republic of Korea. These countries generally had strong routine programs and assured high levels of immunity in younger (<5 years) age cohorts with routine vaccination rather than SIAs.

Countries have also widened the target age range of follow-up SIAs in response to large outbreaks where the age distribution of cases is shifted to older age groups. The WHO guidelines on response to measles outbreaks in mortality reduction settings[23] recommend the age groups to be vaccinated be chosen to fill susceptibility gaps based on the routine vaccination coverage and coverage during SIAs in each birth cohort, age-specific incidence rates, and the age distribution of cases to determine the age group to target.. In these situations a review of routine and SIA coverage data usually reveals a period of low coverage corresponding to the age cohorts affected by the outbreak (see country examples below).

In 2012 GAVI decided to offer funding for measles follow-up SIAs in six large countries (Afghanistan, Chad, DRC, Ethiopia, Nigeria and Pakistan) based on the assumption that these SIAs would target children 9-59 months of age. Four countries expressed an interest in applying and on review of the age distribution of recent cases, only Nigeria requested support for a 9-59 month target age range, with DRC and Pakistan requesting support for 9 months to 9 years of age SIAs and Ethiopia requesting support for an SIA targeting 9 months – 14 years of age.

To provide clearer recommendations to countries and partners on when the target age range for measles SIAs should be expanded beyond 5 years, the Measles-Rubella Working Group of SAGE was asked to review country experience and modelling evidence. The country experience presented below is being used to refine questions to be answered through mathematical models of disease transmission.

[23] Response to measles outbreaks in measles mortality reduction settings. WHO/IVB/09.03 Geneva: World Health Organization. P 20.

## Evidence and rationale for recommendations:

The following case studies provide evidence that uniform high coverage with MCV (>95%) must be reached and sustained in order to achieve elimination and that the timing and target age range for measles SIAs should fill any remaining gaps in population immunity.

***Republic of Korea:***

The target age range of the 2001 MR SIA was based on results of a serosurvey done during a large outbreak. The age distribution of measles cases matched age cohorts with low immunity from the serosurvey. With 96% SIA coverage and >92% coverage with 2 doses in routine, elimination has likely been achieved.

After achieving high coverage with one dose of MMR vaccine and experiencing <1 reported case per million population for 5 years, the Republic of Korea had a large measles outbreak in late 2000 and early 2001. The age distribution of cases was bimodal, with a peak in children aged <2 years of age and in school-age children 6 – 16 years of age. A serological survey of 18,402 school children (7-18 years of age) in late 2000 found that seronegativity was high (>5%) for all age cohorts, ranging from 5.3% at 17 years to 15.4% at 10 years of age. This age group corresponded to children born before the last major outbreak in 1994 and before the introduction of a second dose of measles in routine in 1997. The immunization programme instituted a school entry requirement for 2 doses of MMR vaccine that would ensure children 7 years and younger had high immunity and held an MR SIA targeting children 8-16 years of age in March 2001, achieving 96% coverage based on doses administered. After this SIA routine coverage with 2 doses has remained >92%. Incidence has been <1 per million population and only small, self-limited outbreaks occurred, most linked to importations and / or nosocomial transmission.

***Albania:***

The target age range of the MR SIA covered the age distribution of recent measles and rubella cases. With 98% coverage in the SIA and >93% coverage with 2 doses in routine, elimination has likely been achieved.

Albania reported large numbers of cases in the late 1990s after emerging from a period of isolation. In 1999 the country developed a measles-rubella elimination plan in order to meet regional elimination goals. From 1996 – 2000, 25-35% of cases were aged <5 years while 74% were 5-14 years of age. In the absence of rubella vaccination, rubella was also common in Albania, affecting primarily children <15 years in outbreaks every 5-6 years, including in one in 2000. The country chose to target children 9 months to 14 years of age with MR vaccine in 2000, reaching 98% coverage based on doses administered. MR vaccine was later provided through routine services to women 16-35y in 2001 and men 17-24y in 2003. After these activities routine coverage with 2 doses of MR vaccine (at 1 and 5 years of age) has remained >93%. Incidence of both measles and rubella has since been <5 per million population, except for 2006-7 when the country had outbreak of 90 reported cases linked to importations in disadvantaged, chiefly Roma, communities in 2006-7.

***Kyrgyzstan:***

The age distribution of the MR SIA covered the older half of the age distribution of recent measles and rubella cases and 2-dose routine covered the younger age groups. With 99% coverage in the SIA and >90% coverage with both routine doses, elimination has likely been achieved.

Kyrgyzstan reported large numbers of cases from 1997-1999 despite high coverage with one dose of measles vaccine. In 1997-1999, the outbreak started with 78% of reported cases 7-25y of age and 19% <7y of age and finished with 55% of cases 7-29y of age and 42% <7y. After implementing laboratory confirmation of suspected measles and rubella cases in 2000, the next year the country had a rubella outbreak with 2,017 reported cases: 40% aged <7y, 59% aged 7-25y, 1% >25y. In 1999 the country developed a measles-rubella elimination plan in order to meet regional elimination goals, with the country choosing to target children 7 to 25 years of age with an SIA using MR vaccine in 2001 and to target children <7 years of age through routine immunization. The SIA reached 99% coverage based on doses administered and 94% by coverage survey in the capital Bishkek. Since 2002, coverage of both routine doses (at 1 and 6 years of age) has been >90%. Measles and rubella incidence has been <5 per million population except for measles outbreaks in 2005-7 (120 reported cases) and 2011 (222 reported cases). The 2011 outbreak was linked to an importation from Uzbekistan and affected primarily children born since the 2001 SIA.

***Ghana:***

The age distribution of the initial measles catch-up SIA in 2001-2002 covered the age distribution of measles cases. Though coverage with the catch-up was >95%, coverage of the first follow-up SIA and routine (one dose) were both <90%. Routine improved afterwards to >90%, and second follow-up also attained >90% coverage by survey. Incidence since 2002 has been <20 confirmed cases per million population and no measles deaths have been recorded.

To control large yearly outbreaks of measles, Ghana analyzed the age distribution of cases in 3 districts and found 66% of cases <5 years and 30% between 5 – 14 years of age. Based on these results the country held an SIA targeting children from 9 months to 14 years of age in late 2001 (Central Region) and 2002 (remaining regions), achieving 99% coverage based on administered doses. Routine first dose coverage varied between 78-85% from 2001-2006 and between 86-95% thereafter, and the country held SIAs in 2006 and 2010 targeting children 9 – 59 months of age. SIA coverage was 79% in 2006, based on administrated doses, and 94% in 2010, based on a post-SIA coverage survey. Though reporting through the WHO-UNICEF Joint Reporting Form (JRF) suggests between 100-1,500 cases have been reported each year since the SIA, laboratory confirmed, case-based data from the MOH indicate that 14-394 confirmed cases were reported yearly since the SIA, giving an incidence of 0.62-19 per million population.

***Kenya:***

Initial SIAs targeting children <5 years of age did not control measles, with 37% of cases >5 years. Incidence dropped after an SIA targeting children <15 years of age. Routine coverage (1 dose) was <80% through 2006. Delayed first follow-up SIA allowed a large outbreak to occur. Though routine has improved to >85% since the 2006, SIAs have not targeted the growing proportion of cases aged >5 years. Incidence has remained high except for the year immediately after SIAs in 2009 and 2012.

Kenya experienced regular measles outbreaks in the 1990s-2000s despite reaching 80% coverage with one dose of measles vaccine (per coverage survey results) and conducting subnational SIAs targeting children 9 to 59 months in 1994, 1999 and 2000. As shown in the table below, from 1997-2001, 58% of the 53,508 reported cases were <5 years of age, with 25% aged 6-10 years and 12% aged 11-15 years. Based on these results the country held an SIA targeting children from 9 months to 14 years of age in 2002, achieving 98% coverage based on administered doses. Up until 2005, although first dose measles vaccination coverage was 70-80%, measles incidence was <5 reported cases per million population. A follow-up SIA initially planned for 2005 was delayed until 2006 in order to distribute long-lasting insecticide treated bednets during the SIA. In late 2005 measles cases began to increase, with 153 cases reported in 2005 and 1,847 cases reported in 2006. To control the outbreak the follow-up SIA was done in two phases both involving children 9-59 months of age, first targeting outbreak-affect districts in May 2006 and the second targeting the rest of the country in July, with >100% coverage based on doses administered. Though routine coverage increased to 80% in 2007 and 90% in 2008, measles incidence remained 30 – 50 reported cases per million population until the next follow-up SIA in 2009.

Although 24% of 3,609 cases reported from 2006-2009 were 6-15 years and 14% were ≥16 years, the 2009 SIA targeted children 9 – 59 months of age. After this SIA, achieving 82% coverage based on doses administered, and with routine coverage at 86-93% since 2008, incidence dropped to 2 reported cases per million population in 2010 but increased to >50 per million population in 2011. In 2011, 34% of 2,523 reported cases were aged 6-15 years and 22% were ≥16 years. No data was reported to the JRF in 2012 but >50 confirmed cases per million population were reported through the case-based surveillance system. In 2012 another SIA was done, with plans to target children 9 month to 9 years based on the age distribution of cases, but funds were available only to cover children 9 – 59 months. This SIA achieved 90% coverage based on a post-SIA survey and by 10 September 2013 only 177 confirmed cases have been reported.

Table. Age distribution of cases and SIAs, Kenya, 1997-2012.

| | **1997-2001** | **2002** | **2005/6** | **2006-2009** | **2009** | **2011** | **2012** |
|---|---|---|---|---|---|---|---|
| SIA target | | 9m-14y | 9-59m | | 9-59m | | 9-59m |
| SIA coverage | | 98% | >100% | | 82% | | 90% |
| Age distribution of cases | | | | | | | |
| <5 years | 58% | | | 61% | | 38% | |
| 5-9 years | 25% | | | 19% | | 22% | |
| 10-15 years | 12% | | | 5% | | 12% | |
| ≥16 years | 5% | | | 14% | | 22% | |

***Malawi***

After catch-up and follow-up SIAs targeting the recommended age range and generally achieving >95% administrative coverage, together with >80% routine coverage except for 2000-2004 (<80%), incidence was low for >10 years. A large outbreak occurred in 2010 and was not controlled by outbreak response targeting <5 years or <15 years covering only one district at a time. Though 28% of cases were ≥15 years, nationwide SIA targeting children aged 6 months – 14 years reaching >95% appeared to stop the outbreak. In years since incidence has been ≤2 confirmed cases per million.

Malawi was among the 7 southern African countries that decided to eliminate measles through high routine coverage plus catch-up and follow-up SIAs. In 1997 a catch-up SIA targeted children 9 months to

14 years of age, achieving 89% coverage based on administered doses, was conducted. Follow-up SIAs targeting children 9 – 59 months of age were implemented in 2002 and 2005, each achieving >100% coverage based on doses delivered. Routine coverage was >80% since then except for a dip to 70-80% from 2000-2004. Measles incidence was <100 reported cases per million population through 2005 then dropped to ≤10 per million population until a large outbreak in 2010. This outbreak spread throughout the country with 131,725 reported cases. Outbreak response campaigns targeting children 9-59 months of age early in the outbreak did not stop it from spreading. The age distribution of cases showed that 42% were <5 years of age, 30% were 5-14 years of age, and 28% were older than 15 years. These age cohorts were born during the years of low coverage (2000-2004) or were targeted by the initial catch-up SIA. Age-specific attack rates were highest in <3 years of age, roughly 1% in 3-20 years, and <1% for >20 years. District-level campaigns targeting children 6 months – 14 years or age lead to drops incidence in the target districts, but incidence continued to increase in adjacent districts. A nationwide SIA targeting children 6 months – 14 years of age was done in August achieving >100% coverage by dose administered, with incidence dropping to ≤2 reported cases per million in 2011 and 2012.

***Zambia***

Initial SIAs targeting children <5 years of age did not control measles, with 20-29% of cases >5 years of age. Incidence dropped after an SIA targeting children <15 years of age together with routine coverage (1 dose) >80% and a follow-up SIA coverage with 88% coverage by survey. In 2010 a large outbreak developed with many cases >5 years that continued into 2011 despite a follow-up SIA in 2010 targeting children 9 months to 4 years. Incidence decreased to low levels after an outbreak response in 4 districts in 2011 targeting <15 years and a nationwide SIA in 2012 also targeting <15 years of age.

Zambia attempted to control large yearly outbreaks of measles with SIAs targeting children from 9-59 months of age, first in urban areas in 1999 and in 50% of districts in 2000, with little change in measles incidence. The age distribution of cases is available from selected health facilities in Lusaka from 1996-2000 and an outbreak in Western Province in 2002. As shown in the table below, in Lusaka, 76% of cases were <5 years and 20% were 5-14 years of age, while in Western Province 30% of cases were <5 years, 29% were 5-14 years and 44% were >14 years of age. An SIA targeting children 6 months to 14 years of age was done in the Southern Province in late 2002 and in the rest of the country in June 2003, with coverage reaching >100% in each phase based on doses administered. With routine first dose coverage varying between 84 – 96% and a follow-up SIA in 2007 achieving 88% coverage based on a post-SIA survey, measles incidence averaged 23 reported cases per million population until 2010. In 2010 and 2011 the country had a large measles outbreak with >28,000 reported cases, with highest incidence in the east and north of the country near Malawi and DRC. The age distribution of cases from 2010 showed 55% were aged <5 years, 14% were 5-9 years of age, and 7% were 10-14 years. A follow-up SIA was held in 2010 that followed the AFRO TAG guidelines, targeting children 9-47 months of age and achieving 88% coverage by post-SIA survey. In 2011 the outbreak continued with a decrease in the proportion of cases <5 years to 46% and an increase in cases 5-9 years to 17% and 10-14 years to 9%. In 2011 outbreak response campaigns were held in highly-affected districts of Luapula and Northern Provinces (4 districts in each) targeting children 9 months to 14 years of age, with coverage per district ranging from 73-100% based on doses administered. In 2012 a nationwide SIA targeting children 6 months to 14 years achieved 96% coverage based on a post-SIA survey and that year 561 cases were reported and in the first half of 2013 only 1 confirmed case was reported.

Table. Age distribution of cases and SIAs, Zambia, 1996-2012.

| | Lusaka Dist 1996-2000 | W Prov 2002 | 2003 | 2007 | 2010 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|
| SIA target | | | 9m-14y | 9-59m | | 9-47m | | 6m-14y |
| SIA coverage | | | >100% | >100% | | 88% | | 90% |
| Age distribution of cases | | | | | | | | |
| <5 years | 75% | 31% | | | 55% | | 46% | |
| 5-9 years | 13% | 15% | | | 14% | | 17% | |
| 10-14 years | 7% | 14% | | | 7% | | 9% | |
| ≥15 years | 4% | 40% | | | 25% | | 25% | |

***Viet Nam***

Catch-up SIAs targeted children aged 9 months to 9 years, matching the age range of measles in the South but not in the North, where cases tended to be older. Incidence dropped after the SIAs with routine coverage with 1 dose generally >90%. District-level outbreak responses over the next 6 years did not prevent the accumulation of susceptible children and young adults. In 2008-2010 a large outbreak affected primarily adults not covered by the catch-up SIA and children born since the catch-up SIA, with low incidence in age groups covered by the SIA. Since a follow-up SIA targeting children <5 years in 2010, with 96% coverage, incidence has remained low.

Despite several years of high first dose coverage in the 1990s Viet Nam continued to report several thousand measles cases each year. The age distribution of cases in the late 1990s differed between South and North, with 70% of cases <10 years and 26% 10-14 years in the South and 51% <10 years and 41% 10-14 years in the North (see Table below). SIAs targeted children 9 months – 9 years of age in 1999-2002 (North) and in 2003 (South), achieving 99% coverage by doses administered. First dose coverage remained >90% except for a dip to 83% during a vaccine stock-out in 2007. Outbreaks in 2004-2006 mostly affected children missed by the SIA living in mountainous provinces in the far northwest. In response high-risk districts were targeted for SIAs in 2004 and 2007-2008, with >95% coverage based on doses administered. In addition a second dose of measles vaccine was introduced in 2006 at 6 years of age, reaching >95% coverage by 2008. In 2009 a measles outbreak started in young adults in the North then spread to the South, involving >7,700 cases. In both the North and South most cases were in 17-30 year olds, age groups not covered by the SIA in 2002-2003, and children <8 years, born since the SIA, though in the South more cases were <7 years while in the North more cases were ≥17 years. In 2010 a follow-up SIA was done targeting children 12-59 months of age and the age for MCV2 was lowered to 18 months of age. In 2011 and 2012 incidence has been <10 reported cases per million population.

Table. Age distribution of cases and SIAs, Viet Nam, 2001-2012.

| | 1990s North | 1990s South | 1999-2002 North | 2003 South | 2008-10 North | 2008-10 South | 2010 |
|---|---|---|---|---|---|---|---|
| SIA target | | | 9m-9y | 9m-9y | | | 9-59m |
| SIA coverage | | | 99% | 99% | | | 96% |
| Age distribution of cases | | | | | | | |
| <5 years | 13% | 25% | | <7 years | 31% | 54% | |
| 5-9 years | 38% | 45% | | 8-16 years | 8% | 8% | |
| 10-14 years | 41% | 26% | | 17-27 years | 52% | 32% | |
| ≥15 years | 8% | 3% | | >27 years | 9% | 6% | |

## Discussion

The experience of these 8 countries confirms that measles incidence can be reduced to very low levels with high coverage with two doses of MCV in routine, plus SIAs to fill immunity gaps determined by analyses of cases from recent outbreaks, the history of routine coverage, and in the Republic of Korea a well-timed and well-executed serological survey. Ghana and Malawi also reduced measles to low levels through repeated SIAs and >80% coverage with one dose of MCV in routine. The large outbreaks in Malawi and Zambia revealed gaps in coverage not appreciated during previous years of low incidence. The wide-age range SIAs done in response have reduced measles incidence to low levels, even though 10-30% of cases were aged >15 years. In Kenya, Malawi, Zambia and Viet Nam large outbreaks also revealed susceptibility gaps created by the choice of SIA target age range and poor coverage in some geographic areas. In Kenya and Viet Nam the delayed follow-up SIAs further increased these susceptibility gaps. It is likely that incidence will rebound in Kenya as coverage in both routine and the most recent SIA remains <95%. The age distribution of the outbreaks Viet Nam showed that the initial SIA was effective in lowering incidence in the age cohorts targeted, leaving high incidence in younger and older age cohorts. Adults aged 17-27 years were more affected by the outbreak in 2008-2010. These age cohorts also represented 30-40% of cases reported before the catch-up SIA. It is possible that targeting older age cohorts in the catch-up SIA and / or conducting nationwide follow-up SIAs would have prevented the 2008-2010 outbreak in Viet Nam.

## Estimating susceptibility and immunity gaps in the population

Ideally, the target age range of SIAs would be based on the immunity profile of the population showing the estimated levels of seropositivity by age cohort. Nigel Gay in the 1990s[24] developed cutoffs for seronegativity based on age stratified notifications of measles in England and Wales before vaccination, pre-vaccination serological data from Denmark, and mathematical models of disease transmission (see table below). An immunity profile could be calculated from data on routine and SIA coverage for the past 15-20 years, as in the Measles Strategic Planning (MSP) Tool[25]. Data on routine coverage are usually based on the WHO-UNICEF estimates that rely on doses administered and coverage survey data.

[24] Gay, NJ in: Measles: A strategic framework for the elimination of measles in the European Region; Copenhagen: WHO EURO, 1999, pp 20-2

[25] Simons E, Mort M, Dabbagh A, Strebel P, Wolfson L. Strategic planning for measles control: using data to inform optimal vaccination strategies. J Infect Dis. 2011 Jul;204 Suppl 1:S28-34.

Table. Age-specific susceptibility targets.

| Age group | Maximum proportion susceptible |
|---|---|
| 1-4 years | 15% |
| 5-9 years | 10% |
| 10-14 years | 5% |
| 15+ years | 5% in each cohort |

Coverage achieved by SIAs is typically estimated through three methods. Data on administered doses, divided by the estimated target population, is the most readily available estimate. It comes from data already collected during the campaign, can be calculated at almost all levels of the health system, and is available quickly after an SIA. However, the estimates are often inaccurate and exceed 100% because of inaccurate estimates of the target population, vaccination of children outside the target age range, and inaccurate recording of doses administered. Rapid convenience assessments are sometimes done "systematically" and are used to determine SIA coverage. However, these assessments do not use a probability sample of the population and thus do not produce statistically valid estimates of vaccination coverage. Post-campaign coverage surveys have been done using EPI cluster survey, LQAS, and population-based methods (DHS). However, these surveys often rely on maternal recall as SIA doses are often not recorded or the documentation is lost (cards) or obscured (finger markings).

For many SIAs coverage surveys were not done and some countries have seen large outbreaks after SIAs with high administrative coverage. The MSP tool and disease models relying on SIA coverage data often predict that most cases were born since the last SIA when in fact a high proportion of reported cases are from older age cohorts. Though often resource- and time-demanding, in some cases a well-time serological survey could be helpful to clarify the susceptibility profile when other sources of data are incomplete and / or contradictory.

### Draft Recommendations:

- Ensure high coverage (≥95%) during measles SIAs
- Verify coverage for all measles SIAs through statistically valid and generally accepted methodology
- Encourage recording of doses given during SIAs (by age group, number of zero-dose children vaccinated)
- Measles follow-up SIAs should be extended to target children >5 years of age based on a comprehensive review of the country situation, focusing on the age pattern of susceptibility to measles based on routine and SIA coverage results, the age-specific incidence of measles, the age distribution of measles cases, available seroprevalence data, population characteristics, and programme capacity to achieve high (≥95%) coverage.
- Extending the age range of measles SIAs should be considered when
    - A review of the susceptibility pattern shows age cohorts >5 years of age have high estimated susceptibility
    - A review of surveillance data shows age cohorts >5 years of age have high incidence or make up a significant proportion of the age distribution of reported cases in recent outbreaks
    - A well-conducted serological survey shows susceptibility rates >5% in age cohorts >5 years of age

- Consideration should be given to the trade-offs between strengthening routine delivery versus conducting poor quality wide age range SIAs especially in countries where systems are weak.

## Target age range for MR catch SIAs

### Current Practice and description of the issue

The current practice of rubella vaccine introduction has changed with the publication of the 2011 WHO rubella vaccine position paper. The updated position paper, recommended countries take advantage of the measles platform of two doses of measles vaccine to introduce MR or MMR vaccine. These measles vaccine delivery strategies provide an opportunity for synergy and a platform for advancing rubella and CRS elimination. The updated position paper also supported a paradigm shift in vaccination strategy for introduction of rubella-containing vaccines. The 2000 position paper placed an emphasis on direct protection of women of child bearing age (WCBA). While the revised position paper includes "efforts to vaccinate WCBA" as one of the strategies it places primary reliance on rapidly reducing and finally interrupting transmission of rubella through vaccination of children through an initial wide age range MR SIA, use of combined MR (or MMR) vaccine in the routine childhood immunization schedule, and regular follow-up MR SIAs as necessary. To avoid the potential of an increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater with at least 1 dose of an RCV delivered through routine services or regular SIAs, or both.

As of 2013, two WHO regions (AMR, EUR), have established rubella elimination goals by 2010 and 2015, respectively. In 2003, the region of the Americas established rubella/CRS elimination goal by 2010. To accelerate progress towards the goal, the PAHO TAG recommended that countries conduct wide age range MR SIAs with the age group to be targeted should be based on the country's epidemiology. The upper age limit should be determined from known patterns of fertility and expected susceptibility. In addition, both sexes should be targeted. All countries, except countries with long standing programs[26] conducted wide age campaigns in adult males and females extending up to 39 years in most countries.

The EUR rubella elimination goal is by 2015. By 2009, all countries in EUR had introduced RCV. In 2013, WHO EURO published "Measles and rubella elimination 2015. Package for accelerated action: 2013-2015"[27]. One of their key strategies is to "provide measles and rubella vaccination opportunities, including supplementary immunization activities (SIA), to all population groups at risk for and susceptible to measles and/or rubella."[28] In EUR great progress has been made toward the rubella elimination goal; however, there are still countries experiencing rubella outbreaks and immunity gaps, particularly in the adult population

[26] Aruba, former Netherland Antilles, Canada, French department, Panama, United States and Uruguay
[27] Available at http://www.euro.who.int/__data/assets/pdf_file/0020/215480/PACKAGE-FOR-ACCELERATED-ACTION-20132015.pdf (accessed 16 October 2013).
[28] Susceptible population groups should be defined by evaluating existing epidemiological data on measles and rubella cases, assessing historical vaccine-coverage data or, in some circumstances, conducting seroprevalence surveys

Both the GVAP and the Measles and Rubella Initiative strategic plan: 2012-2020 include two elimination milestones:

- by 2015, Rubella/congenital rubella syndrome eliminated in at least two WHO regions
- by 2020, measles and rubella eliminated in at least five WHO regions.

As of October 2013, only 2 WHO regions have rubella elimination goals, 1 WHO region (WPR) has an accelerated rubella control and CRS prevention goal[29], and 1 WHO region (SEAR) has a rubella control and CRS prevention goal by 2020. Two WHO regions (EMR, AFR) have no regional rubella control/elimination or CRS prevention/elimination goal.

As of October 2013, 135 (70%) countries have introduced RCV into their programs. There are 59 remaining countries, of which 2 additional countries (i.e., Cambodia, Senegal) will introduce RCV into their program in 2013. In order to achieve the GVAP goal, three additional regions will need to adopt an elimination goal for 2020. Almost all the 59 countries that have not introduced RCV are in the 3 regions without elimination goals. Of those 59 countries, 48 countries are GAVI eligible. The current GAVI support is for MR campaigns up to 14 years 11 months of age. However, to achieve the rubella elimination goal which is 7 years away, countries may need to expand the age range to older individuals.

For regions and countries with established elimination goals and countries planning to introduce RCV, the current practice is to review the epidemiology, particularly looking at the age distribution of the cases. To determine the upper age limit, review of the expected susceptibility which may be determined from age distribution of cases or through seroprevalence studies, particularly focusing on the susceptibility of women of childbearing age which may include reviewing the maternal age of CRS cases and age specific fertility rates. In some countries where age distribution of measles cases include adults (>15 years of age), the upper age of the SIA may be driven by the measles epidemiology (e.g., Iran, Kyrgyzstan).

### Weakness of current data and reasons for this, and need for coverage and serosurveys

In many of the countries, rubella cases are being identified through the measles case-based surveillance system. Even though both diseases classically have fever and rash, the fever is usually milder than measles and in up to 50% of rubella cases may present without a rash or be subclinical, so rubella cases will be underreported. In many countries, rubella outbreaks are not investigated so documenting the age distribution of cases may be challenging. For countries without adequate surveillance data, additional studies (e,g, seroprevalence) or investigations may need to be conducted.

### Evidence and rationale for recommendations for MR SIAs:

Both modelling and epidemiology data was presented to the SAGE in 2011 documented the significant impact of introductory SIAs, particularly when targeting up to 14 years 11 months for all countries when the coverage was at least 80%. The WHO SAGE Measles-rubella Working Group was asked to address the following question: "*Under what circumstances should MR catch-up campaigns be expanded to include cohorts >15 years of age?*"

[29] Accelerated rubella control is defined as < 1 case/100,000 population and CRS prevention is defined as <1CRS case per 100,000 live births.

The Working Group identified 2 situations in which the target age range for MR SIAs should be extended beyond 15 years:

1) To accelerate achievement of established rubella/CRS elimination goals; and
2) To fill immunity gaps identified through a thorough analysis of their country data for both measles and rubella.

**1. To accelerate achieving the goal**

Examples of accelerating achieving the established goal come from AMR. In 2003, a regional goal to eliminate rubella/CRS was established. In 2003, 3 countries had not introduced RCV and 7 countries had introduced RCV within the previous 5 years. Between 2003 and 2008, 14 countries conducted adult mass campaigns after introduction of RCV into their programs. The typical upper age range for these campaigns was 29 to 39 years of age including both males and females. However, 3 countries (i.e., Brazil, Chile, and Argentina) had conducted adult female only campaigns. After those SIAs, rubella virus transmission and outbreaks mainly occurred among adolescent and adult males. All three countries conducted subsequent SIAs targeting adolescent and adult males[30]. Transmission was interrupted in those countries. The countries in AMR are in the process of documenting the elimination of measles, rubella and CRS.

**2. To fill immunity gaps to measles and/or rubella in older age-groups**

As of September 2013, all 6 WHO regions have measles elimination goals. However, in many countries, the age distribution of cases has shifted to older adolescents and young adults. Presented to the SAGE WG were two country examples of where the introduction of RCV was integrated with measles epidemiology: Kyrgyzstan (presented above) and Iran.

***Iran***

In Iran, measles vaccination had been introduced 1967; however, between 1967 and 1983, measles vaccination was not routine offered in the public sector thus resulting in coverage <50%. In 1984, measles was offered to all infants and coverage increased rapidly to >90% in the early 1990s and between 1992 and 1996, coverage was >95%. In 1996, a subnational campaign targeting children aged 9 months to 15 years resulting in coverage up to 99%. The epidemiology of measles dramatically changed with the introduction of measles vaccine. Before 1967 (pre-vaccine introduction), the incidence of measles ranged from 581 to 1938 cases per 100,000 population. By 1984, the incidence had dropped to 34.3 and by 1987, the incidence had decreased to 6.1 per 100,000 population. During 1999–2002, the measles incidence increased from 10.2 to 17.5 cases per 100,000 population, and most cases occurred among persons aged 10–25 years. In 2001, Iran officially adopted the regional measles elimination objective. To respond to the measles elimination target, a nationwide campaign targeting persons aged 5 to 25 years was planned.

[30] Subsequent SIAs were conducted during 2007 and 2008 in Chile (1.3 million males aged 19–29 years in 2007), Brazil (70 million males and females aged 20–39 years and 12–39 years in five selected states in 2008), and Argentina (6.5 million males aged 16–39 years in 2008).

As of 2001, Iran had not introduced RCV into their national program. To introduce RCV, Iran conducted a MR campaign instead of measles only. Rubella seroprevalence data from 2001 showed 96% seropositivity among persons aged 14 to 70 years. The campaign had a significant impact on both epidemiology of rubella and measles.

## Using rubella epidemiology data

For countries introducing RCV, most will target 9 months to 14 years 11 months; however, a few countries may want to expand their age group. In evaluating whether to expand the target age group, countries should review their epidemiology including the age distribution of rubella cases. If available, countries should review their seroprevalence data. If available, countries should review the age of mothers of infants with CRS, which will help to identify the susceptible age group. After a decision has been made to expand the age target, countries may want to review their age specific fertility data so they can cover a majority of the women in the childbearing age.

Some of the country examples that were used included: Nepal, Tajikistan, Oman and Cape Verde. Two countries are briefly summarized here to illustrate how a comprehensive review of the available information helped to determine the target age range for the MR SIA.

***Nepal***

In Nepal, the rubella epidemiology documented that >95% of rubella cases were among persons less 15 years of age – that is only 5% of IgM positive rubella cases were occurring in persons ≥15 years of age; seroprevalence data conducted documented that 91% of women 15-39 years had acquired rubella immunity – that is <10% of WCBA were susceptible to rubella. A study in the school for the deaf documented the presence of CRS among the students. The decision was to introduce MR through a wide age campaign targeting persons aged 9 months to 14 year 11 months.

***Oman***

In 1992 in Oman, a rubella outbreak started that peaked in 1993 with 85% of the cases among persons less than 15 years. This outbreak resulted in 60 infants with CRS. In 1994, Oman conducted a nationwide MR campaign targeting persons aged 15 months to 17 years. The Ministry of Health chose to extend the age range due to the ease of reaching persons from 15-17 years of age in school. In 1988-89, a rubella seroprevalence study was conducted among pregnant women and documented that 92% were seropositive. In 1994, MR vaccine was introduced at 15 months of age and switched to MMR in 1997. In 2001, postpartum vaccination was introduced. Since 2006, the number of reported rubella and CRS cases has been < 20 and <2 (mostly 0).

## Discussion

There are two potential situations for expanding the age range beyond 15 years of age, these include to accelerate progress towards the targeted elimination goal and if the available data on measles or rubella support the expansion. Even though there is no magic formula for determining the age range, an approach countries have used in the past has been to consider two important criteria. First countries should review the epidemiology of rubella and measles including the age distribution of cases, if possible at least over the most recent years. If recently investigated outbreak data is available, it is important to

review the age distribution of cases. Seroprevalence data, if available should also be reviewed. Another source to review if available is the maternal age distribution of CRS cases to see if one specific age group is more susceptible than others. After reviewing the available data, countries should determine the appropriate age range needed to achieve the targeted goal.

**Recommendations:**

- Ensure high coverage (≥95%) during MR SIAs
- Verify coverage for all MR SIAs through statistically valid and generally accepted methodology
- Encourage recording of doses given during SIAs (by age group, number of zero-dose children vaccinated)
- MR catch-up SIAs should be extended beyond 15 years either to accelerate the progress toward established rubella/CRS elimination goals or to fill gaps in population immunity based on similar epidemiologic and programmatic considerations as above for M SIAs. Additional information to consider for MR SIAs include levels of immunity among women of child bearing age, epidemiology of rubella and CRS, and population characteristics – e.g., age-specific fertility rates and age of mothers of CRS affected infants.
- However, when countries decide to expand the age limit above 15 years, WHO/SAGE recommends both adult males and females should be targeted. Adolescent and adult female only SIAs are not recommended.
- Need for on-going review of country specific epidemiology to inform additional strategies that may be needed to address persistent immunity gaps

# VII. Vaccination of Health Workers

- A PubMed literature review of nosocomial transmission of measles or rubella as well as a search of existing WHO global and regional policy documents was conducted to determine the risk and guide recommendations for vaccination of health workers
- In both developed and developing countries, nosocomial transmission, usually involving health workers, is an important mode of transmission for measles and rubella outbreaks
- Because of their role in care of patients and vulnerable persons, health workers have a duty of care to be vaccinated
- In addition to vaccination of health workers, enforcement of infection control practices is needed to prevent nosocomial transmission of measles and rubella
- Draft recommendations are proposed that health workers be immune to measles and rubella (either through vaccination or serological testing) and that standard infection control measures be enforced to prevent or reduce the spread of measles and rubella

## Background

Health workers (HW) are critical to the promotion of health globally. Health workers are persons who engage in the promotion, protection or improvement of the health of the population[31]. Health workers include persons who may have contact with patients, visitors or persons with suspected infections or with the organism that causes the disease. Health workers include persons in health care such as health care providers, nurses, laboratory, janitors, secretaries, etc. and persons in public health such as field workers, epidemiologists, laboratorians and community workers. Even though they are associated with the promotion of health, infection risks occur in the setting where they work. In both developed and developing countries, transmission of vaccine-preventable diseases continues to occur in health care settings with health care workers (HCWs), that is persons directly involved in patient care, being the source of exposure for susceptible patients or other HCWs. The consequences of transmission within health care facilities can be serious even fatal and costly. For measles, several outbreak reports document this risk of transmission of measles among HCWs[32,33]. For rubella, several outbreak reports document the risk of transmission of rubella HCWs and patients[41]. In addition, health workers who investigate or respond to suspected cases of infectious diseases are at risk of contracting and/or transmitting the disease[34].

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[31] M.R. Dal Poz, Y. Kinfu, S. Dräger and T. Kunjumen. Counting health workers: definitions, data, methods and global results. WHO publication. 2007

[32] Choi WS, Sniadack DH, Jee Y, etal. Outbreak of measles in the Republic of Korea, 2007: importance of nosocomial transmission. J Infect Dis. 2011;204 Suppl 1:S483-90.

[33] Komitova R, Kunchev A, Mihneva Z, Marinova L. Nosocomial transmission of measles among healthcare workers, Bulgaria, 2010. Euro Surveill. 2011;16(15).

[34] WHO. Dr. Carlo Urbani of the World Health Organization dies of SARS. Accessed WHO website 9/19; http://www.who.int/mediacentre/news/notes/2003/np6/en/

All six WHO regions have goals for measles elimination and two have rubella elimination goals; however, measles and rubella outbreaks continue to occur including outbreaks associated nosocomial transmission. To interrupt the transmission of measles and rubella, uniform and high levels of immunity must be ensured in the population including health workers. To ensure immunity among HWs in order to reduce or prevent nosocomial transmission, we reviewed WHO global and regional recommendations. A literature review was conducted to identify current national recommendations on HWs policy, the reinforcement of and attitudes toward policy and cost of nosocomial transmission.

## Methods:

1) To identify existing WHO recommendations, several data sources were searched including online portals of Immunization, Vaccines and Biologicals (IVB) policies catalogue, IVB documents centre and publications section within WHO webpage and Weekly Epidemiological Records (WER). Eight main keywords related to HWSHWs were used to search for literature: HWSHWs "health care providers", "health workers", "health-care workers", "health workers", "health providers", "health staff", "health care staff" and "health professional". In addition, publication section websites and files from Immunization Vaccines department webpages from the six different regions were screened for all existing WHO and regional recommendations for vaccination of HWs.
2) To identify reviews and policy papers for health workers and nosocomial transmission or public health workers and transmission in the literature, we searched PubMed and references from relevant articles for studies in English. Search terms used were "health care workers, health workers, public health workers", "measles", "rubella" and "nosocomial transmission or transmission".

## Results

The results of the search in the WHO documents identified 2 global documents and 4 regional (AMR, AFR, EUR, WPR) documents that mentioned the importance of vaccination or recommendations for Health workers. The latest two WHO position papers for measles and rubella highlight the importance of vaccinating health workers but do not make a formal recommendation:

- The Measles Vaccine position paper, published in 2009, states that "The importance of vaccinating health workers is underlined by the numerous measles outbreaks occurring in health institutions, affecting both health workers and patients."
- The Rubella Vaccine position paper, published in 2011, states that "The importance of vaccinating health workers has been demonstrated by outbreaks that occurred in health institutions and affected both health workers and patients."

Of the WHO regions, two regions have recommendations to ensure health care workers were vaccinated or had documentation of immunity, two regions strongly encourage the same, while two regions have not formulated any recommendations or guidance on vaccinating or ensuring immunity among health care workers.

AMR and WPR have published recommendations to ensure immunity among health care workers:

- In 2005 in the AMR measles elimination field guide, it states "all health care workers must be immune to measles and rubella." This recommendation has also been re-emphasized by the International Experts Committee on the Documentation of Elimination of measles and rubella.

- In the WPR recommendations, the 2011 TAG "recommends that all countries implement measures to prevent or reduce nosocomial transmission of measles virus, including ensuring immunity against measles among HCWs [and] … investigation and effective isolation of suspected measles cases." In the 2009 accelerated rubella/CRS Strategic Plan, it states for all countries and areas ensure immunity in health care workers to prevent nosocomial transmission of rubella.

AFR, EUR strongly encourage ensuring that all are immune to measles:

- The report from the first AFRO Measles Technical Advisory Group (TAG) meeting in 2005 states that "Countries are strongly encouraged to implement WHO/AFR recommendations on vaccination for all health workers, regardless of previous vaccination status or history of measles.
- The 2005-2010 EUR Strategic Plan recommends that a second opportunity be provided to "those attending schools or universities, those in the military and those working in health care settings.

## Literature review

Throughout the literature are many examples from many countries (e.g., US, Bulgaria, Korean, Italy) documenting the importance of measles and rubella nosocomial transmission and the lack of immunity among health care workers[35,36,37]. A recent review of nosocomial transmission of measles[38] highlighted the frequency of nosocomial transmission of measles, even in developed countries, and the importance of ensuring that health care workers are immune. A second review examining HCW policies for vaccination in EURO[39] found that only 12 of the 30 countries recommend measles vaccination for all HCWs. In two additional countries, it was recommended only for a select population of HCWs (e.g. direct patient care or pediatricians). In Finland HCW vaccination against measles is mandatory. In the remaining 15 countries no recommendations for HCW vaccination against measles are in place. The second review also canvassed recommendations for rubella vaccination and found that it is recommended for all HCWs in 11 countries of the 30 countries. In 3 countries vaccination is recommended for specific groups of HCWs (e.g., pediatricians only, pediatric and maternity departments, HCWs who have contact with pregnant women. As with measles, vaccination of HCWs against rubella is mandatory in Finland. The 15 remaining European countries have not published any recommendations for rubella vaccination of HCWs.

For rubella, similar situation with nosocomial outbreaks have been occurring. The two differences between rubella and measles is the risk of infecting the susceptible pregnant women[40] and infants with

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[35] Barbadoro P, Marigliano A, Di Tondo E, De Paolis M, Martini E, Prospero E, D'Errico MM. Measles among healthcare workers in a teaching hospital in central Italy. J Occup Health. 2012;54:336-9.
[36] Chen SY, Anderson S, Kutty PK, Lugo F, etal. Health care-associated measles outbreak in the United States after an importation: challenges and economic impact. J Infect Dis. 2011 Jun 1;203(11):1517-25
[37] Greaves WL, Orenstein WA, Stetler HC, Preblud SR, Hinman AR, Bart KJ. Prevention of rubella transmission in medical facilities. JAMA. 1982 Aug 20;248(7):861-4.
[38] Botelho-Nevers E, Gautret P, Biellik R, Brougqui P. Nosocomial transmission of measles: An updated review. Vaccine 2012:30:3996-4001.
[39] Maltezou HC, Wicker S, Borg M, Heininger U, Puro V, Theodoridou M, Poland GA. Vaccination policies for health-care workers in acute health-care facilities in Europe. Vaccine. 2011;29:9557-62.
[40] Heseltine PN, Ripper M, Wohlford P. Nosocomial rubella--consequences of an outbreak and efficacy of a mandatory immunization program. Infect Control. 1985;6:371-4.

CRS shed rubella virus and have infected hospital staff[41,42]. In several of the nosocomial rubella outbreaks, either susceptible pregnant women were exposed or some were infected and may have chosen to terminate their pregnancy[43].

The practice of isolation measures for measles and rubella are part of the standard of care and are an important aspect for preventing nosocomial spread. There have been guides/guidelines published by WHO[44] and several countries[45,46],[47,48],[49]. In some of the recent nosocomial measles outbreaks, transmission occurred among the patients without spread to the HCWs. In these articles, it is highlighted that environmental infection control measures were not enforced or conducted, thus reinforcing the importance environmental infection control measures.

## Conclusions

In both developed and developing countries, nosocomial transmission, usually involving health workers, is an important mode of transmission for measles outbreaks. In addition, public health workers are also at risk of acquiring/transmitting infectious diseases. Though no global recommendation for vaccination of HWs including HCWs exists, the WHO measles and rubella position papers highlight the importance of vaccination of health care workers to prevent nosocomial transmission. Policies of WHO regions Health Care workers are evenly split: two regions recommend that HCW be immune, two recommend it, while two regions have no recommendations.

Health workers have a duty of care to be vaccinated. As health workers, they promote, protect and improve health. As health workers, they may be in contact with or treat persons that are vulnerable such as persons with cancer or HIV. Measles infection in the immunocompromised host (eg, persons with malignancies or human immunodeficiency virus [HIV] infection) can be prolonged, severe, and

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[41] Greaves WL, Orenstein WA, Stetler HC, Preblud SR, Hinman AR, Bart KJ. Prevention of rubella transmission in medical facilities. JAMA. 1982;248(7):861-4.
[42] Evans ME, Schaffner W. Rubella immunization of hospital personnel: a debate. Infect Control. 1981 Sep-Oct;2(5):387-90
[43] Polk BF, White JA, DeGirolami PC, Modlin JF. An outbreak of rubella among hospital personnel. N Engl J Med. 1980;303:541-5
[44] WHO. Prevention of hospital-acquired infections a practical guide. 2nd edition 2002
[45] Sehulster L, Chinn RY; CDC; HICPAC. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep. 2003;52(RR-10):1-42
[46] Public Health Agency of Canada. Guidelines for the Prevention and Control of Measles Outbreaks in Canada. Canada Communicable Disease Report, October 2013: 39.3: 1-52.
[47] Health Protection Network. Guideline for the Control of Measles Incidents and Outbreaks in Scotland. Health Protection Network Scottish Guidance 4. Health Protection Scotland, Glasgow, 2010.
[48] Health Protection Agency. HPA Naitonal Measles Guidelines: Local & regional Service. Accessed 16 October 2013, http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1274088429847
[49] Commonwealth Department of Health and Aged Care, July 2000. Guidelines for the control of measles outbreaks in Australia: Technical Report Series No. 5. Accessed 16 October, 2013 at http://health.act.gov.au/c/health?a=dlpol&policy=1151020553

frequently fatal[50]. For rubella, health workers may come in contact and infect susceptible pregnant women which may result in an infant with CRS born.

To achieve the elimination goals for both measles and rubella, countries must ensure high population immunity for both vaccines. Through this review of WHO policies, it has been documented that no global recommendations exist to ensure immunity among health workers. To reduce the threat of nosocomial transmission global recommendations should be put in place to ensure that all health workers are immune to both viruses. These recommendations should include follow-up to ensure that these policies have been implemented in Member States.

Nosocomial transmission will not be prevented only by immunization of health workers.
Another aspect to prevent nosocomial transmission is the enforcement of infection control. Only one region (WPR) had policies in place that we could identify for enforcing infection control policies. In addition to the recommendation of vaccination of health workers, global recommendations should include enforcing good infection control practices.

## Draft Recommendations

The following draft recommendations are proposed to SAGE:

- WHO/SAGE recommends that health workers should be required to demonstrate they are immune to measles (either through vaccination or serological testing)
- WHO/SAGE recommends that health workers should be required to demonstrate they are immune to rubella, as soon as rubella vaccine is introduced into the national program
- WHO/SAGE recommends that standard infection control measures be enforced to prevent or reduce the spread of measles and rubella.
- WHO/SAGE recommends that regions and countries develop plans to operationalize these recommendations.

[50] Strebel PM, Papania M, Finkelkorn A, Halsey, N. Measles vaccine. In: Plotkin S, Orenstein WA, Offit, P. Vaccines, 6th Ed. 2012 Elsevier.

# VIII. Prioritizing the Research Agenda for Measles and Rubella

Twelve high priority research areas were identified to address gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets.

The prioritization process included adaptation of prior prioritization criteria, generation of a list of potential research areas, and identification of experts to participate in an electronic survey.

## Background and Rationale

Research is critical to achieving global disease control, elimination and eradiation goals. The eradication of smallpox was made possible by technical and logistical advances conducted during the course of the program, and the failure of the malaria eradication program of the 1950's and 1960's was in part attributable to the neglect of research (Henderson 1999). The Polio Research Committee was only established two decades after the polio eradication goal was first proclaimed in 1988. Recently, research priorities have been developed for the reduction of child deaths from pneumonia (Rudan 2007, Rudan 2011) and diarrhoea (Rudan 2007, Fontaine 2009, Wazny 2013) and the eradication of malaria (malERA 2011), among others, and are on-going for immunization implementation research.

Several methodological approaches have been developed for systematic priority setting for child health, most notably those developed by the Child Health and Nutrition Research Initiative (CHNRI) (Rudan 2008, CHNRI) and the Essential National Health Research (ENHR). Common to most approaches is the identification of research questions or areas, development of prioritization criteria and application methods, implementation of a prioritization process with appropriate experts and stakeholders, and an analytical approach including scoring and weighting of responses.

The SAGE Working Group on Measles and Rubella was charged with identifying gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets. To identify gaps in evidence and programme barriers, the SAGE Working Group on Measles and Rubella adapted previously developed methodological approaches and built upon the work of an expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011 to begin the process of prioritizing research questions for measles eradication and rubella/congenital rubella syndrome (CRS) control and elimination (Goodson 2012). This report summarizes the methods and findings for the prioritization of the measles and rubella research agenda.

## Methods

### Prioritization Criteria

The Measles and Rubella Working Group adapted prioritization criteria developed by CHNRI ENHR with the goal of designing prioritization criteria that were simple and appropriate for the types of research areas relevant to measles and rubella/CRS elimination targets (Table). Five prioritization criteria were identified to address these needs, each weighted equally and scored from 1 to 4:

1. **Relevance**: The purpose of this criterion was to determine if the proposed research addresses a knowledge gap or if it duplicates prior knowledge or studies. The specific question was: How

large is the knowledge gap to be addressed by the proposed research? Answers and scores included: 1=Large; 2=Moderate; 3=Small; 4=No gap.

2. **Importance**: The purpose of this criterion was to ensure the proposed research addresses a problem of importance to achieving the measles and rubella global and regional goals. The specific question was: How significant is the problem addressed by the proposed research? Answers and scores included: 1=Highly significant; 2=Moderately significant; 3=Low significance; 4=None.

3. **Urgency**: The purpose of this criterion was to assess how urgently the research needs to be conducted, recognizing that some research areas may be of high importance and relevance but may not be needed urgently. The specific question was: How urgently should research on this problem be addressed? Answers and scores included: 1=As soon as possible; 2=Within two years; 3=Within five years; 4=Not essential within the next five years.

4. **Impact**: The purpose of this criterion was to assess the benefit of the proposed research results by assessing their potential merit and usefulness. The specific question was: How likely is it that the proposed research will result in knowledge that will significantly advance regional or global measles and rubella goals? Answers and scores included: 1=Highly likely; 2=Moderately likely; 3=Very unlikely; 4=Not possible.

5. **Chances of Success**: The purpose of this criterion was to assess the feasibility of completing the proposed research within five years. The specific question was: Is it possible to complete studies to answer the research question within five years? 1=Highly likely; 2=Moderately likely; 3=Very unlikely; 4=Not possible.

Respondents also could respond that they were unable to answer or did not know the answer to the prioritization question.

**Table:** Comparison of the Measles and Rubella Research Agenda Criteria to ENHR and CHNRI Prioritization Criteria

| **Measles and Rubella Research Priorities** | **ENHR** | **CHNRI** |
|---|---|---|
| Relevance | Appropriateness | Maximum potential for disease burden reduction |
| Importance | Relevancy | Maximum potential for disease burden reduction |
| Urgency | *Not asked* | *Not asked* |
| Impact | Impact of the research outcome | Maximum potential for disease burden reduction<br>Likelihood of efficacy and effectiveness<br>Likelihood of deliverability, affordability |
| Chances of success | Chances of success | Likelihood of answerability in an ethical way<br>Likelihood of efficacy and effectiveness<br>Likelihood of deliverability, affordability |
| *Not asked* | Ethical appropriateness | Likelihood of answerability in an ethical way |
| *Not asked* | *Not asked* | Likely effect on equity in population |

### Research Areas

The SAGE Measles and Rubella Working Group drew upon several sources to identify potential research areas critical to achieving the measles and rubella/CRS elimination targets. The most important source was the expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011 (Goodson 2012). This panel, consisting largely of experts from the Centers for Disease Control and Prevention, the World Health Organizations and academia, identified more than 130 research questions that were later condensed to 26 key research questions in six domains. These research questions were further condensed and supplemented with additional research areas from four sources: 1) the Measles Landscape Analysis conducted for the Bill & Melinda Gates Foundation; 2) the Global Measles and Rubella Management Meeting in March 2012; 3) the Measles and Rubella Initiative and SAGE Working Group meetings in September 2012; and the Global Measles and Rubella Management Meeting in February 2013. This process resulted in 24 research areas within seven broad domains:

1. Population immunity (6 questions)
2. Monitoring and surveillance (3 questions)
3. Outbreak preparedness and response (4 questions)
4. Public confidence and demand for vaccines (2 questions)
5. Pathogenesis, vaccines and diagnosis (4 questions)
6. Rubella specific issues (4 questions)
7. Integration with polio eradication efforts (1 question)

### Measles and Rubella Experts

Survey participants were identified in three phases: 1) SAGE Measles and Rubella Working Group members; 2) participants of the Global Measles and Rubella Management Meeting in March 2012; and 3) a list of measles and rubella experts (including academics) originally drafted following the expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011. Survey participants who did not respond initially were included in subsequent survey rounds.

### Survey

Each survey question was framed as a broad research area for which potential specific research questions were provided as examples and the order of the questions were randomly scrambled. For example, the question addressing Strategies to increase vaccine coverage among difficult to reach populations was presented as follows:

> Studies to evaluate novel strategies to increase measles and rubella vaccine coverage among difficult to reach populations, including nomadic populations, migrants, refugees and internally displaced persons.
>
> Examples include studies of GIS mapping of susceptible populations, mobile phone reminder recall systems, and house-to-house vaccination strategies.

The goal in selecting the research areas was to address the broad range of potential research gaps with some specificity, while minimizing the number of research areas so as not to overburden the participants. With 24 research areas and five prioritization criteria, participants were asked to answer 120 questions not including the demographic questions.

Surveys were conducted electronically using SurveyMonkey™ in February, April and August 2013. Links to the survey were sent by email with a cover letter explaining the purpose of the email.

The overall prioritization score was the sum of the scores for each of the five prioritization criterion. The maximum score was 20.

## Results

### Respondents

The measles and rubella research agenda prioritization survey was sent by email to 158 individuals of whom 55 (35%) completed the survey. Sixteen (10%) individuals started but did not complete the survey and were not included in the analyses.

### Characteristics of respondents

The respondents represented a range of professional positions, expertise (including rubella) and geographical areas (Table). The majority of respondents (58%) worked for more than 10 years on measles or rubella. However, few respondents worked in the areas of vaccine procurement and economics and few represented the Eastern Mediterranean WHO region. The high proportion of respondents from the Americas reflects in part the number of participants associated with the Centers for Disease Control and Prevention and US based universities.

**Table**: Characteristics of Respondents

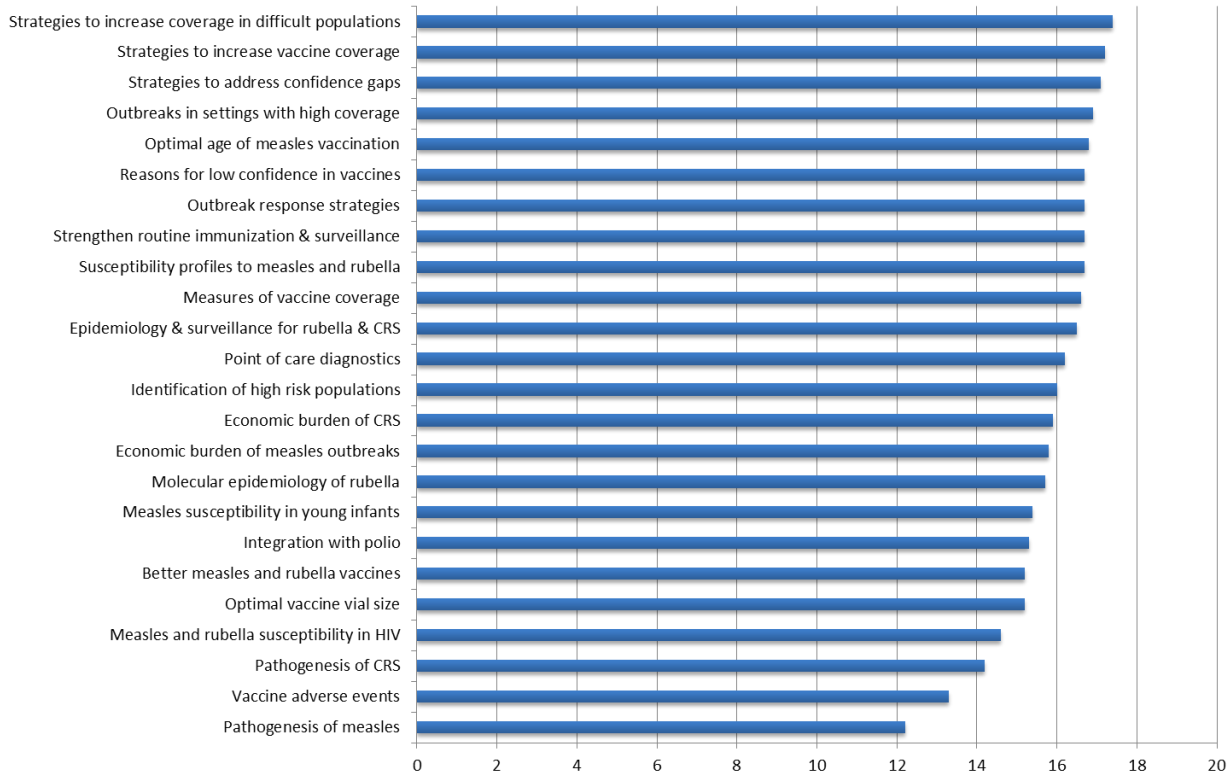
| Characteristic | Proportion of Respondents |
|---|---|
| Professional Position | |
| Global partner | 29% |
| Researcher | 24% |
| Technical advisor | 18% |
| Other | 18% |
| Regional program officer | 7% |
| Country program officer | 4% |
| Measles and Rubella Expertise | |
| Both measles and rubella | 52% |
| Measles only | 41% |
| Rubella only | 7% |
| Duration of Work in Measles and Rubella | |
| More than 20 years | 29% |
| 10 to 20 years | 39% |
| 5 to 9 years | 21% |
| Less than 5 years | 11% |
| Expertise | |
| Epidemiology | 36% |
| Surveillance | 34% |
| Outbreak response | 19% |
| Health systems | 19% |
| Vaccine delivery | 16% |
| Pathogenesis | 10% |
| Immunology | 10% |
| Health behaviors | 10% |
| Vaccine development | 9% |
| Diagnostics | 8% |

| | |
|---|---|
| Molecular epidemiology | 8% |
| Modeling | 7% |
| Vaccine procurement | 3% |
| Economics | 2% |
| WHO Region | |
| Americas | 33% |
| Europe | 14% |
| Global headquarters | 14% |
| Africa | 11% |
| Western Pacific | 9% |
| South-East Asia | 7% |
| Eastern Mediterranean | 2% |
| Organizations | |
| University | 33% |
| Other | 27% |
| World Health Organization | 23% |
| Centers for Disease Control and Prevention | 13% |
| UNICEF | 4% |

## Survey results

The overall prioritization scores ranged from a high of 17.4 (Strategies to increase coverage in difficult populations) to a low of 12.2 (Pathogenesis of measles), with a median score of 16.1 (IQR 15.3, 16.7) (Figure).

**Figure** : Overall prioritization scores for 24 research areas to achieve the measles and rubella elimination targets



The prioritization criteria did not clearly distinguish research areas of high and low priority, although four research areas were clearly of lower priority (Measles and rubella susceptibility in HIV-infected persons; Pathogenesis of CRS; Vaccine adverse events; and Pathogenesis of measles).

The research areas with scores above the median are shown in the box below.

1. Strategies to increase vaccine coverage in difficult to reach populations
2. Strategies to increase vaccine coverage
3. Strategies to address confidence gaps
4. Outbreaks in settings with high coverage
5. Optimal age of measles vaccination
6. Reasons for low confidence in vaccines
7. Outbreak response strategies
8. Strengthen routine immunization & surveillance
9. Susceptibility profiles to measles and rubella
10. Measures of vaccine coverage
11. Epidemiology & surveillance for rubella and CRS
12. Point of care diagnostics

## Discriminatory power of prioritization criteria

The discriminatory power of each of the prioritization criteria differed, although no specific criterion clearly distinguished high from low priority research areas (Table). The range in scores for individual criterion (maximum of four) was greatest for Urgency (range 1.7 to 3.3) and least for Chances of Success (2.9 to 3.6). The range in scores for the remaining three criteria spanned 1.2 points.

**Table**: Median, IQR and range for overall scores and scores for each prioritization criteria

| | Median | IQR | Range |
|---|---|---|---|
| **Overall score** | 16.1 | 15.3, 16.7 | 12.2, 17.4 |
| **Relevance** | 3.2 | 3.1, 3.3 | 2.3, 3.5 |
| **Importance** | 3.3 | 3.1, 3.5 | 2.4, 3.6 |
| **Urgency** | 2.7 | 2.6, 3.1 | 1.7, 3.3 |
| **Impact** | 3.3 | 3.1, 3.4 | 2.5, 3.7 |
| **Chances of success** | 3.4 | 3.3, 3.4 | 2.9, 3.6 |

## Comparisons across prioritization criteria

The rankings of the top six research areas by overall score were compared across the five prioritization criteria to assess consistency (Table). The overall score ranking most closely resembled the Urgency ranking.

**Table**: Ranking of top six overall research areas by individual prioritization criteria

| Top Six Research Areas | Relevance Rank | Importance Rank | Urgency Rank | Impact Rank | Chances of Success Rank |
|---|---|---|---|---|---|
| Strategies to increase vaccine coverage in difficult to reach populations | 1 | 2 | 1 | 2 | 10 |
| Strategies to increase vaccine coverage | 13 | 1 | 3 | 1 | 9 |
| Strategies to address confidence gaps | 2 | 7 | 6 | 9 | 12 |
| Outbreaks in settings with high coverage | 6 | 3 | 4 | 8 | 5 |
| Optimal age of measles vaccination | 15 | 4 | 2 | 4 | 3 |
| Reasons for low confidence in vaccines | 8 | 6 | 5 | 17 | 18 |

## Additional research questions

Fourteen respondents offered additional potential research questions although none was mentioned more than once. Examples include the need for serological assays that distinguish wild-type from vaccine induced immunity, risk assessment of animal morbilliviruses and the potential for cross-species transmission, and management systems for immunization programs.

## Discussion and Next Steps

The SAGE Measles and Rubella Working Group identified twelve high priority research areas to address gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets based on a prioritization process that included adaptation of prior prioritization criteria, generation of a list of potential research areas, and identification of experts to participate in an electronic survey. The research areas of highest priority reflect the urgent need for research on strategies to increase vaccine coverage and thus population immunity, build public confidence in measles and rubella vaccines, and enhance surveillance for measles, rubella and CRS.

There are several limitations to the methods employed that could impact on the prioritization process. First, the prioritization criteria were adapted from previous efforts to establish prioritization criteria for childhood diseases but were not independently validated. Second, the research areas were drawn from prior efforts to establish a research agenda for measles and rubella but were not exhaustive and were framed broadly. Respondents were provided an opportunity to suggest additional research questions and several did; however, these could not be incorporated into this prioritization process. Third, the "universe" of measles and rubella experts was not systematically sampled potentially leading to biased results. Individuals with expertise in vaccine procurement and economics were particularly under-represented. The composition of the respondents almost certainly impacted the findings. Fourth, even with a condensed set of research areas, the survey was burdensome, with respondents asked to address five prioritization criteria for 24 research areas. Respondent fatigue was evident in that some started the survey but failed to complete it. Fifth, the lack of discriminatory power of the prioritization criteria was likely due to the fact that the research areas had all been previously vetted and proposed as potential

priority research areas. Thus, all of the research areas were relevant to to achieving measles and rubella/CRS elimination targets.

The Measles and Rubella Working Group considers this prioritization process a first step in setting, promoting and revising the measles and rubella research agenda. The next step is to disseminate these findings through a published report and at the Global Vaccine Research and Implementation Forum in March 2014. Next, we plan to draft specific research questions, study designs and outcomes for the top six to twelve research areas and will identify potential funding agencies and mechanisms. Finally, the Measles and Rubella Working Group views this list of highest priority research areas as a working document that will be updated and revised as research questions are addressed and the understanding of the epidemiology and control of measles and rubella evolve.

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## IX. Questions to SAGE

The questions to SAGE will be posed following each presentation:

1. Global and Regional progress and challenges:

- Is the programme on track to achieve global and regional targets?
- If yes, what needs to be done to maintain elimination; if no, what additional strategies, tactics, and/or innovations are needed to get back on track?

2. Use of MR vaccine in the routine schedule and determination of the appropriate target age range for M and MR SIAs

- Does the evidence presented support the draft recommendation to use RCV with first dose of MCV?
- Does the evidence presented support the use of the same formulation of MR or MMR vaccine for both routine doses?
- Does the evidence presented support the draft recommendations on the criteria to be used to determine the target age range for M and MR SIAs?
- Is it appropriate to merge the measles and rubella position papers?

3. Vaccination of health workers

- Does the evidence presented support the draft recommendations to vaccinate health workers against measles and rubella?

4. Prioritizing the Research Agenda

- Does SAGE endorse the approach taken by the working group to identify a prioritized list of research topics?
- Is additional work needed before disseminating these findings?

# Report SAGE consultation on smallpox vaccines

# 18 & 19 September 2013

## FINAL DRAFT

## 17 October 2013



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**Contents**

## Introduction

The last case of Smallpox, a disease with a case fatality rate of up to 30%, occurred in 1977. In 1980 the World Health Assembly declared this disease eradicated. Throughout the program a global stockpile of vaccines, had been held in Switzerland, created with donations from Member States. After eradication, a stockpile of vaccine was maintained in readiness for a potential reappearance of the disease. After some time had passed with no reappearance of smallpox, a small proportion of this vaccine stockpile was retained in Geneva, to be used for a proven re-emergence of the disease. In 2004 a WHO Ad-Hoc Orthopoxvirus Committee recommended that the emergency vaccine stockpile be enhanced and updated for use, should an outbreak of smallpox occur. The Committee recommended that the stockpile consist of 200 million doses of which at least 5 million doses would be held in Geneva for emergency use; the balance, representing a virtual stockpile would be retained in the donor countries ready for immediate shipment as necessary.

The WHO vaccine stockpile held in Switzerland includes both vaccines used during the eradication (animal lymph) and vaccines produced in tissue/cell culture. It consists of 600,000 doses (0.01ml/dose) of vaccine as used during the eradication program, which could be expanded to ~ 2.4 million doses,if the vaccine is administered by bifurcated needles plus 300,000 doses produced in tissue/cell culture. The entire virtual stockpile of vaccine held by WHO plus Member States currently consists of 31 million doses.

In order for WHO to make an informed decision (risk-benefit) on which vaccines to stock and to be able to give advice to countries on their own national stockpile, WHO has asked the Strategic Advisory Group of Experts (SAGE) for immunization to address this. In preparation for the annual SAGE meeting that will be held in November 2013, WHO organized a SAGE consultation on smallpox vaccine in September that would advise the SAGE Members. Specifically WHO would like the SAGE to address the following questions:

**Question 1:**
Which vaccine should be recommended to be used during an outbreak of smallpox? (vaccine used during the eradication (animal lymph) , vaccine produced in tissue cell, or further attenuated vaccines).

- Composition of stockpile
- Size of stockpile
- Should we consider different scenarios of risk?

**Question 2:**
Once vaccination is decided in an outbreak, what other groups should be prioritized to be vaccinated while faced with limited vaccine supply?

- Age groups, risk factors/safety aspects, vulnerable populations, ethical considerations
- Which vaccine should be given?

**Question 3:**
Which vaccine should be recommended for preventive use?
What would be the immunization schedule? (First aid responders, army, police, health workers)

## SAGE recommendation 1: Which vaccine should be recommended to be used during an outbreak of smallpox?

The development of smallpox vaccines has a long history extending back to 1796, the year Jenner discovered vaccination. Multiple strains developed over the years, and several different strains were used in vaccines during the eradication As a requirement of the WHO eradication programme, all vaccines to be used had to meet established standards of potency, purity, and stability. Based on studies of adverse reactions post-

vaccination, especially post vaccinial encephalitis, two strains were most frequently used, the New York City Board of Health (NYCBH) strain and the Lister strain, although other strains were also used.

The WHO eradication program was also aided by the introduction of the bifurcated needle as a simple and effective way to do vaccinations. The bifurcated needle increased up to four times the number of vaccinations that could be done with a given volume of vaccine. WHO also recommended that vaccines be lyophilized so that they retained their potency during storage and shipment even in tropical areas and without having a cold chain to maintain their potency.

The vaccines used during the eradication program sometimes produced significant adverse reactions, some of which were occasionally fatal. These included post vaccinial encephalitis, progressive vaccinia, and eczema vaccinatum. Vaccinia was also occasionally transmitted from a vaccinee to close contacts, particularly those with open skin lesions. (F. Fenner, WHO, 1988 (ISBN: 92 4 156110 6). These led to an interest in producing safer vaccines, yet ones that still gave a robust immunity.

The vaccines used during the 1960s and 1970s were produced on the skin of live animals and yielded virus laden lymph that contained some bacterial contaminants. Accordingly, vaccines in recent years have been produced in cell culture. They are produced under current Good Manufacturing Practices (GMP) standard. These vaccines probably have the same risk of serious adverse events as they are produced with the same strain. The most well-developed of such vaccines is ACAM2000, which is derived from a single clone of the NYCBH vaccinia strain, and is licensed in the United States.

Given the safety profiles of vaccines used during the eradication programme and the vaccine produced in tissue cells, major efforts have been made in recent years to produce vaccines that are genetically modified – i.e. are less reactogenic but retain the ability to produce protection against smallpox. There are two major problems to develop such a vaccine. First, there are no established laboratory markers that are known to have perfect correlation with protection from smallpox, and there is no animal model that accurately mimics smallpox. Thus, it is difficult to judge the comparative efficacy/effectiveness of newer vaccines. Second, since the serious adverse effects produced by vaccines used during the eradication programme, occur in rates of a few per 1 million vaccinees, trials to establish the comparative safety of the newer vaccines are difficult if not impossible.

Vaccine candidates that are genetically modified to be less reactogenic and lower rate of adverse reactions to humans either by serial passage of a vaccinia strain on various cell substrates, or by intentional manipulation of the genome using modern genetic techniques, and may be further attenuated or non-replicating vaccines. While many such strains have been produced, very few are sufficiently well developed so that they can be thought of as potential vaccines. Two, LC16m8, a replicating live vaccine produced in Japan from the Lister strain of vaccinia, and Modified Vaccinia Ankara-Bavarian Nordic (Imvanex also designated as MVA-BN or Imvamune), a live but non-replicating vaccine derived from the Ankara strain of vaccinia, have advanced to human trials and are licensed in Japan and in the 28 Member States of the European Union, Iceland, Liechtenstein and Norway respectively.

Ideally, any vaccine proposed for actual use against smallpox should be lyophilized so that it will retain potency for extended periods at room temperature, be administered via bifurcated needles so that syringes and needles for injection are not required, and if possible produce a visible major cutaneous reaction (i.e. "take") that is a marker of successful vaccination.

LC16m8 produces a major cutaneous reaction very similar to that produced by vaccines used during the eradication programme, such as the NYCBH vaccine, is administered by the bifurcated needle, is lyophilized, and meets WHO/TRS No 926, 2004 standards of purity, potency, and stability. Japan has a production facility that is actively producing the vaccine, and indeed is the only facility in the world currently producing a replication competent smallpox vaccine. (SAGE consultation review paper, H. Meyer, Paul Ehrlich Institute for WHO, 2013).

Imvanex is produced as a liquid, requires a cold chain for use, must be given intramuscularly or subcutaneously with a syringe and needle, does not replicate in human tissues, and does not produce a major cutaneous reaction. The approved human vaccination regimen comprises of two doses given four weeks apart to ensure high seroconversion rates. Moreover, although it is believed to be at least as safe as the replicating vaccines, little is known about the likelihood of it producing serious adverse reactions in some vaccinees, as fewer than 7000 persons have been vaccinated with MVA-BN in modern clinical trials. It is therefore not a good candidate for first-line use to control an outbreak.

In controlling an outbreak, countries should use any smallpox vaccine on hand that meets WHO/TRS No 926, 2004 standards of potency, purity, and stability. If no such vaccine is on hand, ACAM2000 or LC16m8 should be sought (which meet WHO/TRS No 926, 2004 standards).

From the WHO stockpile, first, licensed vaccines ACAM2000 (or LC16m8 if donated) should be used as well as other vaccines, based on the current stockpile composition that were used during the eradication. Vaccines used during the eradication should meet WHO recommendations (TRSN° 926, 2004).

### What vaccines should be sought for the WHO stockpile?

A 2004 Ad-Hoc Orthopoxvirus Committee recommended, as a target, a stockpile of 200 million doses of which at least 5 million would be kept in Geneva for emergency use and the balance specifically pledged by countries but held in national stockpiles, ready for emergency shipment as might be required. They also recommended that there be at least two standby facilities that could rapidly produce substantial additional vaccine if needed. The 2004 WHO Smallpox Ad Hoc Committee recognized that the quantities noted might be insufficient should multiple outbreaks appear in different locations. However, given national and international constraints on resources, it simply proposed that the previously stated targets be retained and periodically reviewed as circumstances changed.

Today, smallpox vaccine that meets WHO /TRS No. 926, 2004 standards is in very short supply as has been the case for the past decade. (Therefore no vaccine should be discarded if it is believed to meet WHO/TRS No. 926, 2004 standards). Furthermore there are very few companies capable of large scale production on short notice. Kaketsuken in Japan, is the only facility that currently is producing vaccine. It has a capacity to produce approximately 40 to 80 million doses a year. Sanofi Pasteur has a facility in Massachusetts (USA) that has been under development for some 4 years. It is expected to be in full operation by the end of 2014. Its capacity is expected to be 50 million doses per year.

The consultation group recommended that additional vaccine donations should be considered, as well as funds that could be used to manage the stockpile and purchase additional vaccine. Countries donating vaccine to WHO stockpile should provide the same vaccine as they have in country stockpiles. However, WHO

should not jeopardize other programs or donations by placing the needs for additional smallpox vaccine ahead of other programmatic priorities.

For new vaccine donations for virtual as well as for on-hand storage, both licensed ACAM2000 and LC16m8 should be accepted, as well vaccine used during the eradication, meeting WHO/TRS No. 926, 2004 standards. Vaccine should be bundled with bifurcated needles, lyophilized, and produce a major cutaneous reaction after administration with the bifurcated needles.

The participants recognized that in order to advise on the number of doses for the WHO stockpile, it would be necessary to consider different scenarios. The acceptable range of doses will depend on the type or likelihood of occurrence of the various scenarios considered. Factors that could be considered include, but are not limited to, the cause of re-emergence (natural, bioterrorism), the location of initial emergence (urban, rural, mass-gathering event…), population density and movement and vaccine production capacity. Therefore further work is needed to come up with a meaningful estimate.

### SAGE recommendation 2 Who should be vaccinated during an outbreak?

The epidemiology and transmission dynamics of smallpox are well established. Transmission generally required face-to-face contact with a visibly ill individual with rash. Patients are not infectious during the febrile prodrome, which is usually severe enough to require the patient to go to bed and not be mobile. Once the rash appears virus, is shed from the upper respiratory tract and the patient becomes infectious. The eradication of smallpox was greatly facilitated by this pattern of transmission, with patients rarely spreading the disease to more than 3 contacts. Strict isolation of patients, coupled with vaccination of the small numbers of contacts who attended the patient during the infectious period, quickly eliminated outbreaks. Primary vaccination within 3-4 days of contact generally prevented development of the disease, whereas revaccination of previously vaccinated individuals within one week post-exposure was largely protective. (Mortimer Clin Infect Dis 2003)

Given these facts, and coupled with the occasional serious adverse events following smallpox vaccination, only vaccination of immediate contacts is recommended. Medical personnel who care for patients can be vaccinated immediately after their initial contact. First responders who have direct contact with symptomatic patients such as interviewing them, escorting them to hospital or other care facilities, feeding them etc. should be considered contacts and vaccinated.

Regarding risk factors, for those individuals with bona fide close direct contact, there are no contraindications for vaccination, and thus the risk/benefit ratio favors vaccination.

Contacts of contacts, the so-called "second ring of contacts", should not be vaccinated. They should be identified, and communications established so that they can be vaccinated if the first ring contact actually develops smallpox or symptoms possibly suggesting smallpox.

Laboratory or other health care personnel who collect diagnostic specimens from patients, or who handle or process such specimens, should be vaccinated.

Vaccine used should meet WHO/TRS No. 926, 2004 standards for potency and stability, and be capable of producing a major cutaneous reaction following a single dose administration, preferably with a bifurcated

needle. Vaccine available locally similar to those used during the eradication campaign are acceptable, as are ACAM2000 and LC16m8.

### SAGE recommendation 3: What other groups should be given preventive vaccination?

For preventive use, smallpox vaccination should not be recommended for any groups.

Countries may consider vaccinating laboratory workers in labs working with orthopoxviruses. If a biosafety assessment of such laboratories suggests some risk, workers should be vaccinated with ACAM2000 or LC16m8 or a locally available well-established vaccine that meets WHO/TRS NO 926, 2004 standards.

Regarding vaccination schedule, there is insufficient data on the length of time that optimal protection lasts, although some serologic markers of immunity persist for several decades. Thus the group considered there is not enough scientific evidence to provide any recommendation on the need and frequency of booster immunizations. Since frequent vaccinations decrease the likelihood of adverse events., most labs use a frequency of revaccination with an interval of 2 to 6 years.

Concerning to recently licensed Imvanex (MVA-BN/Imvamune) by EMA, based on the evidence provided for this review and consultation, the group recommended that more clinical data on its efficacy and safety should be produced before any recommendation can be given, even for preventive use. However, in countries where the vaccine is licensed, for individuals who refuse to be vaccinated with replicating live vaccines or have been designated as "high risk" (ie first responders, lab workers in orthopox virus laboratories, etc), and have been medically excluded from receiving standard replicating vaccine because of pre-existing immune deficiencies, immunosuppression, atopic dermatitis, etc. the MVA-BN is likely to be safer than replicating vaccines.

# Summary report on first, second and third generation smallpox vaccines

**Content**



**The first report was prepared for WHO in August 2013 by H. Meyer, Paul-Ehrlich-Institut and updated in October 2013 following comments received after the expert meeting on smallpox vaccines**

**Abbreviations**

AE: adverse event

CAM: chorioallantois membrane

CMI: cell-mediated immunity

ECG: electrocardiography

ECTV: Ectromelia virus

EEV: extracellular enveloped virus

GMP: Good manufacturing practice

GMT: geometric mean titer

IMV: intracellular mature virus

MPXV: monkeypox virus

NYCBH: New York City Board of Health

PFU: pock forming units

PRNT: plaque reduction neutralization test

pvE: post-vaccinial encephalitis

RPXV: rabbitpox virus

SCR: seroconversion rate

SAE: Serious adverse event

WHO: World Health Organisation

## Background

Smallpox has been successfully eradicated by a global effort in the 1960s and 1970s using a panel of live vaccinia virus vaccines. The last naturally occurring case was reported in 1977 in Somalia and in May 1980 the World Health Organisation (WHO) declared that smallpox had been eradicated. In the last decades fears of deliberate release of Variola virus or genetically modified orthopox viruses by bioterrorist attacks led to an intensified research on the molecular and immunogenic characteristics of orthopox viruses as well as to the conduct of vaccination campaigns involving first generation vaccines produced during the eradication era and the development of new smallpox vaccines.

Smallpox is a devastating disease caused by the Variola virus. Variola virus is transmitted by aerosols and droplets from person-to-person or through contact with contaminated clothing and bedding. After infection and a prolonged incubation period of usually 10-14 days (range 7-17 days) the first disease symptoms develop. Typically smallpox disease is characterized by the sudden onset of influenza-like symptoms including high fever, malaise, headache, prostration, severe backache and nausea that last 2-4 days. During the prolonged incubation period there is no evidence of viral shedding and infected persons do not infect others. After this incubation period, lesions erupt in the oropharynx and mouth and one day later the characteristic rash appears on the face, hands and forearms, which eventually spreads over the entire body. Soon after formation of first mucosal lesions large amounts of smallpox are released in the mouth and throat and infected individuals can transmit smallpox to others. The skin lesions start as small reddish macules, which enlarge and become pustule. Over the next 2-3 weeks crusts are formed, which eventually fall off and leave extensive scarring behind. All lesions in a given area progress together through these stages. Other long-term sequelae can include blindness, encephalitis, secondary bacterial infections and arthritis. Two principal forms of smallpox were clinically differentiated during natural outbreaks, Variola major and Variola minor. Variola major epidemics resulted in high case-fatality rates of about 30%, whereas Variola minor caused a much milder form with case fatality rates of approximately 1%. Rarely two fatal disease forms occurred, haemorrhagic and malignant smallpox.

Smallpox vaccines produced and successfully used during the intensified eradication program are called first generation vaccines in contrast to smallpox vaccines developed at the end of the eradication phase or thereafter and produced by modern cell culture techniques. Second generation smallpox vaccines use the same smallpox vaccine strains employed for manufacture of first generation vaccines or clonal virus variants plaque purified from traditional vaccine stocks, whereas third generation smallpox vaccines represent more attenuated vaccine strains specifically developed as safer vaccines at the end of the eradication phase by further passage in cell culture or animals. Second and third generation vaccines are produced using modern cell culture techniques and current standards of Good Manufacturing Practices (GMP). Other groups of vaccines include inactivated vaccines used to prime vaccinia-naïve subjects prior to administration of traditional smallpox vaccines or live smallpox vaccines administered orally as tablets.

This review summarizes published information on different smallpox vaccines stockpiled and/or licensed today primarily for emergency use.

## First generation smallpox vaccines

Smallpox has been successfully eradicated by a global effort using a panel of live vaccinia virus vaccines. Manufacture, use and clinical experience with these first generation smallpox vaccines in the pre-eradication phase were described in detail by Fenner, Henderson, Arita, Jezek, and Ladnyi in 1988. In the following sections main characteristics of first generation smallpox vaccines are summarized as described by Fenner et al 1988.

During the intensified eradication program coordinated by the (WHO) smallpox vaccines produced by 71 manufacturers worldwide were used. Manufacture of first generation vaccines was based on different vaccinia virus strains and production systems (Table 1). The most widely used vaccine strains were Lister, New York City Board of Health (NYCBH), Tiantan (Temple of Heaven), and EM63. These vaccine strains were propagated and harvested primarily from skin of live animals (e.g. calf, sheep, water buffalo), calf lymph or chorioallantois membrane (CAM) of embryonated hens' eggs. From 1967 onwards more standardized vaccine production methods were implemented to meet the WHO requirements for potency, stability and safety of vaccine batches (WHO TRS 1965, No 5). Lyophilisation was recommended and all freeze-dried vaccine batches released had to contain at least $1x10^8$ pock-forming units (PFU) per milliliter (mL). Absence of pathogenic microorganism had to be ensured. Standardisation of manufacture and control of vaccine production was one important factor for the success to eradicate smallpox (Fenner et al 1988).

**Table 1: Pathogenicity of various vaccinia virus strains used during the eradication campaign in endemic settings**

| Vaccinia strain and derivatives | Area used | Pathogenicity in animals and humans |
|---|---|---|
| NYCBH<br>• EM63<br>• Ecuador | USA,<br>Central and South America<br>Africa<br>USSR<br>Asia | low |
| Lister<br>• L-IVP<br>• Merieux 37<br>• Nigeria strains | Europe<br>USSR<br>Africa<br>Asia | moderate |
| Patwadanger | India | moderate |
| B-51 | USSR | moderate |
| TianTan | China | high |
| Copenhagen | Europe | high |
| Bern | Europe | high |
| Ikeda | Japan | high |
| Tashkent | USSR | high |

During the intensified eradication program the vaccines were commonly administered by scarification using a bifurcated needle. In general a minute drop of 2-3 microliter reconstituted vaccine corresponding to a human dose of ~$2x10^5$ PFU was delivered by 10-15 punctures to the skin over the deltoid muscle.

## Experience with first generation vaccines in the pre-eradication phase

*Field effectiveness, post-exposure protection and clinical correlates*

Although controlled clinical trials were never performed with first generation smallpox vaccines, field effectiveness was demonstrated by their success in the global eradication campaign.

Information on protective post exposure efficacy derives from several sets of data on secondary attack rates among vaccinated and unvaccinated family contacts of smallpox cases. Vaccine efficacy has been estimated to be between 90.7% and 97.1%. Moreover the data indicate that the longer the time

between exposure and vaccination the higher the risk that post-exposure vaccination is ineffective to prevent infection or to mitigate severity of smallpox disease (Fenner et al 1988). Based on historical data from the UK it was found that primary vaccination within 3-4 days after smallpox exposure and revaccination within one week after exposure may protect against disease and/or death (Mortimer 2003).

A vaccine-related major cutaneous reaction (vaccine "take") was recognized as clinical correlate of protection against smallpox. No common serological correlate of protection has been established. Although neutralising antibodies are the most reliably parameter correlated with immunity and protection against smallpox infection and disease, it is known from individuals with certain T-cell immune deficiencies that cellular immune responses contribute to protection. After successful vaccination, the duration of protection was thought to be at least three years, with at least some degree of protection likely persisting for 10 years or more (Fenner et al 1988).

*Safety*

Expected vaccine-related common local and systemic reactions with usually mild to moderate severity are local reactions including pain, intense erythema and inflammation at the vaccination site as well as systemic reactions such as fever, malaise, myalgia, headache, chills, nausea, fatique, and lymphadenopathy. These reactions usually resolve within 2-3 weeks. Other complications of smallpox vaccination are autoinoculation and inadvertent infections of close contacts, which are generally self-limited. Vaccinia keratitis was reported after inadvertent autoinoculation and results in lesions of the cornea, which eventually may lead to ocular impairment.

During the eradication phase rare but serious postvaccinial complications were documented. Reports describe generalized vaccinia, eczema vaccinatum, progressive vaccinia (vaccinia necrosum), postvaccinial encephalitis and death.

- Generalized vaccinia is marked by swelling and tenderness of the draining lymphnodes and a viremia detectable between 3 to 10 days, e.g. in pharyngeal swabs of individuals with postvaccinial tonsillitis. Viremia is followed by a disseminated rash. The rash develops 6 to 9 days after vaccination and is composed of lesions that follow a similar progression as the lesion at the vaccination site. Primary vaccinees are at greater risk of developing generalized vaccinia, however in most cases it is self-limited.

- Eczema vaccinatum emerges with constitutional symptoms and vaccinial rash mostly at current or previous eczematous locations. Vaccinated and unvaccinated contacts with eczema or atopic dermatitis are at increased risk even if the eczema/atopic dermatitis is not active at the time of vaccination or contact. Severe cases and fatalities have been observed.

- Progressive vaccinia is a severe complication associated with T cell deficiency. It is characterized by the development of a progressive often necrotic lesion at the vaccination site followed by spreading of lesions to other parts of the body. Early after vaccination patients can lack symptoms of inflammation but later on the disease progresses and is frequently fatal.

- Postvaccinial encephalitis (pvE) is the most serious complication in otherwise healthy persons and is associated with high mortality and morbidity. Approximately 25-35% of vaccine recipients with pvE died within a week, and about 25% had permanent neurological sequelae.

Another serious complication is foetal vaccinia following primary vaccination of women in early stages of pregnancies. It results in stillbirth or death of the newborn.

The frequency of postvaccinial complications was found to be dependent on the vaccine strain employed and was generally higher in primary vaccinees then following revaccination.
Occurrence of serious adverse events during the intensified eradication campaign was intensively reviewed in recent years (Aragón et al. 2003, Kretzschmar et al. 2006).

Kretzschmar et al analysed historical vaccination data on the frequency of post-vaccinial encephalitis (pvE) and death after primary and revaccination with smallpox vaccine with respect to age and vaccinia strain used. The data sets analysed derived from Germany, Austria, Sweden, France, the UK, the Netherlands, the former Soviet Union and from the USA. For primary vaccination the frequency of pvE differed hugely between various vaccine strains. The highest rate of pvE was found with the Bern strain with 44.9 expected cases per million vaccines, followed by the Copenhagen strain (33.3 expected cases per million), the Lister strain (26.2 expected cases per million) and the NYCBH strain with the lowest rate of 2.9 expected cases per million vaccinations. With respect to age-related effects the frequency of pvE was highest among infants in their first year of life and increased constantly with age. For the NYCBH strain the highest frequency was reported in children aged 1 to 3 years. A similar pattern was observed for vaccination related mortality. After primary vaccination highest mortality rates were expected with the Bern strain (55 deaths per million), followed by the Copenhagen strain (31.2 deaths per million) and the Lister strain (8.4 deaths per million). The lowest death rate is expected for the NYCBH strain with only 1.4 deaths per million primary vaccinations. For the Bern, Lister and NYCBH strains mortality is expected to be highest in children younger than 1 year of age and lowest in children approximately 2 years of age. After revaccination the mortality rates are generally much lower than after primary vaccination and the differences between strains after revaccination are similar to those after primary vaccination. In revaccinees older than 20 years of age the rates were 4 to 16-fold lower than in primary vaccinees with the lowest rate expected with the NYCBH strain.

Aragón et al reviewed data on the experience of adverse events after smallpox vaccination in the USA with the NYCBH strain that were published by Neff, Lane, Melin and Ratner (Aragón et al 2003). The data were gathered in the years 1963 to 1968 and represent approximately 13 million primary vaccinations and 18 million re-vaccinations.
Following primary vaccination the risk of post-vaccinial encephalitis (pvE) and death from pvE was highest among infants under 1 year of age with estimated 6.8 cases of pvE and 3.0 deaths per million vaccinations, respectively. The risk in primary vaccinees 1 year of age and older was much lower and ranged between 1.8 and 3.3 cases of pvE per million vaccinations and 0-1.2 deaths per million vaccinations. The risk of developing progressive vaccinia (vaccinia necrosum) was 1.0 case per million vaccinations in all age groups and was highest in individuals 20 years of age and older (5.3 cases per million). Two deaths were reported in subjects experiencing progressive vaccinia. The risk of eczema vaccinatum did not differ across age groups and was reported to be 12.8 cases per 1 million vaccinations and no deaths were reported in subjects with eczema vaccinatum. However, among non-vaccinees that developed eczema vaccinatum after contact transmission from a recent vaccinee, 3 of 132 cases died. The risk for generalized vaccinia was highest in infants in their first year of life and in this age group 103.3 cases per million vaccinations were reported. In subjects 1 year and older the risk was determined to range from 22.4-49.9 cases per million vaccinations. Across all age groups no death due to generalized vaccinia occurred. Accidental infection (inadvertent autoinoculation) was reported for 64.9 cases per million vaccinees with no deaths associated and the risk was comparable across the different age categories.

In revaccinees the risks of developing specific complications and risks of dying from specific complications following smallpox administration were significantly lower than for primary vaccination. After revaccination the risk of pvE, progressive vaccinia (vaccinia necrosum), eczema vaccinatum and generalized vaccinia was 26 times, 1.5 times, 12 times and 29 times lower, respectively, compared to primary vaccinations. Only 2 subjects with progressive vaccinia died in the total group of revaccinees resulting in a risk of 0.1 deaths per million re-vaccinations.

**Experience with first generation smallpox vaccine in the post eradication era**

Based on the knowledge of the safety profile of smallpox vaccines of the pre-eradication era the vaccine use in the post eradication era was restricted to laboratory personnel, military or first responders. The vaccine was in principle contraindicated in pregnant women, persons with known immune deficiencies, patients under immune suppressive therapies, and persons with a history of eczema. More recently due to the experience in large-scale vaccination campaigns myopericarditis was recognised as a serious postvaccinial complication in healthy subjects and this led to further restrictions in the use of traditional smallpox vaccines.

**Lister strain vaccines**

In the last decades several Lister strain vaccines were evaluated in clinical trials or vaccination campaigns.

- *Lister vaccine produced on CAM (Israel)*

During the winter of 2002–2003, the Israeli health authorities launched a campaign to vaccinate first responders against smallpox (Orr et al 2004). In an open study, 159 healthy, previously vaccinated adults aged 24–52 years were immunised by scarification. The vaccine available in Israel is prepared from the Lister strain in chorioallantois membranes of chicken embryos and the virus titer of the vaccine suspension was given to be approximately $10^7$ PFU per mL. Vaccine take and seroconversion rates of 61% and 56%, respectively, were observed. It was found that the level of pre-existing antibodies against vaccinia inversely correlated with the rates of clinical take and seroconversion. Most of the subjects enrolled had been vaccinated 2-3 times before the start of the campaign. The safety and reactogenicity were actively monitored at 3 time points within 18 days after revaccination. The most commonly adverse events among the vaccinees were pruritus, local and axillary pain, lymphadenopathy, fatique, and headache. Only 1 subject reported fever over 38.0°C. No serious adverse events were noted.

Occurrence of adverse reactions smallpox vaccine was defined in a vaccination campaign performed by the Israel Defense Force (IDF) among vaccinees aged 18 years and older between 1991 and 1996 and compared with previous surveys (Haim et al 2000). The majority of recruits were previously vaccinated and approx. 20% were primary vaccinees. Overall a postvaccinial complication rate of 0.4 per 10,000 vaccines was determined. The most frequent complications were eczema vaccinatum (0.15 per 10,000) and generalized vaccinia (0.09 per 10,000) followed by inadvertent inoculation (0.06 per 10,000), secondary infection (0.06 per 10,000) and erythema multiforme (0.03 per 10,000). No cases of postvaccinial encephalitis, progressive vaccinia or mortality were reported. The rates of eczema vaccinatum, generalized vaccinia and inadvertent inoculation were higher in the IDF recruits than in similar surveys conducted in the 1960s. Among 2,480 vaccinees included in a survey of new recruits 1.5% reported minor adverse events including local pain, local swelling, fever and lymphadenopathy. None required hospitalization.

- *Lancy-Vaxina Berna (SSI) manufactured on animal skin*

The first generation smallpox vaccine Lancy-Vaxina Berna was manufactured according to WHO requirements on the skin of sheep using the Lister strain derived from the Lister Institute. In the last decade efficacy, immunogenicity and safety of the vaccine Lancy-Vaxina were evaluated in clinical trials in Taiwan, South Korea and the UK (Hsieh et al 2006, Kim et al 2005, Auckland et al 2005, Pütz et al 2006).

Hsieh et al evaluated the clinical and immunological responses to diluted and undiluted Lancy-Vaxina vaccine in vaccinia naïve and previously vaccinated subjects in Taiwan. A total of 219 healthy adults aged 24 to 65 years were randomised to receive either undiluted or diluted vaccine. All vaccinia-naïve subjects (N=97), who received either undiluted ($10^{9.0}$ PFU/mL) or diluted (1:5 or 1:10) vaccine showed a major skin reaction (vaccine take). In the group of the previously vaccinated subjects (N=122) all subjects were successfully revaccinated by undiluted or diluted (1:10 and 1:30) vaccine except two subjects having received 1:30 diluted vaccine. Evaluation of the neutralising antibody response demonstrated that all vaccinia-naïve and vaccinia-experienced subjects elicited a robust vaccinia-specific immune response regardless of the vaccine preparation (diluted or undiluted) used or the occurrence of a vaccine take. As regards safety the data indicate that dilution of the vaccine was not associated with decreased local reactions and incidences of systemic reactions when compared with undiluted vaccines. However, in vaccinia-naïve subjects receiving undiluted vaccine the lesion size was significantly smaller and most systemic reactions, including fever, headache, muscle ache, fatigue and lymphadenopathy, were more frequently observed than in previously vaccinated subjects receiving undiluted vaccine. No serious or life-threatening events were observed in this study.

Similar results were reported from a study conducted in South Korea also using undiluted and diluted Lancy-Vaxina vaccine (Kim et al. 2005). Two vaccine dilutions (1:1 and 1:10) of Lancy-Vaxina vaccine (vaccine titer undiluted: $10^{7.7}$ PFU/mL; Berna Biotech, formerly SSI) were administered to vaccinia-naive persons (n=36) and persons previously vaccinated >25 years ago (n=76). All vaccinees responded successfully to vaccination as judged by vaccine ”take”. There were no significant differences in the size of the skin lesions, the number of adverse events, the amount of viral shedding, or the level of antibody responses between the undiluted and diluted vaccine groups. Compared with vaccinia-naive persons, previously vaccinated persons exhibited significantly smaller and more rapidly evolving skin lesions and fewer adverse events. No serious adverse events were documented.

The study conducted in health care workers in England and Wales assessed vaccine take rates and occurrence of adverse events following vaccination with the Lister vaccine manufactured by SSI in vaccinia-naïve and previously vaccinated individuals (Auckland et al 2005). The participants were actively followed-up for at least 21 days by diaries. Out of 232 subjects vaccinated 200 completed their diaries and were included in the efficacy and safety analyses. By day 7, 99% of the vaccinees had a vaccine ‘take’. The most commonly reported adverse events were redness (87%) and pain at the vaccination site (71%). Fever recorded as moderate or severe occurred in 25% of subjects and this peaked 4–9 days post-vaccination and lasted usually 3 days. There was no significant difference in the incidence of pain between vaccinia-naïve and experienced subjects. There was a general trend towards increased rates of common adverse events such as axillary lymphadenopathy, itch, erythema, general malaise or flu-like symptoms and headache in naïve vaccinees compared with those with a prior vaccination history. Clinically important but less common symptoms included local skin/soft tissue infection requiring oral antibiotics in 2.5% of patients. In addition, two serious adverse events occurred. One previously vaccinia vaccinated subject was hospitalised 7 days after vaccination with headache, fever and altered conscious level. A clinical diagnosis of encephalitis was made, classified as ‘possibly’ related to vaccination. The patient made a complete recovery. Another SAE occurred in a vaccinia-naïve individual, which was

admitted to hospital 12 days after vaccination with a fever and cellulitis around the vaccination site requiring treatment with intravenous antibiotics. No case of myopericarditis was reported.

An independent group quantified the antibody responses against the intracellular mature virus (IMV) and the extracellular enveloped (EEV) form using a panel of test systems including virus neutralisation assays (Pütz et al 2006). Sera from 92 health care workers enrolled in the vaccination campaign in England and Wales were analysed. The sera derived from vaccinia naïve subjects (N=18), subjects having previously received one (N=58) or two (N=6) smallpox vaccinations and 10 subjects with unknown vaccination status. The results show that both primary vaccinees and revaccinees elicit strong responses against the EEV surface proteins B5, A33 and A56, against the IMV surface proteins A27 and H3, but only low levels of L1-specific antibodies. Comparative analysis showed that the levels of antibodies to B5 induced in humans correlated closely with the magnitude of EEV-specific neutralization in vitro and that B5 is the only target of EEV-neutralizing antibodies after smallpox vaccination. In addition two IMV surface proteins (A27 and H3) were identified as targets for IMV-neutralizing antibodies present in human sera of primary vaccinees and revaccinees.

- *Pourquier vaccine (Lister strain produced from calf lymph, France)*

In 2003, a group of first responders were revaccinated in France using stockpiled smallpox vaccine (Bossi et al 2001). The lyophiilized vaccine was prepared using the Lister strain from calf lymph by the Pourquier laboratories. The virus titer was determined to be $10^{7.7}$ PFU/ml. A total of 226 healthy volunteers aged 27-63 years were vaccinated and actively followed up for vaccine take and adverse events for 28 days post vaccination. Most of the participants were previously vaccinated more than once (80%). Successful vaccination was observed in 95.6% of revaccinees. Side effects were experienced by 27% of participants, which resolved within two weeks. The most frequently reported local and systemic adverse reactions were fever (12%), fatique (6%), local pruritus (8%), axillary lymphadenopathy (3%), headache (3%) and myalgia (3%). No serious adverse events were notified and no inadvertent inoculation of close contacts was reported.

*Regulatory status:*

First generation Lister strain vaccines are stockpiled in many countries worldwide. Some are licensed and some have no active marketing authorisation. However, regulatory mechanisms are in place for approval of these vaccines allowing their immediate use in an emergency.

Published data suggest that in France two Lister vaccines including the Pourquier vaccine are licensed. In Russia the vaccine FCP, a freeze-dried vaccine derived from the L-IVP strain and prepared on calf skin, holds a marketing authorisation for emergency use (Onishchenko et al 2006).

**NYCBH strain vaccines**

Most information on NYCBH strain vaccines derive from Dryvax vaccine, which was intensively used in vaccination campaigns in the USA.

***Dryvax***

Dryvax was produced by infection of skin of calves using the NYCBH strain as seed virus. Recently, studies were performed evaluating clinical and immunologic responses to diluted vaccine in volunteers who had not previously been immunized. The lyophilized undiluted vaccine, when reconstituted, had a virus titer content of $10^{8.1}$ PFU/mL. A total of 680 healthy adults aged 18-32 years were randomized to either

receive undiluted or a 1:5 dilution or a 1:10 dilution of the vaccine. It was shown that at dilutions of 1:5 or 1:10, the vaccine was able to elicit adequate immune responses with 99.1 % and 97.1% developing a vaccine take, respectively. Undiluted vaccine resulted in a success rate of 97.2 % (Frey et al 2002). Determination of the neutralising antibody responses revealed that all participants were seropositive by day 28 and all but one subject were seropositive at day 56 (Belshe et al 2004). In the group that had received undiluted Dryvax 103 out of 106 subjects had a major cutaneous reaction and neutralising antibodies increased from <20 prior to vaccination to a GMT 1262 on D28 but had fallen to 796 on D56. In addition it was found that higher neutralising antibody titers at day 28 and 56 were significantly associated with larger skin lesions, erythema and fever.

In response to fears of bioterrorist attacks two large-scale vaccination campaigns were initiated in 2002 in the USA. The results of the safety assessment of subjects vaccinated as of 30 June 2004 were reviewed by Neff et al 2008. In the program conducted by the Department of Defense (DoD) in military personnel 628,414 individuals were vaccinated with Dryvax. Of the subjects included 71% received primary immunisation and 29% were revaccinated. The majority of vaccinees were males (88%) and the median age of all vaccinees was 26 years. A second program initiated by the US Department of Health and Human Services (DHHS) was designed to immunize health care workers and first responders and 39,566 individuals received Dryvax by scarification. In the DHHS program the rate of vaccinia-naïve subjects and the number of male subjects enrolled was lower than in the DoD program. Primary vaccinations were given to 24% of the participants and 37% of the total cohort were males. The median age was 48 years.

In both programs no cases of progressive vaccinia, eczema vaccinatum, or occupational transmission occurred. Two of 48 cases reported met the case definition for superinfection of the vaccination site, but no pathogenic organism could be isolated. One individual experienced erythema multiforme major (Stevens-Johnson syndrome) and recovered within one week. Out of 42 cases reported as suspect or probable generalized vaccinia only one case could be confirmed. All suspected generalized vaccinia cases were mild and self-limited. None of these case patients had atopic dermatitis or underlying conditions that might be related to an impaired immune system. Other adverse events recorded in the two programs were 97 cases of autoinoculation including inadvertent infection of the eye (17 cases). Of note, inadvertent infection of close contacts of vaccinees (family, friends or intimate contacts) occurred in 47 cases. All contact vaccinations resolved without sequelae.
Among the 628,414 vaccinees in the DoD program one case of encephalitis was reported, the patient recovered fully. In the civilian population one case of post-vaccinial encephalitis was recorded. This individual has some persistent memory loss.
Despite screening inadvertent vaccination was recorded in 236 pregnant women. No unexpected findings were found with respect to spontaneous abortion, preterm birth or congenital abnormalities. No case of foetal vaccinia occurred. Overall 10 subjects with undiagnosed HIV infection (3 vaccinia naïve, 5 revaccinees and 2 with unknown vaccination status; mean CD4 cell count: 483 cells/$mm^3$ post vaccination) were included. All had major reactions to smallpox vaccination, with normal healing and no adverse reactions.
Unexpectedly cardiac complications (i.e. myopericarditis, ischemic cardiac disease and dilated cardiomyopathy) became a cause for concern. Overall 79 cases of myopericarditis have occurred among the 628,414 vaccinees in the DoD program, specifically and disproportionally in male subjects. In the 66 subjects who have been intensively followed, all have recovered normal heart function. In the DHHS program 21 cases of myopericarditis were recorded, 86% occurred in revaccinees and 67% were females. In 14% some persistent mild symptoms continued approx. 40 weeks after diagnosis. A causal relationship of myopericarditis and smallpox vaccination is supported by the close temporal clustering. Onset of symptoms was coincident with peak viral replication at the vaccination site (at 7-14 days) and likely with occurrence of inflammatory responses. In an other publication it was estimated that the observed

incidence within the 30 day observation window of 16.11 per 100,000 was nearly 7.5-fold higher following primary vaccination than the expected background rate among non-vaccinees (2.16 per 100,000) (Poland et al 2005). No increased incidence of myopericarditis was found for the group of revaccinees (2.07 per 100,000).
Ischemic cardiac events occurred in a total of 26 cases (5 fatal) in both programs, but were not clustered temporally after vaccination. An epidemiological analysis identified no difference in the frequency observed in unvaccinated individuals. Consequently the data did not support an excess of ischemic cardiac events among recent smallpox vaccinees.
Seven cases of dilated cardiomyopathy (DCM) were reported 5-40 weeks after vaccination in previously healthy individuals. Out of the 7 DCM cases 2 patients received disability discharges and successful heart transplants. Four DCM cases recovered sufficiently to return to work. Currently it is difficult to determine whether DCM is linked to vaccination because no epidemiological background data from unvaccinated persons are available. There is however a possible link to infection and autoimmune processes.

*Regulatory status*
Dryvax manufactured by Wyeth Laboratories until the early 1980s and manufactured by Aventis Pasteur are no longer licensed in the USA. The use of Dryvax in the USA was revoked as of Feb 29, 2008. (MMWR, weekly, Feb 29 2008 / 57(08); 2007-2008.)

# Second generation vaccines

Advantages of the second generation vaccines produced in cell culture are improved manufacturing processes primarily as regards consistency between lots and minimizing the risk of contaminations by adventitious agents.

- **Lister vaccine produced in primary rabbit kidney cells (RIVM)**

The first cell-culture derived smallpox vaccine was produced in the late 1960s by growing the Lister strain on primary rabbit kidney cells (Hekker et al 1973). The seed virus for the production was prepared in calves and was the same as that used for the production of calf lymph vaccine. The virus was thus not more than one passage removed from animal skin. Satisfactory vaccine potency and stability was demonstrated for the freeze-dried vaccine and initial field studies conducted in the Netherlands with app. 1600 vaccinia-naïve and vaccinia experienced individuals showed that the cell-culture based Lister vaccine induced comparable take rates, immune responses as measured by neutralising antibody titers and had a similar safety profile than the calf lymph derived vaccine (Fenner et al. 1988). Because of these results the cell culture derived vaccine was used together with a calf lymph vaccine in a field trial in Lombok, Indonesia, in 1973 (Hekker et al 1976). Both vaccines tested had comparable virus titers of $3x10^8$ PFU/ml. A total of 61,808 children aged 0 to 14 years were vaccinated: 51,268 (82.9%) with tissue culture vaccine and 10,540 (17.1%) with calf lymph vaccine; 15,390 (30.0%) of those vaccinated with tissue culture vaccine and 2992 (28.4%) of those vaccinated with calf lymph vaccine were primary vaccinees. None of the children in either group experienced disseminated vaccinia, eczema vaccinatum, or vaccinia necrosum. A number of cases of severe malaria, gastroenteritis, and pneumonia occurred in both vaccinated and unvaccinated children. Among those in the study group, illnesses were randomly distributed according to the time of onset and their occurrence appeared to bear no relationship to vaccination. One case of encephalitis occurred that may have been vaccine-related. A 5-month-old girl had a major reaction at the vaccination site and died 2 weeks after vaccination after it had developed high fever, convulsions, head stiffness and felt unconscious. Similar results were obtained with both

vaccines in primary vaccinees and in revaccinees as regards the take rates (appr. 97% in primary vaccinees and 71-74% in revaccinees).

- **Elstree-BN (Bavarian Nordic)**

Elstree-BN is a smallpox vaccine developed by Bavarian Nordic. The Lister vaccine strain was derived from a vaccine sample manufactured by a local German manufacturer. The vaccine is produced in embryonic chick fibroblast cells under current GMP standards and contains not less than $1x10^8$ PFU per mL. Preclinical studies demonstrated that comparable immune responses were induced in macaques by Elstree-BN and the traditional smallpox vaccine Elstree/RIVM produced on calf skin as measured by ELISA and PRNT (Stittelaar et al., 2005). Bavarian Nordic reported similar safety and efficacy compared with the traditional vaccine in a clinical study conducted in 2004 in a small number of subjects (N= 32) (referenced in Wiser et al 2009).

- **VV Lister/CEP (Sanofi Pasteur)**

The second-generation smallpox vaccine Lister/CEP was developed from a batch of a first-generation Lister/Elstree vaccine originally produced by Sanofi Pasteur. The vaccine strain has not been cloned and has undergone only three passages in chicken embryo primary cells during manufacture. Preclinical studies confirmed that further passaging in CEP cells has not resulted in selection of specific viral populations. VV LISTER/CEP showed a comparable safety and immunogenicity profile and induced comparable results in a lethal cowpox virus mouse model as the parental first generation Lister vaccine (Ferrier-Rembert et al 2007).

*Regulatory status:*

Although cell-culture derived Lister vaccines are stockpiled in various countries for emergency use, their regulatory status is not clear. It is assumed that they are currently not licensed in all countries having a stockpile. However, regulatory mechanisms are in place for approval of these vaccines allowing their immediate use in an emergency.

- **ACAM2000 (Acambis/Sanofi Pasteur)**

ACAM2000 is a live attenuated smallpox vaccine produced from a single plaque purified vaccinia virus strain, which originates from the Dryvax vaccine (NYCBH strain). Interestingly it was found that the original Dryvax vaccine represents a pool of vaccinia virus subpopulations which show varying degrees of virulence. Six individual clones were isolated by plaque purification and these clones were evaluated in virulence tests in rabbits and suckling mice. Among the six individual strains isolated significant differences in the neurovirulence was observed with clone CL2 having a reduced neurovirulence in suckling mice but being comparable to Dyrvax vaccine in other characteristics such as lesion size (Weltzin et al 2003, Acambis briefing document 2007). Clone 2 was selected for further development of a new smallpox vaccine initially in human embryonic lung fibroblast cells (MRC-5, ACAM1000) and further on in Vero cells (ACAM2000) (Acambis briefing document, 2007, Nalca and Zumbrun, 2010). Initially safety, efficacy and immunogenicity of ACAM1000 was investigated in a limited number of healthy vaccinia naïve adults (N=60) in a Phase I clinical trial and compared with Dryvax (Weltzin et al 2003). All ACAM1000 recipients had a `vaccine take' and seroconverted, but the mean neutralizing antibody response following vaccination with ACAM1000 was twofold lower than after vaccination with Dryvax (GMT 142 vs 248). No serious adverse events were reported following vaccination with ACAM1000 or

Dryvax (Weltzin et al 2003). Additional human data from a second phase I study in 70 adult subjects confirmed the results of the first trial (Monath et al 2004).

In order to expand the production capacity of the new smallpox vaccine it was decided to use an established large-scale production system based on Vero cells. Further passage of the MRC-5 derived vaccinia virus seed material in Vero cells demonstrated genetic stability of the DNA sequence of Clone 2. In addition, studies in mice and rabbits confirmed that the pathogenicity and immunogenicity of the Vero cell derived vaccine ACAM2000 was comparable to ACAM1000 (MRC-5 derived) and that both candidate vaccine strains were less virulent than Dryvax (Monath et al. 2004). The clinical development program of ACAM2000 encompassed six clinical studies with a total of 3881 adult subjects enrolled (ACAM2000 N=2983, ACAM1000 N=30 and Dryvax N=868). In two phase I clinical studies conducted in healthy vaccinia naïve adults aged 18-29 years it was confirmed that vaccination with ACAM2000 results in high take rates of nearly 100% and that the majority of subjects had antibody responses comparable with ACAM1000 and Dryvax. The lowest effective dose of ACAM2000 was determined in two phase II studies that enrolled either vaccinia naïve or previously vaccinated subjects. In these studies a control group was included that received Dryvax at a standard dose ($1.6 \times 10^8$ PFU/ml). All naïve individuals vaccinated with Dryvax or a dose of $6.8 \times 10^7$ PFU/ml of ACAM2000 showed a take and 96% and 94% seroconverted, respectively, with comparable neutralizing antibody titers.
Additional groups of vaccinia naïve subjects received either 1:5, 1:10, or 1:20 dilutions of ACAM2000 or a 1:10 dilution of Dryvax vaccine. It was found that vaccinia naïve subjects receiving of diluted ACAM2000 had take-rates below the threshold set for efficacy (59% to 86%), whereas over 97% of vaccinees having received a 1:10 dilution of Dryvax had a vaccine take.
Data from vaccinia virus experienced subjects indicated that ACAM2000 was less effective than Dryvax. Only 88% of the ACAM2000 recipients had a take whereas all of the Dryvax vaccinees developed a major cutaneous reaction.

Since the dose range of the ACAM2000 and Dryvax vaccine evaluated in these phase I/II studies varied between the two study vaccines further clinical studies were initiated to investigate ACAM2000 and Dryvax at comparable dose ranges. Two clinical studies, one in vaccinia-naïve and one in revaccinees, compared a dose range of 1.3-2.2 $x10^8$ PFU/ml of ACAM2000 vaccine with Dryvax given in a dose of $1.5x10^8$ PFU/mL). In vaccinia-naïve subjects, the take-rates were 96% and 99% for ACAM2000 and Dryvax, respectively, indicating that both formulations were effective, although the geometric mean antibody titer elicited in the group receiving ACAM2000 were inferior to those receiving Dryvax. In the clinical study in vaccinia-experienced subjects, success rates of 84% and 98% were obtained in the ACAM2000 and Dryvax groups, respectively. Again, the geometric mean neutralizing antibody titers were higher in the Dryvax group than in the ACAM2000 group. In summary these data suggest that Dryvax is superior to ACAM2000 as regards robustness of the antibody response most likely due to the decreased level of virulence.

Serious and nonserious adverse events following vaccination of 2983 people with ACAM2000 (1307 naïve and 1676 experienced) were actively monitored and compared with that of Dryvax.
In the clinical studies 97% of vaccine-naïve subjects and 92% of revaccinees experienced one or more AEs after vaccination with ACAM2000. Common events included injection site reactions (erythema, pruritus, pain and swelling) and systemic symptoms (fatigue, headache, myalgia, malaise, feeling hot, and rigors). In general, occurrence of adverse events was similar in individuals vaccinated with ACAM2000 and Dryvax, but the frequency for some adverse events were lower for several specific adverse events like lymphnode and injection site pain in ACAM2000 vaccinees.

No cases of generalised vaccinia, ocular vaccinia, postvaccinial encephalitis, progressive vaccinia, erythema multiforme, or pvE were reported with ACAM2000. However, in the clinical development program of ACAM2000 10 cases of suspect or probable myocarditis, 7 (5.73 events per thousand vaccinations) in subjects treated with ACAM2000 and 3 (10.38 events per thousand vaccinations) in subjects treated with Dryvax, were identified. The rates of myopericarditis for ACAM2000 and Dryvax were not statistically different in these trials indicating no significant reduction in the risk of developing myopericarditis by ACAM2000 compared to Dryvax. All subjects who experienced myocarditis were previously naïve to vaccinia; no cases were detected in previously vaccinated subjects. Two of the 10 subjects were hospitalised while the others were sub-clinical and received no treatment.

*Regulatory status:*

ACAM2000 is licensed since August 2007 in the USA. The vaccine is manufactured by Sanofi Pasteur Biologics Co. of Cambridge, MA. ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection, however it is not currently recommended for or available to the general public in the U.S. The smallpox vaccine is only available under limited circumstances.

- **CJ-50300 (CJ CheilJedang Cooperation, South Korea)**

CJ-50300 is a freeze-dried smallpox vaccine prepared on MRC-5 cells under serum-free conditions employing the NYCBH strain (ATCC VR-118) without prior plaque purification. The vaccine contains a titer of vaccinia virus of $10^{8\pm 0.5}$ plaque-forming units (pfu)/mL following reconstitution. Preclinical studies in mice and cynomolgus monkeys confirmed that CJ-50300 is comparable with the first generation Lancy Vaxina vaccine with respect to cutaneous reactogenicity, immunogenicity, protection and neurovirulence (Kim et al 2007).
In a phase I clinical trial all vaccinia naïve subjects enrolled (N=18, age range 18-27 years) exhibited cutaneous reactions after CJ-50300 vaccination, whereas no vaccine take was reported in the 6 subjects receiving only placebo (Kim et al 2007). Investigation of the kinetics of humoral and cell-mediated immune responses to CJ-50300 showed that all subjects achieved high neutralizing antibody titers 28 days after vaccination and cell-mediated immune responses 14 days after vaccination as measured by IFN--γ-producing T cell response by enzyme-linked immunospot (ELISPOT) assays. Antibody responses increased up to 28 days after vaccination and were maintained up to 56 days after vaccination. In contrast, cell-mediated immune responses increased up to 14 days after vaccination and steadily decreased thereafter. Frequently observed local and systemic adverse reactions were chill (11%), myalgia (11%), fatique (28%), headache (28%), axillary lymphadenopathy (28%), and pain at the vaccination site (22%). Another clinical study evaluated the efficacy and safety of two different doses of CJ-50300 ($1.0 \times 10^8$ and $1.0 \times 10^7$ PFU/ml,) in healthy vaccinia-naïve adults aged 20-60 years (Jang et al 2010). A total of 123 volunteers were randomized to the two vaccine groups (82 received high dose and 41 received low dose vaccine) and were actively followed up for 28 days for vaccine take and safety. The success rates ("take") were 99% and 100% following administration of the high dose and low dose, respectively. The same rates were observed for seroconversion (4-fold increase in neutralising antibody titers (HD: 99%, LD 100%). Cellular immune response were somewhat lower with 89% in the high dose vaccine group and 95% in the low dose group Differences in the clinical, humoral and cellular responses were not significant between the two vaccine groups. No serious adverse events were observed, except of one case of a possibly vaccine related generalized vaccinia in the high dose group. The two vaccine groups did not differ in the occurrence of common adverse events. Fever, chill, myalgia, fatique, headache, lymphadenopathy and pain at the vaccination site were frequently reported. Satellite lesions were observed in both vaccine groups in 10% of vaccinees.

*Regulatory status:*

Further clinical evaluation of the vaccine CJ-50300 is ongoing in South Korea (NCT01056770). The current regulatory status in not known.

# Third generation vaccines

At the end of the eradication campaign several attenuated smallpox vaccines were developed because of increasing concerns about serious adverse events following vaccination with first generation smallpox vaccines. These vaccines were evaluated in field studies and used for routine vaccination (e.g. LC16m8, MVA,), but they were never tested or used in endemic settings. Consequently they have no proven field effectiveness against smallpox virus infection or disease in humans. Otherwise they were found to have excellent safety profiles specifically as regards serious postvaccinal complications related to traditional smallpox vaccines.

Current knowledge of the immunological mechanisms of protection against smallpox suggests that both humoral and cellular immunity play an important role (reviewed by Amanna et al 2006, Panchanathan et al 2008, Moss 2011) although the underlying mechanisms are not fully understood. Circulating antibody and immune memory may be the more important factors for preventing or at least modifying the severity of clinically apparent smallpox, taking into account that there is enough time for clonal expansion of memory B-cells after exposure. Once clinical disease is established it seems that the ability to mount an adequate T-cell response is important for recovery.

**LC16m8 – (replication competent)**

Prof. Hashizume isolated a replication competent attenuated virus after serial passages of the Lister strain in primary rabbit kidney cells at 30°C. The selected vaccine strain LC16m8 formed small pocks on the chorioallantois membrane of embryonated eggs and was demonstrated to be less neurovirulent in mice, rabbits and monkeys after intracerebral inoculation than the parent Lister strain (Hashizume et al., 1985).

*Pre-eradication era*

Efficacy and safety of the LC16m8 vaccine was investigated between 1973 and 1974 in field studies and approximately 10.000 children 0-5 years of age were closely followed after administration of a single dose by scarification. The results were compared with data gathered with the parental Lister strain in field trials conducted between 1968 and 1971. The observed take rates for the LC16m8 and Lister vaccine were 95.1% (N=10,578) and 93.7% (N=3,662), respectively. One month after vaccination comparable neutralising and HI antibody responses were measured (Japan, Ministry of Health 1975).

Among 8,544 subjects receiving LC16m8 one case of eczema vaccinatum, nine cases of autoinoculation, 28 cases of statellite vesiculation, eight cases of postvaccinal exanthema and three cases of convulsions were reported, all of which were mild, but no case of encephalitis occurred. The causal relationship between the three cases of convulsion and vaccination was not established. The examination of a subset of vaccinated subjects by electroencephalography showed that the number of temporary anomalies was lower in LC16m8 (0/56) than in Lister recipients (6/37) (Fenner et al 1988). Fever rates (7.7% vs 26.6%) and local induration at the site of vaccination (6.1mm vs 15.3mm) were lower in LC16m8 recipients than after Lister vaccination (Japan, Ministry of Health 1975, Hashizume et al 1985, Fenner et al. 1988). Following licensure of the LC16m8 vaccine in 1975 in Japan 90,000 doses were distributed and no reports of serious adverse events were received.

*Post eradication era*

Since the initial development of LC16m8 vaccine, progress was made to further characterize the vaccine virus strain. LC16m8 retains the majority of the vaccinia genome and it was found that there is a 1-base deletion in the B5R gene, which introduces a stop codon within the open reading frame (Takahashi-Nishimaki et al. 1991, Morikawa et al. 2005). This mutation results in a truncated form of the B5R protein. B5R is related to the complement activation gene family and is a major target for neutralizing antibodies (Pütz et al 2006). It is involved in the efficient formation of extracellular enveloped virus (EEV), which is essential for cell-to-cell transmission of the virus and dissemination within the host (Smith et al. 2002). Recently it was found that virus revertants spontaneously emerged from plaque purified LC16m8 vaccine virus after passage in cell culture (Kidokoro et al 2005). These revertant virus clones were characterized by plaque size, dermal reaction in rabbits and pathogenicity in mice. Following i.p. injection in SCID mice the revertant virus clones induced severe rash and killed mice at low dose levels, while no overt symptoms were reported over a 4-week period in SCID mice receiving the LC16m8 vaccine. Sequence analyses showed that the full length open reading frame was reconstituted through a one base insertion that corrects the initial frameshift mutation. Synthesis of full-length B5 protein was demonstrated in western blot analysis (Kidokoro et al 2005).

Animal data

Since LC16m8 vaccine has never been tested against smallpox (e.g. variola virus) in the field, protective efficacy was evaluated in various animal studies using mouse, rabbit and monkeypox models (Morikawa 2005, Saijo et al 2006, Empig et al 2006, Meseda et al 2009, Gordon et al 2011).

Initial data from studies on the protective efficacy of LC16m8 and the parental Lister vaccine strain showed that mice were protected against lethal intranasal challenge with VACV strain WR (Morikawa et al. 2005). Another study compared the protective efficacy of LC16m8 with the parental Lister strain and placebo in the monkeypox model (Saijo et al 2006). Cynomolgus monkeys were immunized with LC16m8 or Lister vaccine by scarification and then 5 weeks later infected intranasally or subcutaneously with monkeypox virus (MPXV) strain Liberia or Zr-599, respectively. All animals in the vaccine and placebo groups survived the intranasal MPXV challenge with $1x10^6$ PFU of the Liberia strain. Whereas no clinical symptoms developed in and no virus could be isolated from animals vaccinated with LC16m8 or Lister, both animals in the placebo group showed clinical symptoms of MPXV infection such as body weight loss, rhinorrhea, papulovesicular lesions and decreased activity. Virus was isolated from peripheral blood starting 4 days after challenge. In a second experiment immunized monkeys received a subcutaneous MPXV challenge of $1x10^6$ PFU (strain Zr-599). Subcutaneous infection with MPXV Zr-599 was fatal to placebo -immunized monkeys and this was accompanied by a decrease in body weight, appearance of papulovesicular lesions and continuous detection of virus in peripheral blood. In contrast monkeys immunized with LC16m8 or Lister vaccine did not develop any MPXV related symptoms, except for local cutaneous lesions observed in the LC16m8 group at the inoculation site of MPXV. All animals maintained their body weight and none of the animals died. Histopathological examination 3 weeks after intranasal or subcutaneous challenge showed no MPXV related findings in the internal organs (lymphoid systems, lung, digestive organs, urogenital tract) of any of the monkeys in the LC16m8 and Lister group, but all organs were affected in animals in the placebo group.

Empig et al. presented data on efficacy employing rabbit and mouse challenge models. In both animal models LC16m8 was compared with Dryvax and placebo. Rabbits immunized with approx. $2x10^5$ PFU of LC16m8 or Dyrvax vaccine were protected against intradermal challenge with low (200 PFU) or high doses (1000 PFU) of lethal rabbitpox virus 28 days post infection. At the high dose challenge all animals in the placebo group died within 10 days whereas in the low dose group 9 of 10 rabbits died.

Determination of infectious RPV in lung tissue revealed no virus in the lungs of animals immunised with either LC16m8 or Dryvax. In contrast high titers of PRV were detected in the lung tissue of all animals of the placebo group. In the inhalation orthopoxvirus challenge model groups of mice were immunized either with $2x10^5$ PFU of LC16m8 or Dyrvax vaccine by scarification or received placebo. All mice were challenged 49 days later with aerosolized ECTV (approx. 1-2 PFU). Ninety percent of mice in the placebo group died within 15 days after ECTV challenge whereas all mice immunized with either LC16m8 or Dryvax vaccine were protected. Assessment of clinical symptoms revealed that most of the mice in each vaccine group had no signs of illness and continued to gain weight following challenge.

Meseda et al. presented data on comparative evaluation of the immune responses and protective efficacy engendered by LC16m8 and Dryvax smallpox vaccines in a mouse model. LC16m8 elicited a broad-spectrum antibody response that neutralized both EEV and the IMV form of vaccinia virus. Mice inoculated with LC16m8 had detectable but low levels of anti-B5 antibodies compared to Dryvax, but both Dryvax and LC16m8 sera neutralized vaccinia virus EEV in vitro. A truncated B5 protein (~8 kDa) was expressed abundantly in LC16m8-infected cells, and both murine immune sera and human vaccinia virus immunoglobulin recognized the truncated recombinant B5 protein in an antigen-specific ELISA. Immunization of mice with LC16m8 and Dryvax conferred similar levels of protection against a high-dose intranasal challenge (100 or 250 LD50) with vaccinia virus strain Western Reserve (WR). Among mice vaccinated with LC16m8, 80% survived either the 100 LD50 or the 250 LD50 challenge. All mice vaccinated with Dryvax survived the 100 LD50 and 60% survived the 250 LD50 challenge.

Studies conducted in immunocompromised animal models demonstrated that LC16m8 is well tolerated, with no serious adverse effects (Kidokoro et al 2005, Gordon et al 2011). Immunisation of SCID mice with high doses of LC16m8 did not induce mortality in contrast to Dryvax (Kidokoro et al 2005). Recently, Gordon et al investigated the immunological basis of the containment of vaccine in the skin by using macaques depleted systematically of T or B cells and vaccinated by scarification with either Dryvax or LC16m8 ($2.5 \times 10^5$ PFU), . B cell depletion did not affect the size of skin lesions induced by either vaccine. Following simultaneous CD4+ and CD8+ T cell depletion LC16m8 was unable to spread and cause satellite or distal lesions whereas Dryvax led to progressive vaccinia with larger skin lesions, a longer resolution time of the lesions and in half of the animals spreading of lesions to secondary sites, indicating that LC16m8 might have a better safety profile in immunocompromised patients than traditional smallpox vaccines (Gordon et al 2011). All animals having received either LC16m8 or Dryvax survived lethal intravenous challenge ($5x10^7$ PFU MPXV strain Zaire 79)

Human data

Results of two clinical trials conducted in healthy subjects were recently published. The first study was performed by the Japanese Self Defense Forces between 2002 and 2005 in 3468 vaccinia naïve and previously vaccinated adults aged 18 to 55 years (Saito et al 2009). Of the 3468 subjects enrolled 247 were excluded from the study due to nonmedical or medical reasons such as active atopic dermatitis. In total 3221 subjects were vaccinated and followed for up to 30 days to assess successful vaccination ('vaccine take', neutralizing antibody response) and occurrence of adverse events including determination of troponin T levels in blood (Day 0 and Day 30) and electrocardiography (ECG) at day 30. Almost half of the subjects had never been vaccinated (47.5%), the vast majority of the vaccinees were men (98.4%) and all were of Asian origin.

Determination of successful vaccination indicates that the proportion of 'vaccine take' was significantly higher in primary vaccinees (94.4%) than in revaccinees (86.6%). In primary vaccinees take rates did not significantly differ across different age categories, although most participants belonged to the groups of the 20-29 (N=1122) and 30-39 years-old (N=367). Only 3 vaccinia naïve subjects were over 50 years of

age. Among revaccinees slightly higher take rates were observed in the 20-29-year-old group (N=84; 95.2%) but the number of subjects enrolled in this age category was low. In a subset of the study population neutralizing antibody responses were measured in serum samples collected prior and 30 days after vaccination by plaque reduction neutralization test (PRNT) using LC16m8 virus. Effective seroconversion or booster response was defined as a 4-fold increase in the $PRNT_{50}$ titer at day 30 days compared to the titer prior vaccination. The geometric mean titer (GMT) prior vaccination was significantly higher in revaccinees (21.0) than in vaccinia naïve subjects (6.1); among the revaccinees the GMT was significant higher in subjects born before 1964 (group D; GMT: 29.5) than in any other age group (group B and C: 14.4 and 19.4). The difference in baseline antibody titers might be explained by the number of doses and/or vaccine received through routine childhood vaccination in Japan. Post vaccination the GMTs were comparable in primary vaccinees and revaccinees. The percentage of primary vaccinees with 4-fold increases in neutralizing antibody titers (90.2%) was significantly higher than that of revaccinees (60.0%) and among the revaccinees it decreased with age. Further evaluations of the immune responses to specific VACV antigens and the neutralizing antibody response to EEV in a subset of sera from 42 vaccinia naïve vaccinees and 43 revaccinees revealed that the antibody responses to LC16m8 were qualitatively and quantitatively different from those seen for the Lister vaccine (Johnson et al 2011). In vaccinia-naïve subjects LC16m8 failed to elicit neutralizing antibody responses against the EEV form but induced a strong neutralizing antibody response to the IMV form of VACV. Antibody responses to specific proteins indicate that the vaccine induces antibodies against a variety of IMV proteins as well as against A56 protein, but not to B5. A56 and B5 are both components of EEV. Since non-neutralizing antibodies against EEV are capable to activate the complement system (Benhnia et al 2009) antibodies against A56 might induce such a response. In contrast, in revaccinees an anamnestic antibody response to B5 protein and neutralizing EEV response was found and these findings are most likely due to the presence of the truncated form of B5 expressed by LC16m8.

Throughout the study no serious adverse events were reported. No abnormal ECG findings or symptomatic heart disease occurred and the troponin T levels in all samples of a subset of the study population were below the detection limit. Due to the timing of the ECG and measurement of the troponin level on day 30 day instead of the more appropriate time from day 7 to14 post vaccination occurrence of asymptomatic myopericarditis can not be excluded. In general the frequency of adverse events was low (13.9%) with a significantly higher frequency of AEs in primary vaccinees than revaccinees. The most frequently reported AEs were swelling of axillary lymph nodes and low grade fever.

In a phase I/II clinical trial performed in the US the safety and immunogenicity of LC16m8 was compared with Dryvax in healthy vaccinia-naïve subjects 18 to 34 years of age (Kennedy et al 2011). The primary endpoints were the neutralizing antibody titers to intracellular mature virus (IMV) measured by PRNT 30 days after vaccination and the rates of AEs attributed to the vaccines. Exploratory endpoints included vaccine take, lesions at the vaccination site, neutralizing antibody titers against EEV and variola virus, cell-mediated immune (CMI) responses, viral persistence and viremia after vaccination. Of the 154 subjects randomized into one of the two vaccination groups 147 subjects (27 Dryvax, 120 LC16m8) had undetectable antibody titers prior immunization and completed the follow-up at day 30. All 125 participants vaccinated with LC16m8 developed a primary lesion at the vaccination site between 6 and 12 days after scarification. The take rate was significantly lower in the Dryvax group (24/28; 86%). The four subjects who did not develop a take most likely received subpotent vaccine due to handling issues. Lesions at the vaccination site as well as the extent of erythema and swelling were on average greater within the Dryvax group than in the LC16m8 group. Viral shedding was investigated in a subset of 27 vaccinees (4 Dryvax, 23 LC16m8). In 2 of the 4 Dryvax recipients viral shedding was observed on day 3 and by day 7 all subjects had detectable virus. In all LC16m8 participants evaluated virus was found

starting from day 7. PCR analyses of blood samples drawn at different time points (Days 0, 3, 7, 13, 22) confirmed absence of viremia at all time points and in all subjects.

All subjects with a vaccine take seroconverted as measured by PRNT assay using Dryvax vaccine strain. At day 30 post vaccination significantly higher geometric mean PRNT titers were elicited in Dryvax recipients than in LC16m8 vaccinees (919 vs 279). Additional immunogenicity analyses were performed on samples from a subset of LC16m8 and Dryvax vaccinees. Data on the kinetics of the neutralizing antibody response demonstrate a comparable timely course but significantly higher titers at day 30 and 60 in the Dryvax group. Comparison of different PRNT assays using various virus strains revealed that Dryvax vaccinees exhibited significantly higher GMT than LC16m8 recipients when Dryvax, Japan-NYCBH or monkeypox strains were used as test virus. On the other hand higher GMTs were observed in LC16m8 vaccinees than in Dryvax vaccinees when the virus used in the assay was LC16m8 or the parental Lister strain. Determination of anti-EEV PRNT titers were hampered by low antibody titers and it was only meaningful when the results were based on a 30% instead of a 50% reduction. Significantly higher anti-EEV GMTs were found in the Dryvax group compared to the LC16m8 group (24 vs 4). Finally, serum samples of 9 Dryvax and 11 LC16m8 recipients were assessed in an anti-variola PRNT conducted at CDC. Significantly higher GMTs were found in Dryvax group than in the LC16m8 group (274 vs 75). T cell responses were assessed by IFN-y ELISPOT and lymphoproliferation. LC16m8 produced somewhat higher lymphoproliferation but lower IFN y ELISPOT responses than Dryvax.

The safety assessment revealed no clinically significant differences in the reactogenicity and safety profile of Dryvax and LC16m8 with the exception that the vaccine site lesion was significantly smaller, less red, and less swollen in LC16m8 vaccinees compared to Dryvax recipients. No serious adverse events related to vaccination were reported. There were no cases of generalized vaccinia, progressive vaccinia, eczema vaccinatum, or myo-and pericarditis.

*Regulatory Status of LC16m8*

The Chiba Serum Institute was issued an unconditional license in 1975 in Japan. KAKETSUKEN was licensed to produce LC16m8 in 2003. LC16m8 has an approved 4-years shelf-life following storage at -20°C and a 2-years shelf-life after storage at 2-8°C. The vaccine is stockpiled in Japan.

**Third generation vaccines based on the replication deficient MVA strain**

Towards the end of the eradication campaign Anton Mayr and his group developed further attenuated vaccinia virus vaccines against smallpox by continually passaging the chorioallantois vaccinia Ankara (CVA) vaccine virus strain on chicken embryo fibroblast cells for more than 570 times. The resulting virus strain, called Modified Vaccinia Ankara (MVA), was found to have multiple mutations and six deletions accounting for a loss of approximately 30 kb of the CVA genome (Mayr et al 1978). MVA has been extensively tested and it was found that it has a limited ability to replicate and a low neuropathogenicity in humans and other mammals. It was also found that by a block in virus morphogenesis non-infectious immature virions and abnormal particles are produced but no infectious IMV and EEV particles. Despite these genomic modifications, MVA has retained stable immunogenic properties. MVA is a strong inducer of type I interferon (IFN) in human cells and it expresses a soluble interleukin-1 receptor, which has been implicated as an anti-virulence factor for certain poxviruses. In contrast to VV, MVA does not express soluble receptors for IFN-γ, IFN-α/β, tumour necrosis factor (TNF) and CC chemokines (Blanchard et al.1998). The virus is described as eliciting a protective immune response against any of the orthopox viruses.

At the end of the eradication campaign MVA was evaluated in clinical trials in 7098 subjects including 5691 children in a two-step vaccination regimen as priming dose prior to regular smallpox immunisation with Lister-Elstree vaccines (Stickl et al. 1974). MVA was administered mostly intradermally or subcutaneously. Each vial contained 2 x $10^6$ freeze-dried infectious units (IU) and was used for two vaccinations after resolution in 0.5 ml saline. Most recipients were vaccinia-naïve children and adults considered to be at risk for adverse reactions to smallpox vaccines. A single dose of MVA elicited a weak haemagglutination inhibiting or virus neutralising antibody response. Following the subsequent vaccinia virus smallpox vaccine dose there was a marked immune response, which was interpreted as MVA priming of specific humoral and cellular immune responses. Mild local reactions including reddening and infiltration were observed at the site of injection (0.2 ml intradermal) in ~75% of 5308 individuals but there were no blisters, pustules or ulceration. Among 7098 subjects fever > 38°C occurred in 2.28% and non-specific general symptoms in 4.11%. There were no SAEs. Pre-vaccination with MVA resulted in a reduced number of side effects following a subsequent dose of vaccinia virus smallpox vaccine and the development of smaller pocks. The vaccine was licensed 1977 in Germany and was administered to over 120,000 subjects however at that time smallpox was no longer endemic in Germany. The MVA dose was well tolerated and the reactogenicity of the second traditional smallpox vaccine dose was reduced. In the majority of subjects the subsequent smallpox vaccination resulted in a revaccination reaction.

Based on these historical experiences several groups developed MVA vaccines or MVA based vectors for the development of new vaccines against other indications. In this review primarily data on Imvanex (Imvamune) manufactured by Bavarian Nordic (BN) is considered since this vaccine recently received a marketing authorization in Europe (ref to www.ema.europa.eu).

Other MVA based vaccines currently under development are ACAM3000 manufactured by Acambis/Sanofi Pasteur and TBC-MVA vaccine manufactured by Therion Biologics Cooperation.

**Imvanex (Imvamune or MVA-BN, reference is made to the EPAR published by EMA)**

BN has developed a third generation MVA vaccine, which is anticipated to represent a safer alternative to traditional first (manufactured on animal skin) and second generation vaccines (manufactured in cell culture) particularly in people with immune deficiencies and skin disorders. Imvanex (also designated Imvamune or MVA-BN) is derived from MVA-584 (i.e. 584th passage in CEF cells) and differs from all other MVA strains in that it has undergone six rounds of plaque purification resulting in a single clone (Suter et al 2009). The growth characteristics in different mammalian cell lines and the pathogenicity in immune-deficient mice demonstrated that the monoclonal MVA-BN strain is significantly different than other MVA strains. In contrast to polyclonal MVA strains, MVA-BN was incapable to replicate in different human cell lines tested. Moreover, experiments with immune deficient AGR129 mice demonstrate that after intraperitoneal inoculation of $1x10^7$ TCID50 each of the various MVA strains evaluated, all animals having received MVA-BN survived the 100-day observation period while mice infected with other MVA strains died within 37 days (MVA-I721) or 94 days (MVA-572). Further experiments confirmed the safety profile of MVA-BN. Immune deficient AGR129 mice inoculated with MVA-BN appeared to be healthy over a 180 day time period and at no time point tested MVA could be isolated from the ovaries of these animals (Suter et al 2009).

MVA-BN has been developed as smallpox vaccines following a standalone regimen rather than in a sequential regimen of MVA followed by a replication competent smallpox vaccine. The vaccine was initially developed as freeze-dried formulation, but was reformulated and is now licensed as liquid formulation (refer to Imvanex EPAR published by EMA).

Animal data

Protective efficacy and immunogenicity of Imvanex were evaluated in animal studies using established animal models (ECTV/mouse, RPXV and MPXV models) and compared to first and second generation vaccines (EPAR 2013, Samuelsson et al 2008, Garza et al 2009, Stittelaar et al 2005, Hatch et al 2013)

Initial studies in mice with the challenge virus WR given by the intranasal route demonstrated a dose-response for morbidity and mortality (EPAR 2013). A dose equivalent to 50-fold the median lethal dose was taken further in testing the protective efficacy of Imvanex. Mice previously vaccinated with Imvanex survived this lethal intranasal dose after challenge. In characterising the dose-response for this protective effect a dose of $1x10^8$ TCID50 was found to be optimal. Lower doses protected mice from death but there was greater morbidity than with $1x10^8$ TCID50. In comparative testing of Imvanex with Dryvax and ACAM2000, 100% seroconversion rates were achieved by day 14 in mice given Imvanex but it took to days 26 to 40 for similar seroconversion rates with Dryvax and ACAM2000. Mice vaccinated with Imvanex were able to survive a lethal challenge with ECTV, whereas unvaccinated mice did not and only mice that seroconverted after Dryvax immunisation survived. All mice given Imvanex did seroconvert; however, only 79% of mice given Dryvax seroconverted. Lung titres of ECTV were reduced to 0 in mice vaccinated with Imvanex but 2 of 10 mice given Dryvax failed to completely clear the virus, although titres were much lower than in unvaccinated mice.

Samuelsson et al demonstrated that MVA-BN is capable to activate dendritic cells by TLR9-dependent and independent pathways and protect mice from lethal infection with ECTV. In wild type mice protection from death was achieved when $1x10^8$ TCID50 of MVA-BN was administered by subcutaneous injection at the same time as a lethal dose of ECTV ($1x10^5$ TCID50) given intranasally.

Garza et al evaluated the protective efficacy of Imvamune against aerosolized RPXV in a rabbit model. Rabbits were immunised with either PBS buffer, a single dose of Dryvax, a single low dose of Imvamune ($1x10^7$/dose), a single high dose of Imvamune ($1x10^8$/dose) or received two doses of a high dose of Imvamune at a 2 week interval. Four weeks after the last vaccination all animals were challenged with a lethal dose of aerosolized RPXV (~500 LD50). All animals in the control group succumbed to the disease, whereas all of the animals that received Dryvax or any of the different doses of Imvamune survived the challenge. The rabbits vaccinated with Dryvax, or a single low or high dose of Imvamune showed minimal to moderate clinical signs of the disease. The only clinical sign displayed by rabbits that had been vaccinated with two doses of Imvamune was mild transient anorexia in just two out of eight rabbits.

Protection against lethal challenges with MPXV given by the intravenous routes was investigated in macaques (EPAR, EMA). With the intravenous challenge, two subcutaneous doses of Imvanex given 28 days apart at $1x10^8$ TCID50 were shown to induce protection from death when monkeys were subsequently exposed to $5x10^7$ PFU/ml MPXV. A control groups having received ACAM2000 was also shown to be effectively protected. Results from two additional MPXV challenge studies investigating dose-response in a dose range of $1x10^2$ and $1x10^3$ to $1x10^7$ TCID50 were performed. One study used intravenous challenge and one used inhalational challenge methods. Immunogenicity was assessed using ELISA and PRNT. In the ELISA the MVA-derived antigen and in the PRNT assay vaccinia virus strain WR was used as test antigen. Statistically significant correlations were found between dose of Imvanex and probability of survival, and between dose of Imvanex and each of PRNT and ELISA titres. However, it was evident that vaccinated monkeys that developed PRNT and ELISA titres at levels comparable to those who survived could still succumb to the MPXV challenge. Despite the statistically significant correlation, survival of an individual monkey could not be accurately predicted based on its PRNT or ELISA response. In one study, there were two monkeys that did not survive despite seroconversion by day 42 and there were two monkeys who had not seroconverted by day 42 but survived. These results suggest that PRNT

and ELISA titres are not absolute correlates of protection and that other immune mechanisms, particularly cellular immunity, may contribute to protection.

Stittelaar et al investigated the protective efficacy of MVA-BN (Imvanex) in a lethal respiratory MPXV challenge model. MVA-BN was either administered subcutaneously in a 2-dose regimen ($10^8$ TCID50/dose) at an interval of 4 weeks or administered as single priming dose ($10^6$ TCID50) followed by a standard dose of a traditional smallpox vaccine given 10 days later intracutaneously. Two traditional smallpox vaccines prepared from the Lister Elstree strain in cell culture (Elstree-BN and Elstree-RIVM) were included in the study and six macaques each received a standard dose by intracutaneous vaccination. A control group of six animals received a sham vaccination. All animals were challenged intratracheally 15 weeks after the last vaccination with either $10^6$ PFU (sublethal) or $10^7$ PFU (lethal) of MPXV (strain MSF#6). All smallpox vaccination regimens used in this study evoked protective efficacy against sublethal and lethal MPXV challenge by the respiratory route. Differences were found in the viral loads of throat swabs. The strongest reduction in viral loads was found in animals vaccinated with the prime-boost regimen of MVA-BN/Elstree-RIVM followed by Elstree-RIVM alone.

In a recent study the protective effect against disease of either a single or two doses of Imvamune (Imvanex), and of a single dose of ACAM2000 was evaluated in cynomolgus macaques following an aerosolised severe/lethal dose ($2.6 \times 10^5$ PFU) of the central African strain Zaire 79 of MPXV virus (Hatch et al 2013). It was found that all animals in the Imvamune 2-dose group and the ACAM2000 were protected from death, while 67% (4/6) in the Imvamune 1-dose group survived the lethal challenge. All animals in the control group having received TBS buffer succumbed to infection between day 7 and 11 post-challenge. Radiographs taken at the time of severe clinical signs at day 9 indicate that all animals in the ACAM2000 group were found normal, whereas all animals in the control group had severe clinical signs. A wide spectrum of conditions was observed in the Imvamune 1-dose and 2-dose group ranging from normal to severe oedema. One animal in the 2-dose group had moderate to severe pulmonary oedema but recovered fully.
Assessment of MPXV load in blood and throat swabs revealed that there was incomplete suppression of challenge virus replication in the blood and throat of monkeys vaccinated with one or two doses of Imvamune. In contrast, vaccination with ACAM2000 achieved complete viral suppression. The viral load detected in throat samples of animals in the Imvamune 1-dose group was comparable to the control group with $10^4$-$10^5$ PFU live virus per ml. In the Imvamune 2-dose group live virus was detected in two out of 6 animals; one animal excreting MPXV at low levels (50 PFU/ml) and one animal at levels of $4.6 \times 10^4$ PFU/ml.
There was no significant difference ($p>0.05$) between the levels of neutralizing antibody in animals vaccinated with ACAM2000 (132 U/ml) and two doses of Imvamune (69 U/ml) 6 days prior to challenge with MPXV. However, significantly lower levels of neutralising antibody were detected in animals immunized with a single dose of Imvamune (13 U/ml).

Human data

Three clinical studies were performed, to assess the dose-response relation in healthy adults with or without prior history of smallpox vaccination, to evaluate the best route of administration and to define the optimal dosing of Imvanex with respect to immunogenicity and safety. In these studies an earlier freeze-dried formulation of Imvanex was employed. In summary 5 different dose levels ($1x10^6$, $1x10^7$, $2x10^7$, $5x10^7$, $1x10^8$ $TCID_{50}$) and two routes of administration (s.c. and i.m.) were investigated. The highest dose responses were found with the highest dose level of $10^8$ $TCID_{50}$ regardless of the route of administration. A combined analysis of the GMT responses (ELISA and PRNT) and SCRs (ELISA and PRNT) 14 days post dose 2 in vaccinia-naïve subjects enrolled in the three dose finding studies indicate a linear dose response relationship based on serological data. Vaccinia-naive subjects having received the highest dose level subcutaneously achieved a SCR of 77% and a GMT of 29 based on the PRNT assay. Data from booster vaccinations of healthy vaccinia experienced subjects are only available from one study. Subjects with confirmed history of smallpox vaccination (last vaccination over 10 years ago) were given one dose of $10^8$ $TCID_{50}$ subcutaneously. No other dose level or dosing regimens were evaluated. Based on the PRNT results 88.9% of these subjects seroconverted post booster and had a neutralising GMT of 41.3.

Of special interest is a study conducted in 2002, during a time when Dryvax was still licensed in the US and permitted for use in clinical trials (Frey et al 2007). This dose-finding study was sponsored by NIH and evaluated the immunogenicity of different vaccination regimens of Imvanex followed by administration of a single dose of traditional smallpox vaccine (Dryvax). In addition one group received Dryvax only. Post vaccination follow-up of clinical take rates revealed that clinical take rates were high in all vaccination groups (>90%) except for two groups having received either 2 doses of $5x10^7$ (53.8%) or 2 doses of $1x\ 10^8$ intramuscularly (66.7%). The clinical takes in subjects with prior Imvanex vaccinations were however attenuated as shown by the degree of the local lesions, the reduced healing times and viral titers in local lesions. In general the attenuated clinical takes appeared to be revaccination reactions as observed after revaccination with smallpox vaccines in vaccinia experienced subjects.

A subset of blood samples of this study was reanalysed by CDC in a PRNT using the variola strain strain Solaimen, a Bangladesh isolate (Damon et al., 2009, Hughes et al 2012). In total 106 sera from 53 of the 90 participants enrolled were retested. Blood samples were from subjects having received either the highest dose level of Imvanex of $10^8$ TCID50 subcutaneously (26 subjects) or intramuscularly (15 subjects) or vaccinated with Dryvax (14 subjects). Paired sera collected prior to vaccine dose and at the times of 'peak' response, based on plaque PRNT data against either MVA or Dryvax, were evaluated by a variola (VAR) PRNT. Individuals' sera in the Dryvax arm were evaluated 28-30 days post-vaccination; individuals vaccinated with MVA were evaluated 14 days after the second s.c. or i.m. dose. When the individuals at peak times post-vaccination are scored for the ability to demonstrate a 60 or 90 % VAR PRNT titre at various serum dilutions, the ability to neutralize variola virus elicited by the MVA regimens is as robust as that elicited by Dryvax. A comparison of neutralisation assays using different test viruses (Dryvax, MVA or Variola) showed significantly different 90% neuralisation titers. It was found that using Dryvax as the neutralisation antigen results in significantly lower 90% PRNT titers than using variola. In contrast using MVA as test antigen resulted in significantly higher 90% PRNT titers than using variola as test antigen.

Different vaccination schedules as regards timing of the second dose were evaluated in another study (EPAR, EMA). The data clearly indicate that an accelerated vaccination scheme (2 doses at day 0 and 7) is unfavourable compared to the regular scheme of 2 doses given 4 weeks apart as the latter resulted in higher antibody titers and response rates.

Based on the results of the dose finding and regimen finding studies the standard regimen of 2 doses of Imvanex given 4 weeks apart was evaluated in vaccinia naïve healthy subjects, subjects with history of AD and HIV infected patients. In vaccinia experienced subjects one and two-dose vaccination regimens

were assessed. Moreover antibody persistence was studied over a two year period in a subset of initially vaccinia naïve subjects and in subjects with known history of smallpox vaccination. A subset of initially vaccinia naïve subjects received a booster vaccination given two years after primary vaccination and was followed for 4 weeks.

Immunogenicity and safety of Imvanex was evaluated in five main studies and several supportive studies. The studies were conducted in Europe, USA, Mexico and Puerto Rico. The study population was 18 years of age and older and male and female subjects were enrolled.

The neutralising antibody response was evaluated by plaque reduction neutralisation (PRNT) assays using the Vaccinia virus strain Western Reserve. An overview on the seroconversion rates (SCR) achieved in vaccinia-naïve and vaccinia experienced individuals, who received 2 doses of Imvanex 4 weeks apart is given below (ref to EPAR, EMA).

Seroconversion rates observed in vaccinia-naïve subjects as measured by PRNT

| **SCR - PRNT** | | | **at Day 7 or 14** | **Day 28** | **Day 42** |
|---|---|---|---|---|---|
| **Study** | **Health status** | **n** | **SCR %<br>(95%-CI)** | **SCR %<br>(95%-CI)** | **SCR %<br>(95%-CI)** |
| POX-MVA-005 | Healthy | 183 | 45.1<br>(37.7; 52.6) | 56.7<br>49.1; 64.0) | 89.2<br>(83.7; 93.4) |
| POX-MVA-008 | Healthy | 194 | 5.4<br>(2.6; 9.8) | 24.5<br>(18.6; 31.2) | 86.6<br>(81.0; 91.1) |
| | AD | 257 | 5.6<br>(3.1; 9.3) | 26.8<br>(21.4; 32.7) | 90.3<br>(86.0; 93.6) |
| POX-MVA-009 | Healthy | 66 | 12.1<br>(5.4; 22.5) | 10.6<br>(4.4; 20.6) | 82.5<br>(70.9; 90.9) |
| POX-MVA-011 | Healthy | 88 | 11.1<br>(5.2; 20.0) | 20.9<br>(12.9; 31.0) | 77.2<br>(66.4; 85.9) |
| | HIV | 351 | 15.7<br>(11.9; 20.1) | 22.5<br>(18.1; 27.4) | 60.3<br>(54.7; 65.8) |

Seroconversion rates observed in vaccinia-experienced subjects as measured by PRNT

| **SCR - PRNT** | | | **At Day 7 or 14** | **Day 28** | **Day 42** |
|---|---|---|---|---|---|
| **Study** | **Health status** | **n** | **SCR %<br>(95%-CI)** | **SCR %<br>(95%-CI)** | **SCR %<br>(95%-CI)** |
| POX-MVA-005 | Healthy | 200 | 78.5<br>(72.2; 84.0) | 69.8<br>(63.0; 76.1) | NA |
| POX-MVA-024 | Healthy | 61 | 73.8<br>(60.9; 84.2) | 71.2<br>(57.9; 82.2) | NA |
| POX-MVA-011 | Healthy | 9 | 75.0<br>(34.9; 96.8) | 62.5<br>(24.5; 91.5) | 85.7<br>(42.1; 99.6) |
| | HIV | 131 | 46.0<br>(37.0; 55.1) | 59.7<br>(50.5; 68.4) | 75.6<br>(67.0; 82.9) |

The analyses of peak PRNT responses across the pivotal studies POX-MVA-005, POX-MVA-008 and POX-MVA-011 indicated that in vaccinia naïve healthy subjects SCRs of 89.2%, 86.6% and 77.2% were determined using the standard vaccine regimen of 2 doses given 4 weeks apart.

Following 1 or 2 doses of Imvanex mean neutralising antibody titers of 6 and 45, respectively, were measured in healthy vaccinia naïve subjects, whereas a single dose of Imvanex elicited mean neutralising antibody responses of 192 in vaccinia experienced individuals 2 weeks after the booster immunisation. Analyses of antibody persistence revealed a fast decline in antibody titers in vaccinia naïve subjects following vaccination with one (MVA/Placebo group: GMT of 2) or two doses (MVA/MVA group; GMT of 7) of Imvanex. PRNT GMTs in both groups were lower two years after primary vaccination with Imvanex than baseline GMTs of vaccinia experienced subjects (GMT: 24), who had their last smallpox vaccination over 10 years ago. Moreover neutralising antibody titers observed 2 years post booster vaccination of vaccinia experienced subjects were significantly higher than in vaccinia naïve subjects having received either one or two doses of Imvanex. These findings suggest that the antibody response following traditional smallpox vaccination is more robust than that induced by Imvanex. Booster vaccination two years after primary vaccination of vaccinia naïve subjects with Imvanex however evoked a memory response in all subjects regardless whether they were primed with one or two doses. Based on the PRNT 98.7% of subjects seroconverted within 2-4 weeks following the booster vaccination. Following the booster neutralising GMTs of 166 and 117 were obtained for subjects primed with two or one dose of Imvanex, respectively. In vaccinia experienced healthy subjects 77.6% to 78.5% seroconverted after a single booster vaccination and 85.7% to 90.0% after two booster vaccinations.

In vaccinia naïve subjects with history of AD SCRs of 90.3% were observed after a standard 2 dose vaccination regimen suggesting sufficiently high titers especially as this group of patients are at high risk in developing serious adverse event following traditional smallpox vaccination.

Vaccinia naïve HIV infected subjects reached SCR of 60.3% post dose 2 and vaccinia experienced HIV infected subjects had SCRs of 75.6% post dose 2. In some subgroups even lower response rates were observed. No information is available whether these patients would benefit from additional vaccine doses and it remains unclear whether mitigation of smallpox disease is to be expected by vaccination with MVA alone.

The currently available data on the cell mediated immunity are variable and inconclusive.

Safety data from 14 clinical trials with a total 1547 vaccinia naïve and 534 subjects previously vaccinated either with smallpox vaccines or Imvanex were evaluated. The most frequently reported adverse reactions were injection site reactions and mild to moderate systemic symptoms such as headache, myalgia, nausea. These reactions typically resolved within one week. In general, occurrence and frequency of adverse events were comparable in primary vaccinees and revaccinees. In subjects with atopic dermatitis erythema and swelling at the injection site as well as headache, myalgia, nausea and fatique was more frequently observed than in healthy subjects. Worsening of atopic dermatitis was observed in 7% of subjects with atopic dermatitis.

Four serious adverse events possibly linked to vaccination were described. One healthy, vaccinia naïve subject experienced grade 3 extraocular muscle paresis after the second vaccination and one HIV patient with low CD4 counts experienced grade 3 pneumonia during the main study period. In the follow-up period 2 further SAEs were reported that were considered possibly related. One case of grade 2 sarcoidosis was observed in a vaccinia naïve healthy subject and one case of a cardiomyopathy was recorded in a HIV patient.

Inadvertant vaccination of pregnant women occurred in 13 cases, with no untoward findings.

No case of known postvaccinial complication was notified in human clinical trials. Moreover there was no case of myopericarditis, however, elevated troponin T levels were observed in some vaccinees and less than 25% of all subjects with abnormal troponin T levels or ECG findings were consistently investigated.

*Regulatory Status of Imvanex (Imvamun)*

Imvanex received a marketing authorization by the European Commission in July 2013. The European Public Assessment report is available and published by EMA. Results of some of the clinical studies performed to evaluate the immunogenicity and safety of Imvanex were published by Vollmar et al 2006, Frey et al 2007, von Krempelhuber et al 2010 and Greenberg et al 2013.

**Data from studies with other MVA smallpox vaccines**

Data from a recently published study evaluating MVA as an alternative to Dryvax in vaccinia-naïve and vaccinia-expierenced adult subjects show that intramuscular administration of two doses of $10^6$ PFU of MVA three months prior to Dryvax challenge reduced the severity of lesion formation and a decreased magnitude and duration of viral shedding (Parrino et al 2007). Moreover an increased post-Dryvax vaccine specific CD8 T-cell response and augmented antibody response against EEV-specific A33R and B5R surface proteins were evoked in vaccinia naïve subjects. Pre-challenge however, lower neutralising antibody responses were elicited in the MVA vaccine groups compared to the Dryvax only vaccine group. Similar results were published by Seaman et al. 2010, who evaluated the effect of ACAM3000 given by different routes of administration and challenged with Dryvax. Interestingly the intradermal route was found to induce a immunological response comparable to those of a 10-fold-higher dose given subcutaneously.

# Other smallpox vaccines

**Inactivated vaccines**

The inactivated vaccine Ospavir is based on the L-IVP strain (Lister derivative) and is produced on chorioallantois membrane of embryonated chicken eggs. Virus suspensions containing 1-5x$10^9$ PFU/mL are inactivated by gamma-irradiation and formulated with stabilisers prior to freeze-drying (Perekrest et al 2013). The vaccine was tested in a field trial in 1977 (Marennikova and Macevic 1978). A two-step procedure was evaluated with Ospavir administered intramuscularly as priming dose followed 1 to 7 days later by administration of a booster dose comprising of traditional live smallpox vaccine containing the L-IVP strain. One case of postvaccinal encephalitis occurred in a child with congenital macrocephaly among some 23,000 vaccinated subjects all of whom were over 3 years of age. It is unclear whether protective efficacy can be achieved by the two-step vaccination regimen, but the prime-boost vaccination regimen elicits a strong immune response (Prof George Ignatyev, personal communication). Further published data suggest that primary vaccination of children, adolescents and adults with the inactivated vaccine resulted in low to moderate reactogenicity and that both doses had comparable reactogenicity profiles (Gavrilova et al 2009).

*Regulatory status*

The inactivated vaccine Ospavir (priming dose) and the traditional freeze-dried smallpox vaccine (booster dose) are made from the strain LIVP on the skin of calves. Both are licensed in Russia by Microgen (personal communication Prof George Ignatyev, personal communication).

**Oral smallpox vaccines**

At the end of the eradication phase an oral form of live smallpox vaccine (TEOVac) has been developed in Russia. The vaccine contains vaccinia virus strain B-51 strain produced on the chorioallantois membranes of embryonated hens' eggs (Onishchenko et al. 2006). The B-51 strain was found to be of moderate pathogenicty in rabbits (Marennikova 1975) and the oral vaccine was used in a smallpox outbreak setting in Ethiopia in 1972-1973 (reviewed in Voroyev et al 2003). Of the 329 subjects vaccinated and with known contact to smallpox patients 70.2% (231 subjects) were primary vaccinees. Smallpox disease occurred in 1.7% of subjects vaccinated orally. Two children with confirmed vaccination status and 2 adults with unclear vaccination status developed smallpox disease within 1 to 9 days of vaccination. In a control group of 623 subjects with known contact to smallpox vaccine 133 were found to be vaccinia naïve. Smallpox disease was observed in 7.9%-9.1% of subjects having received smallpox vaccine by scarification 5 days after contact with smallpox patients. These historical data suggest that oral vaccination with TEOVac is protective against smallpox disease.

TEOVac was evaluated in a clinical trial in 6,000 adult subjects (Vorobyev et al 2003). The majority of subjects receiving TEOVac ($0.8\text{-}2x10^7$ PFU/tablet) were revaccinees having previously received oral smallpox vaccine (N=5047). Of the subjects enrolled 231 were vaccinia naïve subjects and received TEOVac for primary vaccination. Neutralising antibody titers of ≥1:25 were measured in 63% and 48% of revaccinees having received the vaccine 1 year or 12 years earlier by oral administration. All vaccinia-naïve subjects evaluated developed neutralizing antibodies titers of ≥1:25, respectively. No serious adverse events were reported in the group of revaccinees and no adverse events related to skin, neurological or allergic reactions were observed in revaccinees and primary vaccine recipients. Compared to traditional smallpox vaccine given by standard skin scarification (sc) TEOVac was found to be less reactogenic in revaccinees. Mild adverse events were notified in 5.2% of TEOVac participants and in 34.7% of subjects vaccinated by scarification. Moderate to severe general reactions were found in 0.2% of the orally vaccinated compared with 1.7% in the sc group. Local reactions were reported in 0.5% in the oral group and in 100% of the sc group (Vorobyev et al 2003, Onishchenko et al 2006).

Adverse events reported in the literature include fever, gingival edema, faucial hyperemia, enlargement of subaxillary lymph nodes, (ulceronecrotic) tonsillitis, lymphadenopathy asthenia and systemic postvaccinal reactions of medium severity. The main cause of local inflammatory reactions was found to be opportunistic superinfections (Melynikov et al 2005). Frequency of specific adverse events is unclear.

*Regulatory status*

TEOVac is licensed in Russia (Onishchenko et al 2006).

# Ethical considerations

Recommendations for smallpox vaccination are based on benefit – risk assessments. Usually such assessments do not only consider the specific characteristics of the vaccine but include considerations on the vulnerability of the population as well as the probability of a smallpox attack and on the pathogenicity and virulence of the orthopox virus strain deliberately released.

In principle two scenarios must be assessed separately: the pre-event and the post-event scenario.

Due to the absence of smallpox disease and the known risks of severe adverse events with first and second generation vaccines a significant part of today's population has contraindications not allowing the general use of first and second generation smallpox vaccines in a pre-event scenario. Currently strict

restrictions on the use of smallpox vaccines are applied for vaccination of military personnel, first responders and laboratory workers with risk of exposure to orthopox viruses. With the availability of new and safer smallpox vaccines the decision to recommend these third generation vaccines will depend on the probability of a smallpox attack and the likelihood of their effectiveness to protect from exposure to smallpox or other orthopox viruses.

In the event of deliberate release recommendation of universal smallpox vaccination will depend on several factors, including attack rates, pathogenicity and virulence of the orthopox virus released, the effectiveness of universal immunization compared with ring vaccination, the expected harm of vaccination and the effectiveness of the vaccines used.
Recent publications estimated that use of first and most likely also second generation smallpox vaccines would result in high rate of complications and death, if a vaccine is used in a mass vaccination campaign today (Kretzschmar et al 2006). It was assumed that everybody over 30 years were vaccinated previously and that 20% of the population have contraindications. Under these assumptions a mass vaccination conducted in Germany with a population size of 82 million would lead to 46.2 deaths with the NYCBH strain and mass vaccination with the Lister strain would lead to 268.5 deaths. These death rates likely underestimate the actual numbers to be expected and make them most likely unacceptable for universal vaccination campaigns especially, if the virus strain deliberately released has low pathogenicity and/or low virulence. In contrast, due to missing information on the effectiveness of third generation vaccines their use in a post-exposure setting might not prevent smallpox disease or further virus spreading from person-to-person and therefore would make them most likely unacceptable for ring vaccinations except for high risk groups (e.g. AD and HIV patients).

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## Key ISCL Challenges Impacting Immunization Programs

The Immunization Supply Chain and Logistics (ISCL) systems designed in the 1980's have supported the achievement of acceptable coverage rates using coping mechanisms to overcome enduring challenges in vaccine storage, distribution, and management. The dedication, intelligence, and creativity of health workers acting within an ISCL designed for low-resource settings has substituted for an abundance of assets and capital. Despite their efforts, national vaccination programs struggle to meet the demands of routine immunization and supplemental campaigns and are not in position to respond to the influx of new vaccines.

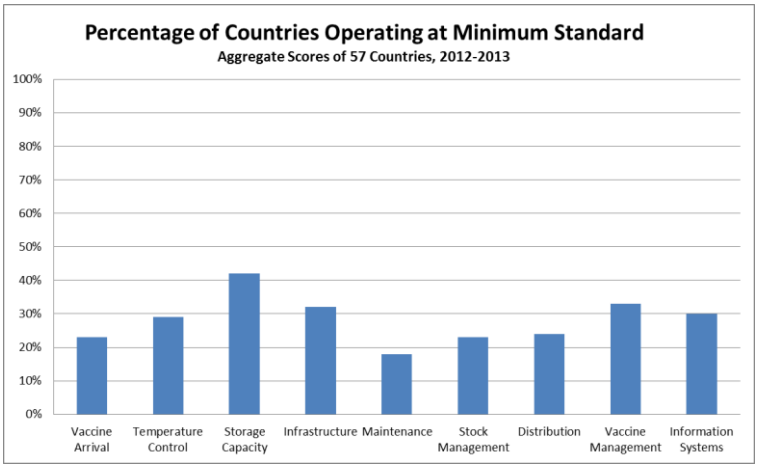
The introduction of new vaccines and higher coverage targets has increased demands on ISCL systems. Comparing the requirements of ISCL systems in the 1980's to the present, it is clear that the landscape has grown inherently more complicated, as national vaccination programs prepare to:

- Provide protection against 2.5 times as many diseases[1]
- Increased age ranges from infants to adults[2]
- Administer 3 times as many doses per child[3]
- Store and transport 4 times more vaccine volume per fully immunized child[4]
- Increase 6-fold the spending on vaccines to fully immunize one child[5]
- Serve a global target population size that has doubled[6]

ISCL systems originally designed to manage fewer and less expensive health biologicals are not keeping pace with the changing landscape of national vaccination programs, resulting in stock-outs, potential administration of ineffective vaccines, avoidable wastage, and inadequate cold chain capacity, all of which have considerable access and cost implications.

A recent study[7] of 57 GAVI-eligible countries shows that a vast majority of ISCL's are underperforming. Analyzing average scores, as depicted in Figure 1, reveals that less than 25% of countries are operating at even a minimum standard within the criteria of Maintenance, Stock Management, and Distribution. Further, the best scores show that only 30% of countries are meeting minimum standards for Temperature Control.

**Figure 1 - Percentage of GAVI-eligible countries with ISCL operating at minimum standards, based on Effective Vaccine Management assessments, 2012-2013[8]**




Clearly, current processes and coping mechanisms are not adequately keeping pace with the changing vaccine landscape. To be able to continue to serve their populations, it is essential that national vaccination programs analyze their supply chains as a means to improve availability of potent vaccines and related supplies and reduce avoidable wastage without compromising the goals of increasing coverage.

[1] Varies by national immunization schedule; represents maximum. In 1980, standard vaccines included diphtheria, pertussis, tetanus, measles, polio and tuberculosis. In 2010, the additional vaccines include pneumococcal conjugate , rotavirus, hepatitus B, hib, yellow fever, rubella, japanese encephalitis, and meningitis A.

[2] Generally, vaccinations for the first 30 years focused on infants and women of reproductive age. The current mix of vaccines is provided for infants, children (measles), pre-teens (HPV), and adults (Meningitis A and tetanus/diphtheria).

[3] Represents maximum, assuming the maximum number of doses as above. In 1980, this included 1 BCG, 3 DTP, 3 OPV, 1 measles. In 2010, the total number is based on 2012 WHO immunization position papers.

[4] Based on projected volume per fully immunized child for 20 countries according to introduction plans. This compares 2001 volumes for traditional vaccines with 2020 expected volumes, where growth is driven by penta, pneumococcal conjugate, rubella, and HPV. Additional surge capacity is required for mass campaigns.

[5] Based on 2008 projections. WHO Bulletin, 62 (5):729 -736 (1984); Optimize Vaccine Supply Chains, Optimize (2009); State of the world's vaccines and immunization, WHO (2009); Vaccine volume calculator, S. Kone, WHO (2011); Immunization position papers, WHO (2012). Historical analysis of cMYPs in GAVI-eligible countries, L. Brenzel and C. Politi (2012)

[6] United Nations Population Division, World Population Prospects: The 2010 Revision, medium variant (2011)

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# Vaccination: rattling the supply chain

The introduction of new vaccines, combined with a push to expand immunization globally to reach every child, is straining vaccine supply chains to the limit. New thinking on the way vaccines are delivered is needed. Gary Humphreys reports.

WHO/Umit Kartoglu

Health worker in Niger shows bottles with vaccine vial monitors.

The first decade of this century was perhaps the most productive in the history of vaccine development, seeing the release of a plethora of new life-saving vaccines for rotavirus diarrhoea, types of meningitis and pneumonia, and for human papillomavirus (HPV) infections that cause cervical cancer. "We are in a very different situation now compared to 10 years ago," says Dr Osman Mansoor at the United Nations Children's Fund (UNICEF) in New York. Mansoor, who is UNICEF's senior health adviser for the Expanded Programme on Immunization and New Vaccines, notes that more vaccines are in the pipeline. In fact more than 80 vaccines are in the late stages of clinical testing, and 30 of them are designed to protect against major diseases including dengue and malaria.

At the same time, the global vaccine market is booming: since 2000, global revenue from the sale of vaccines has almost tripled reaching more than US$ 17 billion by mid-2008. While most of this expansion is accounted for by sales of new and more costly vaccines in industrialized countries, more vaccines are also reaching developing countries due to the efforts of the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization), a public–private partnership established in 2000 to increase immunization in poor countries.

WHO/Umit Kartoglu

It is important to have adequate supplies of vaccine for each vaccine session, especially when women and children, such as these in Niger, must travel long distances on foot.

The World Health Organization (WHO) and UNICEF estimate that just over 80% of the world's children now have access to immunization, as measured by coverage of the third dose of DTP (diphtheria, tetanus and pertussis) vaccine, while an increasing number also have access to powerful new vaccines. "In the past, countries relied on a package of vaccines against six diseases," says Project Optimize Coordinator Modibo Dicko, referring to WHO's Expanded Programme on Immunization, which was launched in 1974. "Now some countries are doubling the number of vaccines they offer."

As encouraging as all this seems, the scaling up of immunization programmes and the introduction of new vaccines is putting an unprecedented strain on delivery systems that have not changed in decades. James Cheyne, a supply-chain consultant, who started his career in vaccine logistics in Burma (now Myanmar) in 1977, is in a good position to judge those systems since he has had a hand in designing several himself.

Cheyne cites the unnecessary layering of distribution networks as one of his main concerns. "Typically there is a central store that supplies the regional stores, which then feed the provincial stores and district stores that in turn supply the local health centres," he says, pointing out that while this layering made sense 30 years ago, because the lines of communication were weak, these days low-cost telecommunications technology has changed things. "You don't need a store for each administrative level anymore because we have cell phones and the person from the health centre can call the central store directly," Cheyne says.

Making better use of that kind of technology is a core aspect of the work being done by Project Optimize, a collaboration between WHO and PATH (formerly the Program for Appropriate Technology in Health), a nongovernmental organization.

For Michel Zaffran, the director of Project Optimize, information technology is key in combating one of the biggest problems faced by vaccine distribution systems – overstock in supply. On the face of it the idea that immunization programmes are hampered by too much vaccine seems paradoxical. But, in fact, the overstocking of vaccines increases cold storage costs and generates waste (when vaccines are lost, damaged or not used before their expiry date, and when not all vials in a multi-dose vial get used).

"We want to have as little buffer stock as possible, but still we want to

have enough vaccine to vaccinate the children," Zaffran says, arguing that this means putting in place information systems and technologies that give managers a real-time picture of how much stock they have throughout a country and whether the quantities meet the requirements of their immunization strategy.

According to UNICEF's Mansoor, an even more pressing problem is when there are shortages of vaccine supplies to meet demand for children who turn up for vaccination sessions.

These problems can be further exacerbated when the volume of vaccine flowing through the system increases, as has been the case since 2000, and vaccines have become bulkier, partly due to manufacturers' packaging policies. As Zaffran explains, increased price is one of the main drivers of this trend: "In the early days when the vaccine cost around US$ 0.10, WHO encouraged health workers to open a vial for one child even if it meant wasting nine doses. There were wastage rates of 60% or 70%. Now that we are introducing vaccines, which cost several dollars a dose, things have changed."

> "Countries are postponing the introduction of these vaccines because they do not have the capacity."
>
> *Michel Zaffran*

According to Dicko, the cost of newer vaccines is between US$ 3.50 and US$ 7.50 per dose (when procured through UNICEF) and sometimes more. Newer vaccines are often in single or two-dose packages. While this helps to reduce wastage, it also means that they require more cold chain space per dose compared with the traditional EPI (Expanded Programme on Immunization) vaccines that come in 10- and 20-dose vials.

Another significant driver of increased bulk is more sophisticated packaging. Until 2009, the only pneumococcal conjugate vaccine (against a range of child infections including pneumonia and meningitis) was only available in a pre-filled syringe that required nearly 20 times as much storage space as in a 10-dose vial. "New vaccines require upwards of five times the amount of physical space in cold storage," says Dicko, who cites the problems faced by Turkey as an example of the sort of challenges that result. "In 2005 Turkey needed only 2600 $m^2$ of cold storage in order to accommodate its stocks of vaccine. When they introduced the first generation of pneumococcal vaccine in 2008, Turkey's storage space requirement jumped (four times) to 11 400 $m^2$. They had to rent cold storage space." Turkey found a solution, but not every country does. For Zaffran it is not too strong to describe the situation faced by many countries as a "crisis". "Countries are postponing the introduction of these vaccines because they do not have the capacity," he says. "Some countries are actually delaying the time when the vaccines arrive, even when they have been paid for by others because they do not have the capacity either at the central level or in the country."

The kind of problem faced by Turkey is also causing people to rethink the use of the cold chain, the temperature controlled supply chain, which has traditionally been used for virtually all vaccine delivery. "Most vaccines are stored at a temperature of between 2 and 8 degrees Celsius," explains Cheyne, referring to guidance that is described on the vaccine packaging.

"One vaccine has the potential of being kept for six months at 45 degrees, but the requirement is still to keep it at temperatures between 2 and 8. It makes absolutely no sense at all," he says. Moving some vaccines from the cold chain to a temperature-controlled chain at, say, 25 degrees, would make room for other vaccines or enable countries to cut back on storage costs Cheyne argues. UNICEF's Mansoor sees another advantage. "For me, the issue is not so much getting vaccines out of the cold chain but getting them beyond the cold chain to reach into areas where there is no refrigeration so that more children can benefit," he says.

For Mansoor the move makes even more sense given the availability of vaccine vial monitors (VVM), which are now on the label of virtually all vaccines shipped by UNICEF. The labels carry the image of a circle containing a white square. "The white square gets darker with cumulative heat exposure. If the vaccine has been subjected to heat that risks making it subpotent, the VVM shows this when the colour of the inner square is the same or darker than the outer circle," Mansoor explains. Currently there is no equivalent detection method for freezing, which is much more damaging to some of the newer vaccines than heat in current cold chain arrangements. Like Cheyne, Dicko thinks there are many candidates for removal from the cold chain, citing as examples the vaccines against hepatitis B, Japanese encephalitis, cholera, diphtheria, tetanus and HPV infections. However, he says, this list cannot be drawn up without the consent of the manufacturers and the regulatory authorities. "It cannot be done outside that process," he says, "but we are building evidence that it can and should be done".

WHO/Umit Kartoglu

Vaccine supplies packed in cold boxes and strapped to a motorbike for delivery in a rural area in Niger.

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Review

# The imperative for stronger vaccine supply and logistics systems

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ABSTRACT

With the introduction of new vaccines, developing countries are facing serious challenges in their vaccine supply and logistics systems. Storage capacity bottlenecks occur at national, regional, and district levels and system inefficiencies threaten vaccine access, availability, and quality. As countries adopt newer and more expensive vaccines and attempt to reach people at different ages and in new settings, their logistics systems must be strengthened and optimized.

As a first step, national governments, donors, and international agencies have crafted a global vision for 2020 vaccine supply and logistics systems with detailed plans of action to achieve five priority objectives.

Vaccine products and packaging are designed to meet the needs of developing countries.

Immunization supply systems support efficient and effective vaccine delivery.

The environmental impact of energy, materials, and processes used in immunization systems is minimized.

Immunization information systems enable better and more timely decision-making.

Competent and motivated personnel are empowered to handle immunization supply chain issues.

Over the next decade, vaccine supply and logistics systems in nearly all developing countries will require significant investments of time and resources from global and national partners, donors, and governments. These investments are critical if we are to reach more people with current and newer vaccines.



**Contents**



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## 1. Current issues facing vaccine supply chain and logistics systems

Since 2000, national-level Expanded Programmes on Immunization (EPIs) have seen their vaccine portfolios grow from 6 basic antigens to the 12 now recommended by the World Health Organization (WHO) for all countries [1]. Additional vaccines are recommended for specific population groups and regions, and more are in the product development pipeline [1,2]. These vaccines have great potential to reduce morbidity and mortality associated with pneumonia, diarrhea, cancers, and other diseases. However, access to all vaccines hinges on the ability of supply and logistics systems to receive, store, and transport vaccines at proper temperatures and get them to the right places in a timely manner [3].

With few exceptions, vaccine supply and logistics systems around the world are unable to keep pace with growing immunization programs [4–10].

### *1.1. Impact of vaccine schedules and presentations on cold chain volume requirements*

The most visible impact of new vaccines is an increase in the volume of products that need to be stored, tracked, and transported. Fig. 1 shows per-dose volume requirements for various immunization schedules. For countries introducing both rotavirus and 10-valent pneumococcal conjugate vaccines (moving from schedule C* to schedule E in Fig. 1 below), the total volume increases by as much as 143% per dose, assuming wastage rates remain constant [11]. This figure does not reflect the fact that closed vial wastage rates are substantially higher for vaccines in multi-dose vials than in single dose presentations. This means that more doses must be ordered, stored, and managed than implied by the figure [12,13].

In a recent analysis of 20 countries planning to introduce pneumococcal and/or rotavirus vaccine in 2011 and 2013, researchers from WHO and PATH compared vaccine volume requirements with available capacity [14]. Fig. 2 shows how planned vaccine introduction impacts capacity utilization at the national store between 2011 and 2015, assuming no new equipment is purchased beyond already planned expansions and no changes are made to current delivery strategies.

Figs. 3 and 4 show how the introduction of new vaccines impacts capacity at regional and district levels. Because only a portion of regional and district-level facilities were assessed, these graphs show the proportion of assessed facilities for which the required capacity exceeds available capacity by at least 25%. When compared to Fig. 2, one can see how capacity constraints at one level can sometimes be overcome by moving products to another level. Nonetheless, Figs. 3 and 4 show that regional and district stores in some countries are and will continue to face severe capacity constraints requiring new equipment or new delivery strategies.

### *1.2. Choices for cold chain equipment*

Choosing the right cold chain equipment is strategically important, as such choices can facilitate changes in delivery routes and frequencies, which in turn could have an impact on vaccination schedules and strategies. For example, the availability of cold boxes with long hold-over times for stationary storage may enable countries to provide the birth dose of hepatitis B vaccine in remote areas with no access to electricity [15]. New direct-drive solar refrigerators without batteries are a reliable choice for areas with only intermittent access to electricity, but they require adequate sunlight. Domestic refrigerators may be an attractive and low-cost choice but do not often meet minimum WHO Performance, Quality, and Safety (PQS) specifications and can damage vaccines through unreliable temperature control [16–19]. To navigate equipment choices, countries need more information and tools that allow them to assess trade-offs and select equipment that best fits their needs and programmatic goals. Budgets need to be made available. Equipment manufacturers, in turn, need adequate demand to spur new

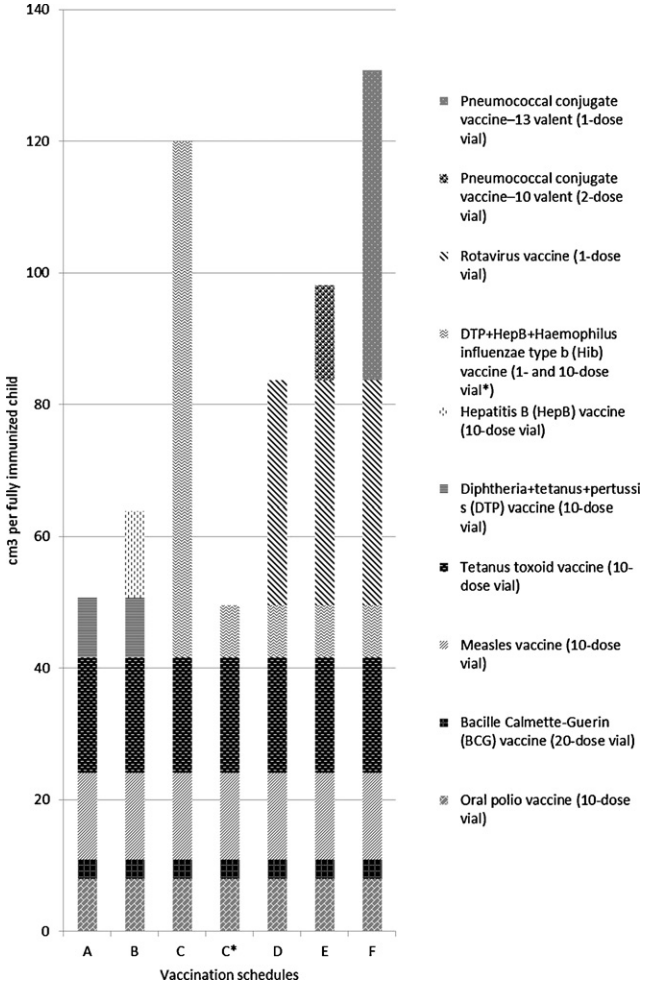


**Fig. 1.** Vaccine volume requirements for various immunization schedules. *Notes*: Volumes shown in the graph are for full immunization (e.g., all recommended doses). Schedule A: traditional EPI vaccines: 4 doses oral polio, 1 dose BCG, 2 doses measles, 3 doses DTP, and 4 doses TT vaccine. Schedule B: traditional EPI vaccines, plus 3 doses HepB vaccine. Schedule C and C*: traditional EPI vaccines, replacing DTP with 3 doses pentavalent (DTP + HepB + Hib) vaccine. Schedule D: Schedule C* plus 2 doses rotavirus vaccine. Schedule E: Schedule D plus 3 doses pneumococcal conjugate vaccine–10 valent. Schedule F: Schedule D plus 3 doses pneumococcal conjugate vaccine–13 valent.

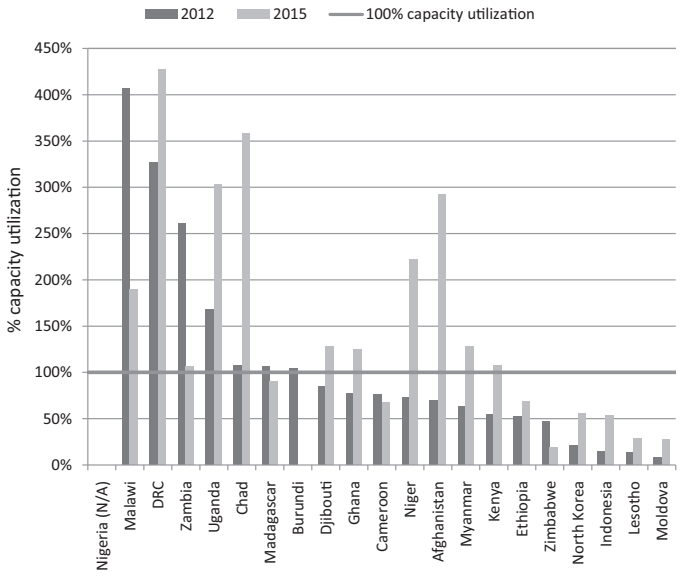


**Fig. 2.** Percent of national store occupied by vaccine in 20 GAVI-eligible countries (actual and planned). *Notes*: For most countries, the data source is either an effective vaccine management (EVM) assessment or a cold chain equipment manager (CCEM) comprehensive inventory. Data show the percentage of the national store occupied by current and planned vaccines based on New and Underused Vaccine Initiative group internal tracking tools. Reductions in capacity utilization from 2011 to 2015 are explained by planned equipment upgrades or by a switch from mono-dose to multi-dose presentations of pentavalent vaccine. The order of countries in the *x*-axis reflects highest to lowest capacity utilization in 2011. In some countries, reliable data was not available (N/A).

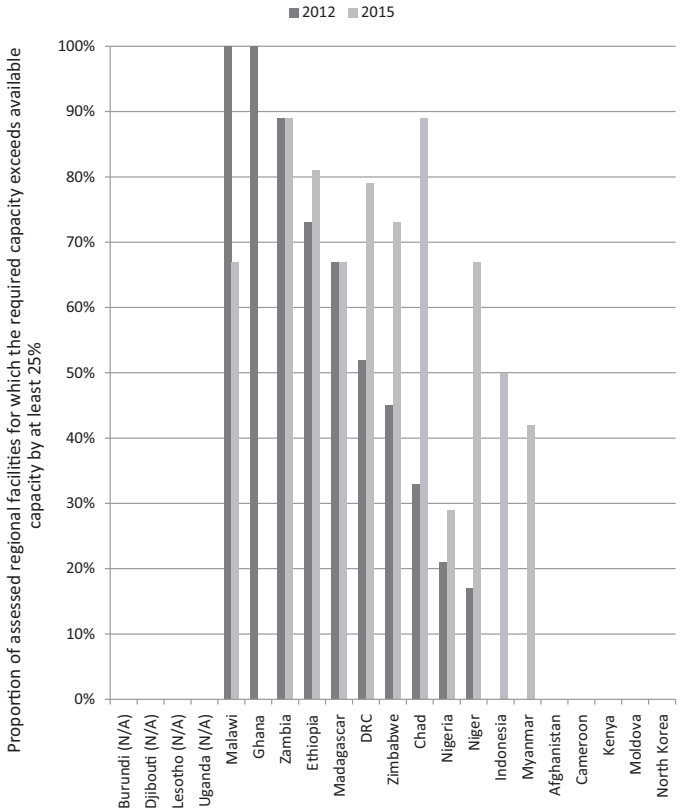


**Fig. 3.** Proportion of assessed regional facilities for which the required capacity exceeds available capacity by at least 25%.

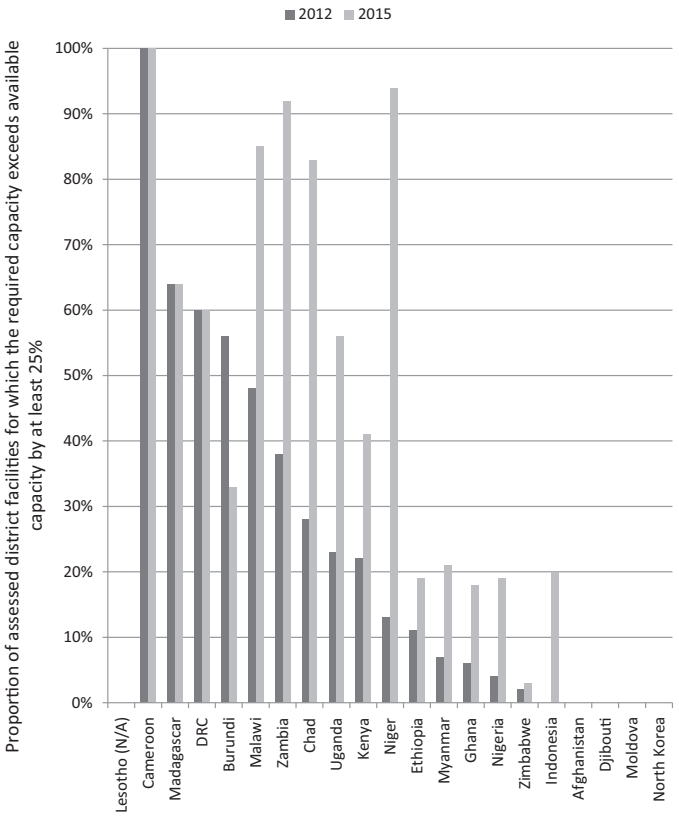


**Fig. 4.** Proportion of assessed district facilities for which the required capacity exceeds available capacity by at least 25%. Figs. 3 and 4 notes: For most countries, the data source is either an EVM assessment or a CCEM comprehensive inventory. The order of countries in the *x*-axis reflects highest to lowest capacity utilization in 2011. In some countries, reliable data was not available (N/A). In other countries (those on the right side of the graph), required capacity exceeded available capacity by at least 25% in none of the facilities sampled.

innovations, and national governments need options for bulk procurement or other methods of stimulating price reductions.

### 1.3. Cold chain maintenance and temperature control

New equipment requires installation and maintenance, which necessitates the availability of properly trained technicians, replacement parts, a system to monitor equipment performance, and the capability to rapidly respond to breakdowns and failures. Although existing supply chains should already have maintenance plans in place, recent cold chain assessments reveal consistent deficiencies in this area [12]. With the introduction of new vaccines, however, common equipment failures—a broken refrigerator, a leaky ice pack, lack of fuel—can easily damage thousands of dollars of vaccines, which makes proper installation and maintenance critically important [13]. It is also increasingly important that health staff have updated tools and knowledge to monitor equipment performance and maintain safe temperatures in cold rooms, cold boxes, and refrigerators [20,21].

### 1.4. Immunization-related information systems

Supply chain assessments over the last five years suggest that managerial oversight has been largely neglected and underestimated [12]. Larger and more valuable inventories put increased pressure on managers to make accurate forecasts for product needs, allocate stock more efficiently, make the right investment decisions, and optimize distribution channels. To handle these responsibilities, managers need accurate and timely information

that allows them to verify product and equipment needs, validate coverage rates, monitor temperature in the cold chain, and identify weak links in the supply chain. This may require implementation of more advanced information systems, installation of computers, tailored software systems, monitoring equipment, accountability indicators, and mobile phone or Internet access.

### 1.5. Human resources for the vaccine supply chain

As new vaccines enter the system with different handling requirements and different schedules, targeting different populations at different times of their life, staff members may need to be reallocated. Health workers also require training to handle new vaccine products, use and monitor new cooling equipment, or operate software systems. Maintenance teams require training, funding, and transportation to install, maintain, and repair refrigerators, or the function may need to be outsourced. Managers must learn how to use information to forecast needs, allocate stock, manage staff and resources, modify delivery routes and frequencies, act rapidly where equipment becomes dysfunctional, and recommend policy changes.

### 1.6. Vaccine cost and wastage

Many newer vaccines are very complicated to make and are considerably more costly than traditional vaccines. For example, diphtheria–tetanus–pertussis vaccine in a 20-dose vial was only US$0.14 per dose through UNICEF in 2012 [22]. In comparison, pneumococcal conjugate vaccines were 50 times more costly at US$7.00 per dose in a one- or two-dose vial through UNICEF in 2012 [23].

The expense associated with newer vaccines makes supply chain issues extremely important. WHO estimates that in some countries, 50% of all vaccine doses are wasted either before or after a vial is opened [20]. Most closed-vial vaccine wastage can be attributed to supply chain issues including accidental freezing, expiry, vaccine vial monitor indication, breakage, theft, and loss [20,24]. Unless these supply chain issues are solved, closed-vial vaccine wastage will continue to consume much-needed vaccine and unnecessarily inflate the cost of vaccination programs.

### 1.7. Coping mechanisms

As immunization programs grow, supply systems have coped with increased volume and complexity in several ways. However, short-term coping strategies can cause more problems than they solve. Overstocking cold rooms is unavoidable when vaccine stock exceeds storage capacity, but the practice can compromise first-in, first-out stock management practices, impair air circulation and temperature maintenance, and/or result in expired vaccines [14]. Increasing the frequency of deliveries to lower-level facilities can mitigate central storage capacity issues. However, stocking more vaccines at lower levels can also lead to simultaneous stockouts and overstock situations in different parts of the country because vaccines are stored where there is space, rather than where vaccines are needed [8,9]. Reducing buffer stock levels is somewhat desirable, but in the absence of reliable stock management strategies, this can lead to stockouts as well.

As we stand at the beginning of what is now called “the Decade of Vaccines,” countries have wrung every drop of value from short-term solutions. Purchasing new refrigerators and increasing delivery frequencies will alleviate immediate pressures, but these strategies will not solve perennial problems that have been highlighted for years in vaccine supply chain assessments and other studies [4,6,12,13,16,24]. Coping strategies will not make supply systems more efficient, nor will they accelerate access. In the absence of systematic improvements in vaccine supply and logistics systems, new vaccines cannot easily reach target populations and may even compromise the availability of traditional vaccines [4,8,9].

## 2. A global plan of action for vaccine supply and logistics systems

Over the past 15 years, the field of supply chain and logistics management has steadily evolved in the private sector. Capitalizing on advances in information technology, all manner of consumer products, including perishable and temperature-sensitive products, now routinely travel to even the most remote villages on predictable and reliable schedules [25]. Today, an Internet connection is sometimes all that is required to track shipments, check inventories, estimate the date and time of delivery, and request changes or new products.

Applying lessons from the commercial sector and from recent demonstrations in low- and middle-income countries, it has finally become feasible to build state-of-the-art supply and logistics systems that can handle a growing and more costly portfolio of vaccine products.

In 2011, national governments, donors, and international agencies developed a global vision for vaccine supply and logistics systems:

By 2020, state-of-the-art supply systems meet the changing needs of a changing world; they enable the right vaccines to be in the right place, at the right time, in the right quantities, in the right condition, at the right cost [26].

The vision stands on five key pillars that are considered indispensable for optimal immunization supply systems. To determine how to strengthen these pillars, cross-organizational working groups were formed in 2011 to analyze the landscape of ongoing activities and technologies and develop “vision action plans” that propose activities to help achieve the vision. Each pillar is described below with examples of progress made and the way forward. Complete landscape analysis summaries and action plans can be downloaded online [26,27].

### *Vaccine products and packaging are designed to meet the needs of developing countries*

*Concept:* Not only do vaccines need to meet internationally recognized standards of quality and safety, but manufacturers and immunization programs must agree on attributes and product specifications that facilitate use in developing-country environments, including their supply chains.

*Major progress:* Over the last five years, several mechanisms have been created and supported to improve public/private-sector collaboration and help ensure that vaccine products meet low- and middle-income country needs. The Vaccine Presentation and Packaging Advisory Group (VPPAG) was launched to bring vaccine manufacturers, public health policy experts, and developing-country representatives together to reach consensus on vaccine product attributes that are both feasible for industry and address immunization program opportunities and constraints. Within the VPPAG, discussions are currently under way to minimize and potentially standardize packaging sizes to make for a more efficient fit inside cold boxes during storage and transport. Manufacturers are also discussing the utility of placing barcodes on vaccine vials, which would allow for better stock management and lot tracking.

In addition, WHO has established a set of prequalification requirements for vaccines to address developing-country program needs in its Programmatic Suitability for Prequalification (PSPQ)

requirements. Many of the PSPQ requirements were derived from VPPAG recommendations. The VPPAG and the PSPQ process help ensure that careful consideration is given to vaccine product features and packaging so that the resulting products will be better suited for their intended contexts of use.

*Way forward:* As new vaccine products become available, national authorities need better data and tools to support decision-making around vaccine product selection. One such tool is being developed under WHO's Vaccine Price, Product, and Procurement (V3P) project [28]. Both national and global vaccine procurement bodies need to change the mindset from *cost per dose procured* to *cost per dose delivered*, as the latter better reflects the true costs of introducing a new vaccine. For example, it may make sense to purchase a more expensive presentation of a vaccine if doing so reduces vaccine wastage and/or reduces risk of human error and/or improves timely delivery of vaccines and increases coverage among vulnerable and currently unreached populations. Such analyses will require that countries have adequate data on the performance and costs of their immunization programs and supply chains. In addition, better dissemination of information on the features of available vaccine products will be needed to inform product selection [28,29].

## 3. Immunization supply systems support efficient and effective vaccine delivery

*Concept:* In most health systems, there are multiple supply and logistics systems that perform essentially the same functions (e.g., sourcing, procurement, storage, and distribution) and travel the same routes to reach the same populations. Delivery routes often follow administrative levels rather than the shortest distance, and expensive or cumbersome tasks that could be accomplished more efficiently by private-sector operators (e.g., vehicle or equipment maintenance, transport, vaccine storage and requisition) generally remain the purview of government staff [4,5].

Redesigning such systems to be as streamlined as possible may require outsourcing certain functions to private or parastatal agencies or require integrating certain functions with other supply chain systems [30,31]. Even in countries where integration and outsourcing are not options, opportunities exist to adopt best management practices and continuous quality improvement systems [32].

Truly effective, agile supply systems also make use of supply chain equipment—vehicles, refrigerators, cold rooms, and cold boxes—that can handle increasing volumes of vaccine within stringent temperature limits and apply heuristics to maintain and replace them when necessary.

*Major progress:* New evidence is being generated and collected to describe how various system design changes have worked in different settings. South Africa and Thailand have outsourced various supply chain functions to parastatal agencies/private companies, and their experience has been documented in detail [33,34]. Other efforts to streamline delivery routes and integrate vaccine supply chain systems with pharmaceutical and other delivery systems are being demonstrated in Senegal and Tunisia in collaboration with project Optimize [35]. Evidence describing the cost and impact of these efforts on immunization supply, wastage, and political processes will be available early in 2013.

The growth in commercial cold chain capacity in some countries—even in remote rural areas—is creating higher availability of repair staff, mechanics, spare-part sites, etc., which can be leveraged to ensure better maintenance of equipment without investments in dedicated staff and infrastructure [36].

The development of direct-drive (i.e., battery-free) solar refrigerators has spurred the creation of two new PQS categories and generated momentum among manufacturers to improve products for health centers with solar potential [18,37].

*Way forward:* Preliminary results from project Optimize collaborations with the Ministries of Health of Senegal and Tunisia show that system redesign can be highly political, as it often involves increases and decreases in responsibility, budget, and authority of various departments, agencies, and personnel. This highlights the importance of continuing to monitor and learn from countries that have redesigned their supply and logistics systems, perhaps developing public-private partnership models that other countries can apply and build upon. It also underscores the need for leadership from high-level political offices to be involved in discussions on improving the efficiency and effectiveness of vaccine supply chains.

## 4. The environmental impact of energy, materials, and processes used in immunization systems is minimized

*Concept:* Environmental impact can be minimized both in terms of energy and resource efficiency and waste reduction and management. The rising cost of fuel and electricity combined with their environmental impact makes energy efficiency an important focus for supply chains [38]. Impacts can be reduced by making better use of solar power and other forms of alternative energy, replacing inefficient gas and kerosene refrigerators with energy-efficient cooling equipment, allowing certain thermostable vaccines to travel in controlled temperature chains without the need for ice packs, and reducing transport distances or choosing more energy- and environment-friendly transport options such as sea freight or electric vehicles [39–44].

The environmental impact of waste from vaccination programs can also be reduced by implementing safe and environmentally sound sharps-disposal procedures, minimizing the size of packaging materials, and reusing and recycling non-sharps waste and packaging materials [45–47].

*Major progress:* By leveraging small amounts of funding and providing incentives for innovation in equipment manufacturing, WHO and PATH have enticed several new and existing cooling equipment manufacturers to improve or create new products that take advantage of solar and passive solar cooling technologies [48]. Simultaneously, WHO has created several new PQS standards for categories of products that had not previously existed, namely the direct-drive solar refrigerator, extra-large cold box, and stationary passive cooling container [18]. Grand Challenges Explorations grants from the Bill & Melinda Gates Foundation are promoting efforts to reduce the environmental impacts of vaccine and packaging waste.

*Way forward:* Manufacturers of cooling equipment need ongoing incentives to invest the necessary time and energy into research and development for new technologies that minimize environmental impact and operate in areas with minimal energy infrastructure [43]. They also need a mechanism for increased dialog and feedback between countries and procurement agencies to better understand user needs, financial realities, and the political landscape. Without such dialog, it is likely that manufacturers will return their focus to more profitable and predictable markets.

In waste management, partners need to include financial and technical support and other incentives that reward and encourage innovative waste-management strategies, particularly for mass vaccination campaigns with target populations in the millions. For example, it might be possible to add a "disposal tax" to syringes that can be used to build incinerators or develop a recycling program for plastic waste.

## 5. Immunization information systems enable better and more timely decision-making

*Concept:* Information technology has long been a core feature of modern supply chains [49]. When deployed successfully,

computerized information systems can facilitate information sharing, speed order processing, and improve decision-making, thus enabling smooth and efficient supply chains [50]. Some developing countries have begun to create their own computerized logistics management information systems to manage vaccine supplies and in some cases link to immunization registries, but these efforts are disparate and lessons learned in software development are not being shared or built upon to improve immunization information systems [51]. As more countries move toward computerized information systems, they can prioritize information systems with ideal characteristics.

Ideal information systems are:

- Integrated and interoperable with other health information systems.
- Built on reliable data collected at the place where the events occur and aggregated or disaggregated as needed.
- Flexible, adaptable, and compatible with different contexts, programs, and changes over time as needs evolve.
- Driven by the needs of end-users, managers, planners, recipients of health services, and other stakeholders.
- Affordable and sustainable so decision-makers can evaluate the wider cost implications of adopting an information system across the health system.
- Reliable and secure from unauthorized use.
- Built upon a consistent design framework with standards, common data, common software applications, and technologies that are properly supported by clear design and user documentation.
- Designed and used for evidence-based decision-making.

*Major progress:* Countries have high interest in software-driven solutions, and a few logistics management information systems based on Microsoft Excel or Access have been successfully scaled and sustained [52]. These tools represent improvements over paper-based systems, even if they do not meet all the requirements of a successful information system. OpenLMIS, a project recently launched by VillageReach, is trying to build on early successes by documenting best practices for selecting and designing logistics software systems and by sharing open-source systems or components along with information and instructions on how to modify and continue to share improvements [53]. The Rockefeller Foundation, PATH, and Public Health Informatics Institute released a Collaborative Requirements Development Methodology (CRDM) for logistics management in 2010 [54]. CRDM is a systematic method of identifying user requirements and system specifications. Its use greatly improves the likelihood that a new system will be effective, sustained, and compatible with the health system it supports.

*Way forward:* Global partners need to develop a unifying vision or agreed-upon standards for integrated logistics information systems and promote flexible, affordable software components—whether open source, commercial off the shelf, or custom built—that can meet the needs of multiple countries. This will enable countries to build upon (rather than reinvent) functional systems and to share tools, components, and knowledge more readily.

Creating or choosing information systems that meet the ideal characteristics (above) should also be a top priority for global and national immunization program decision-makers who are keen to use electronic data for decision-making.

## 6. Competent and motivated personnel are empowered to handle immunization supply chain issues

*Concept:* Human resources across national health programs can be inconsistent and loosely defined. Because people working along immunization supply chains wear many hats, there is a need to strengthen human resources in general with standard procedures for recruiting, training, retaining, and motivating workers. Key personnel working on logistics or supply chain functions should be aware of and held to competency frameworks that describe the key skills and knowledge they are expected to maintain [55]. Levels of supervision must exist to ensure that health personnel have the resources, training, and tools needed to meet minimum standards of performance. And, adequate staff need to be hired, trained, and supported to perform the functions required [56].

*Major progress:* Global and national partners through the People that Deliver Initiative are building consensus around a competency framework for supply chain managers that defines the specific skills a supply chain manager should have [57]. In addition, several training initiatives as well as professional-level degrees are now offered in the field of supply chain management [26].

*Way forward:* Developing-country governments that do not outsource the entire supply chain function to an external agency need to start attracting, hiring, and recognizing professionally trained supply chain managers for their vaccination programs and shift their view of supply chain management from a marginal function to a core driver of immunization performance. Such professionals must be able to contemplate a career path in the public sector in order for them not to be lost to the private sector [56]. Also, programs that offer professional training in supply chain management should be made available in additional regions and supported with seed funding from donors interested in immunization program performance.

### *Launching supply chain revitalization efforts*

As global partners work to address upstream challenges related to vaccine attributes, cooling equipment, and software system standards, national partners are working out ways to gain efficiencies in the design of their supply chains, make wise procurement decisions for both vaccine products and cooling equipment, and make use of existing information to drive decisions. Gaining political support for supply chain investments is a key step in making progressive and real changes in the vaccine supply system rather than pursuing a "business as usual" approach.

Countries that use the EVM assessment—and the ensuing management improvement effort—to launch higher-level discussions within their Inter-Agency Coordinating Committee or National Immunization Technical Advisory Group and in relevant government departments will likely progress faster. These more strategic discussions raise awareness of anticipated supply chain bottlenecks and propose meaningful *system-wide* solutions that may come with varying levels of cost and complexity. Embarking on this process will require countries to carefully reconsider their current system design—which often involves taking political or financial risk—in order to get more from their supply chain systems [58]. Global donors and agencies must help subsidize these efforts and provide support to countries to move beyond incremental solutions to supply chain problems. Technical agencies must set standards, share knowledge, provide on-the-ground support, and coordinate efforts so that countries are able to learn from and build upon each other's experiences and successes. Finally, the private sector has an increasingly large role to play as it continues to innovate and fine-tune vaccines and cold chain equipment to better meet the needs of low- and middle-income countries.

## 7. Conclusion

For the last 30 years, the role of vaccine supply chains in protecting and managing the movement of vaccine products and

immunization supplies has been largely taken for granted. The introduction of a number of newer and more expensive vaccines has placed significant pressure on vaccine supply chain systems to perform at a level for which they were not designed. Compared to the investments made in vaccine products themselves, the investments needed in supply and logistics systems are marginal but absolutely critical if we are to see the health gains promised by newer vaccines.

Fortunately, global and national partners have agreed on a vision for future supply chain systems and identified gaps and action plans for five key areas of vaccine supply chains. Investing time and resources in these areas will enable immunization supply chains to meet the needs of 21st century immunization programs [26].

All this work will make it easier for countries to select solutions that not only address short-term needs but meet longer-term demands of immunization programs. The progress made so far will also make it easier for global partners to maintain the ongoing momentum for innovation and policy adaptation.

In this Decade of Vaccines there is a tangible opportunity to build supply systems that are efficient and as effective as the vaccines they handle.

## Conflict of interest

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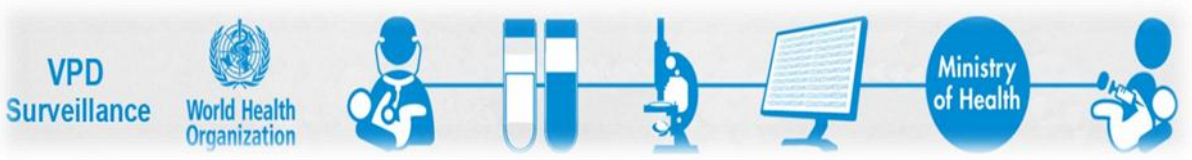


**EXECUTIVE SUMMARY**
**2013 GLOBAL STRATEGIC REVIEW OF THE INVASIVE BACTERIAL VACCINE PREVENTABLE DISEASES AND ROTAVIRUS SURVEILLANCE NETWORKS**

## Genesis of the strategic review

Since 2008, WHO has been coordinating global sentinel hospital surveillance networks for invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus (RV) to provide quality data to assist with planning of public health programs around vaccine introduction and use. The objectives set for the network in 2008 were:

- During the pre-vaccine introduction period:
  - Document presence of disease, describe the disease epidemiology and provide data for estimating disease burden;
  - Establish a system to measure impact after vaccine introduction;
  - Identify circulating serotypes and measure serotype distribution; and
  - Monitor antibiotic sensitivity.
- During the post-vaccine introduction period also:
  - Assess disease trends over time;
  - Monitor vaccination program impact;
  - Monitor changes in circulating strains/serotypes; and
  - Develop a platform for effectiveness and safety evaluation.

The longer term vision has been to establish sentinel surveillance for selected vaccine preventable disease (VPD) in low- and middle-income countries to complement existing active surveillance for polio, measles/rubella and passive surveillance and reporting for other VPDs.

In February 2013, following 5 years of network coordination, WHO launched a full strategic review of both networks with its informal Technical Advisory Group for new vaccines surveillance (iTAG) to identify the networks' strengths and weaknesses and to prioritize future actions. The iTAG assessed the networks capacities to document vaccine impact via the accelerating introductions of pneumococcal conjugate and rotavirus vaccines in the light of the call for quality case-based surveillance in the 2011-2020 Global Vaccine Action Plan. Recognizing the resource constraints in the targeted countries and competing health priorities, it was deemed imperative to determine best strategies to target human and financial resources.

At the review's outset, the iTAG and WHO recognized that while great strides had been made in the development of both IB-VPD and RV global surveillance networks, improvements were still required to ensure strong and effective networks that meet the ultimate goal of providing reliable data. IB-VPD surveillance was particularly recognized to be more complex than RV surveillance due to lack of adequate methods for laboratory confirmation of pneumococcal pneumonia, the rarity of meningitis as compared with diarrhoea, the difficulties of specimen collection and transport, and the complex bacterial laboratory diagnostic testing required.

Prior to this review, in November 2012, WHO had established the following criteria for IB-VPD surveillance, in order to prioritize sites for support:

- Presence of a country surveillance management team, consisting of focal points at Ministry of Health (MoH), sentinel hospital, sentinel hospital laboratory, and for data management;

- Countries conducting only Tier 1 meningitis surveillance enrol at least 100 suspect meningitis cases[1] in children <5 years of age[2];
- Data is reported regularly to WHO according to the schedule agreed with the WHO Regional Office; and
- The hospital sentinel sites participate in the WHO IB-VPD laboratory external quality assessment programme.

**Objectives and methodology of the 2013 strategic review**

The strategic review was conducted under the oversight of the iTAG that has been advising WHO on the conduct of sentinel surveillance since July 2011. The iTAG and WHO agreed on the following objectives for the strategic review:

1. Assess whether and to what extent the original 2008 objectives for the networks were met.
2. Critically assess the Ministry of Health (MoH) perspective, laboratory networks, and WHO activities for capacity building, funding, and data management and the use of data; and
3. Provide conclusions and recommendations for strengthening the networks including defining any needed complementary approaches for IB-VPD surveillance, and critically assess the networks' future utility as a platform for other vaccine preventable disease (VPD) surveillance.

The strategic review consisted of several methods including analysis of surveillance data; questionnaires to obtain MoH perspectives; external review of laboratory function; external review of data management; review of the literature and GAVI applications to evaluate whether WHO surveillance data has been used in decision making; internal review of WHO activities and funding disbursement.

Analysis of surveillance data was conducted on all data available to WHO, including IB-VPD case-based data collected by 4 Regional Offices (ROs) and data aggregated by sentinel site in 2 ROs. For RV, data for analysis was aggregated by sentinel site. Data from over 90 databases were consolidated and cleaned. IB-VPD variables were mapped across Regions, and the first uniform IB-VPD data analysis performed. Due to the volume of data and paucity of time, the iTAG and WHO agreed that sites would be categorized and analysis focused on sites that met defined performance characteristics to determine whether they achieved the original 2008 objectives.

For IB-VPD, sites that reported data during 2010 to 2012 were categorized as:
- New sites: site began reporting in 2011 or 2012
- A Sites: met both of the following criteria
    - Reported data in ≥11 months per year for at least two years during 2010-2012.
    - Enrolled ≥100 suspected meningitis cases per year for at least two years during 2010-2012 (tier 1) or enrolled ≥500 suspected meningitis/pneumonia/sepsis cases per year for at least two years during 2010-2012 (tier 2).
- B Sites: met both of the following criteria
    - Reported data in ≥10 months per year for at least two years during 2010-2012.
    - Enrolled a total of ≥100 suspected meningitis during 2010-2012 (tier 1) or enrolled ≥500 suspected meningitis/pneumonia/sepsis cases during 2010-2012 (tier 2).
- C Sites: Sites that improved in consistency of reporting and case enrolment between 2011 and 2012 but did not meet the criteria of A or B sites.
- D Sites: All other sites.

[1] Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign OR very patient aged under 5 years of age hospitalized with a clinical diagnosis of meningitis.

[2] Countries that do not enroll 100 suspect meningitis cases during 2013 but that significantly increased the number of enrolled cases over 2012 will be considered for funding on a case-by-case basis.

For RV, analysis focused on sites that reported ≥ 10 months of data during 2011 and 2012 as well as enrolled ≥ 100 cases during those years.

The iTAG and WHO collaborated closely during the strategic review via monthly conference calls to agree on the scope of the review and data analysis plan, as well as to assess progress made, and review data that had been collated. Additional ad hoc technical discussions focused on IB-VPD or RV specific issues and data. The results of all methods were reviewed at a 5 day meeting beginning the week of the 16th of September 2013, which brought together the iTAG, WHO and its partners to formulate agreed conclusions and recommendations.

## Key findings of the 2013 strategic review of the IB-VPD and RV surveillance networks

### 1. IB-VPD surveillance findings

In 2008, the IB-VPD network comprised 36 reporting countries (69% GAVI-eligible) with 91 sites (60% in GAVI countries) that enrolled 16,124 children with meningitis and 20,098 children pneumonia /sepsis. In 2012 the network comprised 58 reporting countries (79% GAVI-eligible) with 150 sites (70% in GAVI countries) that enrolled 20,098 children with meningitis and 35,480 children with pneumonia and sepsis. Sites[1] that received financial support (e.g. sites in GAVI-eligible countries), in general, performed better. Excluding the 37 new sites, 48 (52%) of the 93 GAVI sites conducting meningitis surveillance were categorized as A, B, or C sites while only 10 (20%) of the 51 non-GAVI sites were (Table). Among the 34 category A sites conducting meningitis surveillance, 32 (94%) were located in GAVI-eligible countries.

Table: Invasive bacterial vaccine preventable disease surveillance sites conducting meningitis surveillance by category based on data reported to WHO, 2010 to 2012.

| **Sites Conducting Meningitis Surveillance** | **Category of Site** | | | | |
|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **Total** |
| | **# (%)** | **# (%)** | **# (%)** | **# (%)** | **# (%)** |
| GAVI sites | 32 (94) | 14 (64) | 2 (100) | 45 (52) | 93 (65) |
| Non-GAVI sites | 2 ( 6) | 8 (36) | 0 | 41 (48) | 51 (35) |
| Total | 34 (100) | 22 (100) | 2 (100) | 86 (100) | 144 (100) |

*The 37 new meningitis sites are excluded; 28 of these sites are in GAVI-eligible countries.

The strategic review team agreed that the current IB-VPD network had met the original 2008 objectives for documenting presence of disease (e.g. 61 of 65 countries that reported data during 2008 to 2012 documented presence of pneumococcus), using surveillance as a platform to conduct special studies (e.g. Brazil and Mongolia), and using data to inform vaccine introduction decisions. Capacity for conducting surveillance had been built, not only for meningitis but for other VPDs (such as typhoid detection). Some countries had 2 years baseline data of pneumococcal isolates and 1 year post-PCV introduction data. However, the laboratory network assessment (see Annex) suggested that countries, regions and HQ were not working together as a network. The data generated was not being used in the most efficient and effective manner (see Annex). Because of the need for high-quality data and resource constraints, it was concluded that the investment of financial and technical support should be focused upon a smaller number of sites.

### 2. RV surveillance findings

During 2008-2012, 265 sites in 67 countries reported any data to WHO. Among sites that reported data during 2011-2012, 79 sites (80% GAVI-eligible) in 37 countries (86% GAVI-eligible) met the inclusion criteria. Thirteen of the 37 countries had introduced RV vaccine nationally, and 1 country introduced sub-nationally. Most sites included in the analysis met the

[1] Year-to-year variability in the number of reporting countries and sites exists due to reasons including in-country conflict, and political change.

targets for the 6 established surveillance performance indicators. Among these sites, the mean RV detection of the 75,353 tested children was 36%, with the largest percentage positive (42%) in the 6-11 month age group. Sixty-five deaths among RV positive cases were reported, with the case fatality ratio ranging from 0% to 5.9% of cases by site. RV seasonality differed by region and by AFR sub-region, with seasonal peaks seen more obviously in AMR, EUR, WPR and the AFR south sub-Region. Guatemala had sites that met the inclusion criteria and had at least 2 years pre- and two years-post RV vaccine introduction data. In Guatemala, the proportion (mean) of children hospitalized with diarrhoea with RV dropped from 42% in the 2 years pre-vaccine introduction was 42% to 28% in the second year post introduction.

The strategic review team agreed that the RV network met the original 2008 objectives for documenting presence of disease, describing disease epidemiology, using surveillance as a platform for special studies in some countries, and using the data for policy decisions. At least 37 (55%) of 67 participating countries had collected at least 2 years of pre-vaccine introduction data that met the inclusion criteria for quality as defined via the strategic review.

### 3. Assessment of IB-VPD and RV laboratory networks

The independent assessment of the laboratory networks found both laboratory networks had made '…*huge advances in strengthening national and regional laboratory capacities, standardization of laboratory testing, improving laboratory quality and performance, and establishing functional international networks. Both, however, remain in a state of development. Of the 2 laboratory networks, the RV network is significantly closer to achieving effective support of the programme. The RV laboratory network has inherent advantages over the IB-VPD laboratory network in that not only is laboratory testing significantly less complex, but laboratory requirements are more compatible with those of existing global networks, including polio and measles/rubella. … While WHO has been very effective in providing and contributing to technical guidance of the laboratory networks, provision of overall management and oversight has been less impressive. …The fidelity with which laboratory data is entered into the reporting system and the completeness of reporting is clearly inadequate. This problem can be addressed to some extent by ensuring strict linkage between laboratory data and clinical and epidemiology data through the more effective use of unique case ID numbers. This is not a technical problem; it is one of network management and oversight.*' (full report in Annex).

### 4. MoH perspectives

Standardized questionnaires were received from 27 MoH respondents in AFR, 13 in EMR, and 8 from WPR. Respondents noted the main reasons for establishing surveillance were to assess disease burden, prepare for vaccine introduction, monitor vaccine impact, and to strengthen bacterial laboratory capacity. Overall, 89% of respondents felt surveillance provided information to advocate to, or within, the government on the importance of rotavirus diarrhoea or paediatric bacterial meningitis. National surveillance was reported as the most important factor in the decision to introduce a vaccine or to continue national funding for a vaccine, followed by availability of other national data (e.g. special studies, passive national health systems) and disease burden estimates from WHO or the literature. MoH respondents noted a desire to increase the number of existing sentinel sites in order to obtain more representative data for their country.

### 5. WHO support to the network

To achieve the aim of good quality data, WHO recognized the necessity of a solid infrastructure for surveillance; thus, WHO's activities during the past 5 years have been to develop the building blocks such as instituting laboratory external quality assurance, standardized sentinel site assessments, and training. In addition, WHO provided sites with specimen collection and laboratory supplies including rapid diagnostic kits. Access to advanced laboratory testing was provided via molecular testing at reference laboratories. Regional and global meetings brought together network members to share experiences and foster the feeling of belonging to a

network, supported by the dissemination of twice yearly global surveillance bulletins. To improve quality, IB-VPD communication tools (posters and pamphlets) to support specimen collection, identifying bacterial causes of meningitis, and data management were also developed and distributed to sites. A field-based method for estimating the denominator of at-risk children at a sentinel hospital was developed for meningitis surveillance to better understand catchment populations and enable estimation of incidence of meningitis hospitalizations.

From 2008 to 2012, GAVI provided $45.5 million in support of both surveillance networks of which $8.8 million (19%) supported WHO staff and $36.7 million (81%) supported surveillance activities. In general, two-thirds of activity funds supported the surveillance infrastructure of the reference laboratory network, regional/global meetings, trainings, technical support, and one-third supported sentinel sites including purchase of supplies. Additional funding provided by the U.S. Centers for Disease Control and Prevention included $530,000 for standardized site assessments, middle income countries and the data landscape analysis, as well as provision of 3 full-time staff and additional technical support.

The current year-to-year funding with uncertainty around funding sustainability has caused hesitation by countries and WHO to implement improvements. This uncertainty has been a particular problem for reference laboratories as the year-to-year funding prohibits hiring of staff and long-term planning. This has led to one reference laboratory withdrawing from the network.

### 6. Data landscape analysis findings

The assessment found the '*data management process is variable by WHO RO, and the data transfer and reconciliation process is cumbersome and time-consuming. Thus, it is warranted to explore new and different options to streamline the current system, while taking into account the unique setting and needs of each WHO RO. The general data flow in each RO is consistent … Data capture occurs at a sentinel site, sent to the country office, and then sent to the regional office and then finally submitted to HQ. Two of the ROs have opted to only collect aggregate data while the other 4 collect case-based data…Every RO has implemented a standard paper case report form, however … Each country and even site…may have made modifications to the standard forms to allow for capture of other variables... Every RO has implemented some type of standard data collection tool, however there is not any standardization across the tools. Some of the major factors affecting the quality of data …include relationship with Regional Reference Labs* [RRL] *with inability to link RRL data* [to the individual case data] *due to lack of use of unique identifiers and the general availability of resources and funding. A future data management system …needs to be flexible and dynamic to account for the different data infrastructures and approaches of each RO. The goal of the new system would to provide a centralized system which would allow for decentralized management and control of data in a case-based format'* (full report in Annex)

## Key conclusions and recommendations from the 2013 strategic review

### 1. IB-VPD surveillance: Conclusions and recommendations

The IB-VPD programme is at a critical juncture in its development, and decisive changes will be necessary to produce high-quality data. It was recognized that building a strong and effective IB-VPD surveillance network is both complex and challenging. The overall opinion amongst all partners involved was a strong desire to continue strengthening the network; however, it was agreed that the quality of the network must be urgently improved, and that both technical and financial support should be targeted to a smaller number of sites. In the short-term, these sites would be those that met the defined funding criteria and minimum standards (in general, the A, B, and C category as well as new sites joining the network since 2011). The strategic review team recognized that the category D sites, in general, required investment of considerable human and financial resources before capacity is generated to produce quality data; thus, exclusion of Category D sites would enable focus on the other sites to further improve quality.

Furthermore, it was discussed and agreed by ROs, HQ, and partners that collection and sharing of case-based data across all levels is essential to conduct the necessary data analysis to monitor and evaluate the programme, as well as to link clinical and laboratory data particularly of serotype/group data. Data analysis should be conducted more frequently and actively used to monitor surveillance performance and outcome. Strengthening serotype/serogroup data availability and usefulness is also of importance.

*Recommendations for the IB-VPD Network Size and Scope*

- Network participation requires meeting minimum data quality standards regarding consistent reporting, enrolment of cases, laboratory, and surveillance performance indicators. In principle, all (GAVI and non-GAVI eligible) countries should be encouraged to participate in the network; however, network size may need to be limited as WHO support to countries to ensure generation of high-quality data is subject to financial and human resource constraints;
- In the coming year, the current number of sites in each country should not be expanded unless there is a compelling reason to do so. Since MoH expressed a desire to expand the number of sites, WHO should engage MoH officials in further discussion around this issue;
- Only sites that meet the established funding criteria should receive funding in 2014. Sites categorized as D, in general, do not meet these funding criteria, and should not be provided with GAVI funds, if located in GAVI-eligible countries. This decision should be based on data provided during the first 6 to 9 months of 2013, and countries should be notified of the decision by February 2014 (which is prior to receipt of 2014 funding);
- During early 2014, additional work is required to clearly define longer-term network objectives, as well as performance and funding criteria. Detection of a minimum number of pneumococcal cases per site per year in countries which have not introduced PCV should be included as a metric. Additionally, sites should be further categorized as:
    - ‘Fully recognized site’: site has been assessed within the past 2 years using the WHO standardized assessment tool, and is providing quality data for measuring vaccine impact (in pre-PCV introduction countries) or for monitoring serotype epidemiology (post-PCV introduction countries);
    - ‘Supported site” site receives funding from WHO, agrees to share case-based data on a quarterly basis, and is either a fully recognized site or working towards that;
- Networking should be strengthened to share resources and to enhance laboratory collaboration with measles/polio surveillance efforts.

*Recommendations for Data Management and Dissemination*

- Institute a common case-based data system that shares standardized data across sites/regions/reference labs/HQ, with real-time verification and analysis capacity, and with improved data quality;
- Strengthen data management capacity for data analysis, interpretation and dissemination at all levels; and
- Modify the WHO Global Bulletin to show all reporting countries but limit analysis to a subset of sites reporting quality data, including reporting for at least 12 months and enrolling a minimal number of cases.

*Recommendations for the IB-VPD laboratory network:*

- Conduct in-depth Regional reviews of laboratory networks function and output to identify region-specific issues and provide region-appropriate priority activities;
- Reduce the number of participating network laboratories to more closely match programme capacity to fully support and supervise these laboratories to an extent that guarantees confidence in reported laboratory results;
- Review and revise the roles and responsibilities of WHO Regional and Global laboratory coordinators to place more emphasis on active management of network performance;
- Every effort should be made to assess every laboratory at least once each year;
- Continue the external quality assurance, and ensure quality control (all positive specimens and 10% sample of negative specimens should be submitted in a ‘blinded’ fashion for RRL

testing) with data analysis to validate test and laboratory performance;
- Report serotype/serogroup data at least twice yearly to WHO HQ and more frequently to ROs to enable more prompt detection of problems with subsequently actions to improve quality;
- Standardize sample selection for serotyping/grouping; and
- Link case-based clinical and epidemiological data from sentinel sites to local laboratory results and polymerase chain reaction results as well as serotype/group data from RRLs, which may require modification of existing data management systems.

*Recommendations for sentinel sites*
- Ensure sites meet a definition of a sentinel site so surveillance objectives can be met;
- Initiate zero reporting to enable differentiation between no cases enrolled or no report submitted to WHO;
- Develop strategies to improve performances at all sites (GAVI and non-GAVI) based on findings from monitoring and evaluation of the surveillance system; and
- Prioritize site assessments using external reviewers, MoH, local institutions, etc.

## 2. RV Surveillance: Conclusions and recommendations

The review team concluded that the RV surveillance network was overall generating quality data useful for decision makers. However, further targeted enhancements to the network would enhance its capacity to provide more standardized information to national, regional, and global policy makers. In particular, all sentinel sites must meet the standard definition for a site so that calculations of rotavirus positivity are based on hospitalized children, rather than children seen at peripheral clinics. Additionally, genotyping data generation should be further strengthened by development of standardized protocols for specimen selection and linking of case-based data that includes clinical and vaccination data.

*Recommendations for the overall RV surveillance system*
- Network participation requires meeting minimum data quality standards regarding consistent reporting, enrolment of cases, laboratory, and surveillance performance indicators. In principle, all (GAVI and non-GAVI eligible) countries should be encouraged to participate in the network; however, network size may need to be limited as WHO support to countries to ensure generation of high-quality data is subject to financial and human resource constraints;
- The current surveillance performance indicators should be examined for usefulness; and
- Encourage further networking including laboratory collaboration with measles, polio, IB-VPD surveillance and sharing of resources.

*Recommendations for Data Management and Dissemination*
- Countries should report case-based data to all regional offices and HQ, and gathered data should be further standardized;
- RRLs should report genotype data to ROs twice yearly to ROs, as feasible within current resource constraints; and
- Global Bulletins should be modified to show all reporting countries on a map, but limit analysis to subset of reporting sites that report every month and enrol $\geq$ 100 cases annually.

*Recommendations for the RV laboratory network*
- Standardize sample selection for genotyping;
- Begin to establish the linkage of case-based data to genotype data;
- Examine country-level genotype distribution in addition to distribution at regional and global levels;
- Build additional technical capacity at the national laboratory (NL) level, if possible; and
- Funding permitting, include all sites in the EQA programme.

*Recommendations for sentinel sites*

- Ensure sites meet a definition of a sentinel site so surveillance objectives can be met;
- Update eligibility criteria for inclusion in data analyses to include 12 months reporting and ≥100 specimens at a single site (no satellite sites)
- Initiate zero reporting to enable differentiation between no cases enrolled or no report submitted to WHO; and
- Develop strategies to improve performances at all sites (GAVI and non-GAVI). Strategies may be based on findings from monitoring and evaluation of the surveillance system.

### 3. IB-VPD and RV future vision and complementary approaches for IB-VPD surveillance: Conclusions and recommendations

*Recommendations for complementary approaches to IB-VPD surveillance*

For IB-VPD, there is an urgent need to improve the quality of the data, and to monitor ongoing serotype epidemiology. However, it is anticipated that data quality will be unable to quickly reach the desired level in all countries, particularly those with the weakest health and hospital systems. Thus, a complementary strategy to IB-VPD surveillance for measuring vaccine impact is required.

- Develop tools and processes (models) that allow PCV impact assessment by input of quality data from IB-VPD as well as complementary existing data sources including pneumonia morbidity and mortality.

*Recommendations for assessing future utility for surveillance of other VPDs*

Both the IB-VPD and RV sentinel hospital surveillance networks have developed a surveillance platform of improved epidemiological and laboratory capacity. Careful consideration is warranted to determine whether other VPD surveillance activities can be added to this platform, without jeopardizing the quality of IB-VPD and RV data.

- Define how to best build upon these networks to conduct surveillance for other VPDs, including those prevented by current vaccines and future vaccines such as typhoid, as well to increase capacity for outbreak detection.
- Appropriate surveillance approach(es) for other VPD's should be developed based on the specific disease characteristics (incidence, hospitalization, diagnostic testing characteristics, etc.) and the key objectives for surveillance of that disease.

*Recommendations for monitoring implementation of the strategic review's recommendations*

- The iTAG should continue to engage in the on-going progress made from implementation of these recommendations via quarterly teleconferences or meetings, and advice WHO on any corrective actions that may be required.

*Recommendations for funding*

- Improvement of the data management system with a move to case-based data (including linking of data from reference laboratories) and more on-going data analysis, interpretation and dissemination will require additional financial support. Longer term funding would enhance commitment to make changes in the system.

# The Informal Technical Advisory Group for New Vaccines Surveillance

# Assessment of the

# 2013 Strategic Review of the Invasive Bacterial Vaccine Preventable Diseases and Rotavirus Sentinel Surveillance Networks

**Introduction and background:**

The informal Technical Advisory Group (iTAG) would like to acknowledge the foresight of WHO in requesting a strategic review of the Rotavirus (RV) and Invasive Bacterial-Vaccine Preventable Diseases (IB-VPD) Surveillance Networks. As WHO and partners consider how the next phase of surveillance for RV and IB-VPD should be designed, reviewing the accomplishments and challenges during the first five years of network development has provided valuable insights into approaches that have been successful and identified areas of needed improvement. The accompanying Executive Summary and report provide the detailed scope, process, and results of the strategic review. This document highlights the iTAG's identification of several overarching issues and policy considerations.

The RV and IB-VPD networks have accomplished the 2008 objective of documenting the presence of disease; the resultant data have contributed to decisions of many countries to introduce RV vaccine and Pneumococcal Conjugate Vaccine (PCV). As a result, strategic surveillance objectives for many countries have changed from making the decision to introduce vaccine(s) to monitoring the impact(s) of vaccine introduction and obtaining data to support eventual country vaccine financing. In addition, the RV network has successfully initiated monitoring of rotavirus genotype distribution in all regions, and has promising results for the potential ability of the network to monitor impact of vaccine introduction. The laboratory capacity built for IB-VPD in some sites has detected disease due to other etiologic agents, as well as outbreaks of meningitis. Pneumococcal serotype information has been collected from previously under-represented countries and regions. The ability of most IB-VPD sites or network to serve as a platform to monitor impact of PCV introduction remains to be demonstrated.

The review process has confirmed that the capacity needed for a site to successfully implement RV surveillance is quite different from that needed for IB-VPD surveillance. Gastroenteritis is a common, easily recognized clinical condition, and sample collection to test for RV is non-invasive. IB-VPD Tier 1 sites are conducting surveillance for meningitis, and bacterial meningitis at a population level is an infrequent albeit severe condition, requiring a substantial population per site in order to detect more than a small number of cases. For the IBD-VPD Tier 2 sites which are also conducting surveillance for bacteremia, sepsis and pneumonia, case confirmation is challenging. Blood cultures are not routinely performed in many countries and widespread use of antibiotics prior to seeking medical care—coupled with poor blood culturing techniques—hinder isolation of bacteria. Also, bacteremia occurs in a small percentage of pneumonia cases, and diagnostic testing for non-bacteremic pneumococcal pneumonia is

neither sufficiently sensitive nor specific with present assays. For both IB-VPD tiers, establishing laboratory capacity to isolate bacteria from normally sterile body fluids consistently and reliably remains a challenge in many sites; as Ray Sanders, the consultant who reviewed the network laboratory activities notes, the laboratory testing required for the RV network is “significantly less complex".

Since 2008, when the IBD-VP network development began, the field of PCV impact evaluation has gained substantially more experience in monitoring the changes in hospitalized pediatric pneumonia (i.e., impact on a syndromic outcome that is not specific for pneumococcal pneumonia). It may now be possible to monitor PCV impact on hospitalized pediatric pneumonia in selected sites, to complement the original focus on Invasive Pneumococcal Disease as an outcome. However impact monitoring by using a pneumonia syndrome endpoint is also complex and feasible in only selected settings. RV surveillance for monitoring vaccine impact may also require special studies on vaccine effectiveness and intussusception, which may not be feasible in all sites.

In order to support country decision making for vaccine introduction and for sustaining vaccine programs, countries need to be able to estimate vaccine impact. New tools for such assessments are becoming available, including increased experience with models in which countries can use either their own data, data from special studies, or global burden of disease data to estimate the impact of introducing pneumococcal or rotavirus vaccine on their country’s morbidity and mortality, as well as the cost-effectiveness of vaccination. Surveillance networks may need to consider how data generated through the network and other data sources could be used as inputs into such models, in place of monitoring actual disease impact data at the country level.

The iTAG review identified certain areas where modifications would substantially enhance the utility of the data and the allocation of resources.

**Issues identified during the review:**

1) As noted in both the laboratory review and the data landscape review, the system has developed and tends to function as six separate regional networks, rather than as a single network. Implementation of the IBD-VPD and RV networks has largely been designed and managed at the regional level. Some degree of regional flexibility is appropriate and necessary to permit accommodation of the surveillance to regional and national level needs and realities. However the network also needs overall project management and accountability, and the ability to undertake global assessment and analyses.

2) While the analyses of the system in the accompanying report provide useful information about the networks, additional analyses of the IB-VPD data at a global level that were proposed as part of the review were not feasible in the available time frame. Issues limiting analyses included the lack of case level data in an agreed upon standard format, as well as difficulty linking specimen laboratory results from some laboratories with the clinical and epidemiologic data on the same patient. This was also an issue with data collection with the

RV network, although not as critical. The ability within the network to do real time performance monitoring was therefore limited.

3) The resources to support a network of this size at the country, regional and global level are insufficient and could benefit from more strategic allocation. Two specific examples were noted by the iTAG during the review. At the global level, there were inadequate resources for management, and data processing and analysis (exacerbated by the data system issues noted elsewhere in this document). The review also noted substantial differences in the regional staffing and management of the network(s). For example, the number of sites/countries supported by each Regional Office and Regional Reference Laboratory varied widely. In a region with a large number of sites, the regional staffing is unlikely to be sufficient to support the recommended on-site assessments of either the surveillance program or the site laboratories.

   In addition the decreased funding available in 2014 increases the urgency of decisions about appropriate resource utilization and sizing the network relative to the resources.

   Representatives from the Regional Offices also note that the current approach of year-to-year funding has made it difficult to undertake longer-term planning and investment at all levels of the networks.

4) For the IB-VPD network, preliminary data suggest a wide range in the number of laboratory confirmed cases per site, with some sites identifying small numbers of cases, and showing substantial year-to-year variability.

5) The value of the networks for countries and regions includes the technical standards for surveillance that are established (which can serve as models for other countries to follow); the access to technical assistance, reference laboratories, and reagents; and the communication and collaboration that occur among participant countries and sites, including countries which are not GAVI eligible, but may be encouraged to undertake surveillance and introduction of vaccines.

**Recommendations:**

1) The RV and IB-VPD networks should build on the experience and results of the past five years to refine appropriate objectives and strategies to meet future surveillance needs.

   A) For RV, the network appears capable of meeting the primary objectives, monitoring the impact of vaccine introduction and monitoring changes in genotype distribution. It is important to define the minimum data required to meet surveillance objectives at the national and regional

levels. Specific modifications for the RV network proposed in the review report will strengthen the network's ability to meet these objectives.

B) For IB-VPD, the network should refine the objective and performance criteria for surveillance for Invasive Bacterial Disease, incorporating what has been learned from the initial experience. An updated objective should include the requirement that participating sites demonstrate the ability to document a substantial number of IPD cases, in order to establish a credible baseline of IPD for at least two years before vaccine introduction. A performance criteria of an average of 20 to 30 cases of invasive pneumococcal disease each year before vaccine introduction is proposed, based on the analysis of sentinel site comparability to population level trends in the US active surveillance systems. This target also reflects the concern that sites with smaller numbers are likely to exhibit greater year to year variability, increasing the potential for misleading interpretations of secular trend data, especially regarding non-vaccine serotypes. Relatively few sites may be able to identify this number of IPD cases annually in the target age range. However, focusing the surveillance resources on a smaller number of sites with more interpretable data may provide a better model of what can be accomplished by surveillance, and encourage countries considering vaccine introduction to invest country or donor resources in surveillance (see below).

C) For countries and sites that are not currently able to meet the above performance criteria for IBD/IPD, other approaches to the core objectives should be explored.

1. To address the objective of monitoring vaccine impact, WHO could explore the use of a hospitalized pediatric pneumonia endpoint in a limited number of sites where population size and available data sources suggest that such an approach might be feasible, building on the conclusions from the PCV impact meeting.

2. To meet country needs for decision making on vaccine financing, WHO could explore encouraging the use of existing or future modeling approaches to estimate the impact of introducing pneumococcal vaccine on country specific morbidity and mortality, as well as the cost-effectiveness of vaccination.

3. Monitoring the impact of pneumococcal vaccine on NP colonization, especially for vaccine serotype strains, has also been proposed as an alternate method for countries to bridge to disease impact data from similar settings, using WHO –recommended methodologies for nasopharyngeal swabbing. WHO should consider the conclusions from the PCV impact meeting regarding the possible utility of this approach; concerns include the technical requirements for undertaking NP colonization surveys, the costs for such surveys, and the complexity of extrapolating from NP colonization data to disease impact especially for non-vaccine serotype disease.

D) An additional objective for IB-VPD surveillance is to support improved bacteriologic capacity to identify other important pathogens and outbreaks. Monitoring of anti-microbial susceptibility also remains an important question. However, the experience of the past five years suggests that either these objectives should be achieved by special studies in a limited number of well-resourced centers, or there needs to be a substantial improvement in sentinel site and laboratory performance, with increased technical assistance, site assessments, and close to real time performance monitoring.

The iTAG encourages efforts to further develop IB-VPD surveillance capacity to meet these objectives, and also to support sites that seek to eventually meet the performance criteria proposed in B above. WHO should encourage countries to explore strategies for supporting this capacity building, through alternative (or "supplemental") funding such as GAVI's Health Systems Strengthening, in-country support for VPD surveillance, and other sources. However the iTAG also notes that site funding is not the only needed input; the ability to support the network with access to technical assistance, reference laboratories, reagents, site assessments, data reporting systems, communication and collaboration also require substantial resources which are currently limited.

2) It is essential for the future that RV and IB-VPD surveillance each function as single global networks generating credible well-defined data. The network should also facilitate efficient use of the data collected for core network functions such as monitoring system performance in real time, contributing data for laboratory quality assurance, and evaluating the performance of new diagnostic methods. This will require modification of data systems and implementation of policies which facilitate relevant data collection and timely analysis.

Specific needs include:

A) Use of a standard approach for variable names and coding
B) Use of unique identification numbers for patients and/or specimens, policies which ensure that laboratory results (site and RRL) are linked with clinical and epidemiologic data on each specimen/patient, and policies that assure an appropriate sample of specimens are tested in Regional Reference Laboratories
C) With appropriate security safeguards, sharing of case level records among all levels of the system
D) System flexibility to incorporate new laboratory tests when officially added as standard procedure
E) Zero or negative reporting from sites, so that absence of cases or variables can be differentiated from lack of reporting
F) Software with editing and verification capability to improve data quality

Since it is unlikely that the time or funds will be available for development of entirely new data systems, the iTAG recommends a rapid evaluation of the feasibility of modifying existing web-based systems used within the networks to meet the above system requirements. The process of the

strategic review itself has resulted in substantial work to map the variable names across sites and to understand what the values for variables mean from site to site, which should contribute to progress toward a single network. The need for stronger networking, communication, and policies at all levels cannot be over-emphasized.

3) There should be better targeting of resources linked to the refined objectives.

The iTAG commends the thoughtful effort by the IB-VPD network to define performance criteria for joining the network and for continuing to participate as a network site. These criteria have also been used to identify sites which have not met the criteria over the past two years. Given the decreased resources available for 2014, the iTAG concurs with focusing resources on those sites that are able to meet the performance criteria and eliminating funding for the sites that have not.

Looking beyond 2014, funding and human resources should be more closely aligned with the refined objectives and strategies above. While the iTAG agrees the funding cycle should permit more than year-to-year funding, especially when staff must be hired, it is also critical that continuation of funding be contingent on sites meeting meaningful performance criteria. There should be performance agreements for all participants in the network, including the surveillance sites, regional offices, regional reference laboratories, global reference laboratories, and WHO HQ, specifying in detail responsibilities as well as resources to be received. Estimates for the approximate number of site visits to be made and specimens to be processed would contribute to a more realistic estimate of the number of sites that could be supported given limited human and financial resources. Available resources should be allocated to assure data capable of meeting system objectives; the number of sites that can be supported is finite.

The iTAG recommends that WHO implement structured performance-based agreements with all participants. Sites/countries could consider the refined list of objectives and identify, based on their experience to date, which approach for vaccine impact monitoring (e.g. IPD, hospitalized pneumonia, modeling, etc.) they would be best suited to undertake. Funding for reference laboratories could be linked to best estimates of the number of site visits to be done and the number of specimens to be processed.

While capacity building is a goal of the RV and IBVPD surveillance programs, regular monitoring and accountability are needed to ensure a level of performance that provides data to meet country and region specific needs. The network provides technical specifications and support; it also provides funding to country sites to establish successful models. Other countries can then build on these models, using country funds or other sources such as GAVI HSS funds. As countries introduce vaccines they are committing themselves to large investments in the future for vaccine procurement; surveillance costs are small compared with vaccine purchase costs but are essential to vaccine sustainability. The vision for the networks is that countries have models for disease surveillance that enable countries and regions to build credible, high quality surveillance systems which will provide reliable data on vaccine preventable diseases.