World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

November 2012

Strategic Advisory Group of Experts on Immunization

6-8 November 2012

CCV, Geneva

SAGE November 2012

This booklet contains key background documents for the meeting of the Strategic Advisory Group of Experts on Immunization (SAGE), 6-8 November 2012.

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

http://apps.who.int/immunization/sage/meetings/2012/november/en/

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

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World Health Organization

Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
6 – 8 November 2012
CCV/CICG, Geneva

Tuesday, 6 November 2012

Time	Session	Purpose of session, target outcomes and questions for SAGE	
9:00	**Welcome - introduction** H. Rees, Chair of SAGE		20 min.
9:20	**Report from Director, IVB - Session 1** Global report including key updates and challenges from regions, J.-M. Okwo-Bele, WHO, 30 min. Discussion: 1h 30 min.	**FOR INFORMATION**	2h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Report from Director, IVB - Session 1, (Contd.)**		
11:50	**Report from GAVI - Session 2** Report from the GAVI Alliance, S. Berkley, GAVI Alliance, 20 min. Discussion: 20 min.	**FOR INFORMATION**	40 min.
12:30	**Lunch**	**Break**	**1h**

13:30	**Reports from other Advisory Committees on Immunization - Session 3** Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min. Discussion: 10 min. Report of the Immunization Practices Advisory Committee (IPAC), S. Deeks, Chair of IPAC, 10 min. Discussion: 10 min. Report of the Expert Committee on Biological Standardization (ECBS), E. Griffiths, Chair of ECBS, 10 min. Discussion: 10 min. Report of the Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC), A. Hinman, Chair of IVIR-AC, 20 min. Discussion: 20 min.	**FOR INFORMATION**	1h 30 min.
15:10	**Coffee/tea break**	**Break**	**30 min.**
15:40	**Global polio eradication initiative - Session 4** Context: Major developments since SAGE April 2012 meeting, B. Aylward, WHO, 10 min. Discussion: 10 min. Polio Endgame Strategy, Legacy & Budget, 2014-2018, A. Freeman, GPEI Project Manager for Development of the Endgame Documents, 20 min. Discussion: 30 min. Role of IPV in OPV cessation – report of the SAGE Polio Working group. E. Miller, Chair of SAGE Polio Working Group, 20 min. Discussion: 50 min. Accelerating polio emergency eradication efforts - is there a role for expanding the target age groups for bOPV campaigns and/or including IPV in campaigns. H. Jafari, WHO, 20 min. Discussion: 40 min.	**FOR DISCUSSION AND DECISION** Update SAGE on major developments since the April 2012 SAGE meeting Request SAGE's input on what additional issues should be addressed or considered in the polio endgame strategy, and to optimize the legacy of the Global Polio Eradication Initiative. Request a decision on the role of IPV in OPV cessation - should the current SAGE recommendation be revised in light of additional information on IPV options, prices, supply, delivery routes and impact on mucosal immunity. Request SAGE's view on the role for expanding the target age groups for bOPV campaigns and/or including IPV in campaigns.	3h 20 min.
19:00	**Cocktail**		

Wednesday, 7 November 2012

08:00	**DoV – GVAP - Session 5** GVAP key steps to implementation, J.-M. Okwo-Bele, WHO, 10 min. Discussion: 10 min. Decade of Vaccine M&E/Accountability Framework, T. Cherian, WHO, 15 min. Discussion: 45 min. GVAP Costing, Financing and impact update and tracking commitments, G. Gandhi, UNICEF, 15 min. Discussion: 30 min. Independent review of progress and reporting to governing bodies, P. Duclos, WHO, 10 min. Discussion: 15 min.	**FOR DISCUSSION AND DECISION** Discuss DoV M&E/Accountability Framework structure and provide feedback on the reporting process particularly where WHO leads and next steps. Request endorsement of the GVAP indicators to be presented to WHO EB. Provide feedback and endorse the DoV commitment guidelines for increased emphasis on immunization as part of the UN Secretary General's Global Strategy for Women's and Children's Health. Provide feedback on the process to undertake resource tracking process and update the GVAP cost, financing, and impact projections for 2015. Provide feedback on the proposed review process and reporting cycle.	2h 30 min.
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Hib immunization schedules - Session 6** Overview of Hib burden and progress with vaccine introduction (and questions to SAGE), P. Fine, London School of Hygiene and Tropical Medicine (LSHTM), 10 min. What evidence is available on the current Hib vaccine schedule versus alternative schedules, M. Santosham, Johns Hopkins University, 20 min. Impact and incremental benefits of various Hib vaccines schedules given the disease epidemiology in young children and the actual age at vaccination, C. Sanderson, LSHTM, 20 min. Expert group conclusions: What are the optimal schedules for Hib vaccines for children living in different epidemiological settings? J. Abramson, SAGE member, 10 min. Questions to SAGE and plenary discussion, 1h.	**FOR DECISION** What are the optimal schedules for Hib vaccines for children living in different epidemiological settings? What evidence is available on the current Hib vaccines schedules versus alternative schedules OR What schedules does the evidence favours (i.e. effectiveness, co-administration, operational issues, costs) for children living in different epidemiological settings?	2h
13:00	**Lunch**	**Break**	**1h**

14:00	**Measles and rubella status report - Session 7** Presentation on progress and challenges to achieving global and regional goals, SAGE member of WG, P. Figueroa, Chair of the SAGE measles-rubella working group, 20 min. Discussion: 40 min. Presentation on opportunities and plans to overcome the challenges, P. Strebel, 20 min. Discussion: 10 min.	**FOR DISCUSSION** Are we on track to achieve global and regional goals? Are current plans, strategies, and resources adequate to achieve global and regional goals? If not, what additional strategies, opportunities, and/or innovations are needed?	3h 30 min.
15:30	**Coffee/tea break**		**30 min.**
16:00	**Measles and rubella status report - Session 7, (Contd.)** Discussion continued: 30 min. Presentation on the draft framework for verifying elimination of measles and rubella, N. Crowcroft, SAGE measles-rubella working group, 10 min. (by phone link) Discussion: 20 min. Aerosol measles vaccination, M. Greco, Chair of the aerosol product development group and A.-M. Henao, WHO, 20 min. Discussion: 40 min.	Are the definitions, criteria, and indicators of quality of surveillance appropriate for verifying elimination? What is the potential role (if any) of a measles aerosol vaccine to accelerate measles control /elimination efforts? What additional evidence is required to further inform policy and recommendations for use in the field?	
18:00	**End of meeting**		

Thursday, 8 November 2012

08:30	**Vaccination in humanitarian emergencies - Session 8** Introduction and overview of the process; and the three components of the work, H. Rees, SAGE, 15 min. The decision-making framework, R. Waldman, Working Group member, 30 min. Discussion: 2h 15 min.	**FOR DECISION** Request SAGE's review and endorsement of the decision- making framework on the use of vaccines in acute humanitarian emergencies.	3h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Vaccination in humanitarian emergencies – Session 8, (Contd.)**		
12:00	**Lunch**	**Break**	**1h**
13:00	**New vaccine introduction in middle-income countries: current initiatives to address financial challenges - Session 9** What is the new context regarding middle-income countries and new vaccine introduction? • Report from Macedonia, S. Manevska, Ministry of Health, The former Yugoslav Republic of Macedonia, 10 min. • EURO report, L. Mosina, WHO EURO, 10 min. Discussion: 10 min. What has been done so far to implement SAGE 2010 recommendations? M. Kaddar, WHO, 15 min. Discussion: 15 min. What is to be done to respond to country needs and comply with WHA and SAGE recommendations: What WHO and partners are exploring and planning to do? Sarah Schmitt, WHO Consultant, Meredith Shirey, UNICEF, M. Kaddar, WHO, 20 min. Discussion: 40 min.	**FOR DISCUSSION** To report to the SAGE on activities conducted by WHO and partners to implement the 2008 and 2010 recommendations. To share the lessons learned from activities and investigations of middle-income countries needs to overcome and address obstacles and challenges to sustainable new vaccine introduction. To present the options detailed in the GVAP companion paper. To seek for SAGE advice on the proposed operational strategies, activities and co-ordination mechanism(s) and request guidance on the priorities, scope, timing and the role of WHO.	2h
15:00	**Closing**		
15:20	**End of meeting**		

World Health Organization

Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
6 - 8 November 2012
Geneva, Switzerland

SAGE members

Professor Jon S. Abramson Department of Pediatrics **Wake Forest University Baptist Medical Centre** Medical Center Blvd Winston-Salem 27157 NC **United States of America**	*tel:* +1 336 716 2512 or 7134500 *fax:* +1 336 716 9699 or 716 7100 *e-mail:* jabrams@wfubmc.edu
Dr Yagob Yousef Al-Mazrou Secretary General **Council of Health Services** Riyadh 12628 **Saudi Arabia**	*tel:* +966 1 215 4906 *fax:* +966 1 293 6769 *e-mail:* yalmazrou@chs.gov.sa
Dr Narendra Kumar Arora (Vice-Chair) Executive Director **The INCLEN Trust International** Second Floor, F-1/5 Okhla Industrial Area Phase 1 New Delhi 110020 **India**	*tel:* +91 11 477 30000 *fax:* 91 11 47730001 *e-mail:* nkarora@inclentrust.org
Professor Zulfiqar Ahmed Bhutta Head Maternal and Child Health Division **The Aga Khan University** P.O. Box 3500 Stadium Road Karachi 74800 **Pakistan**	*tel:* +92 21 493 9202 *fax:* +92 21 493 4294 *e-mail:* Zulfiqar.bhutta@aku.edu
Professor Juhani Eskola Deputy Director General, THL Health Protection **National Institute for Health and Welfare** Mannerheimintie 166 P.O. Box 30 00271 Helsinki **Finland**	*tel:* +358 206106006 *fax:* +358 20 610 6020 *e-mail:* juhani.eskola@thl.fi
Professor J. Peter Figueroa Public Health, Epidemiology & AIDS, Department of Community Health & Psychiatry Faculty of Medical Sciences **University of the West Indies** Gilbraltar Camp Road Mona, Kingston 7 **Jamaica**	*tel:* +1 876-970 6542 *fax:* +1 876 977 6346 *e-mail:* peter.figueroa10@gmail.com
Dr Xiaofeng Liang Deputy Director-General China Center for Disease Control and Prevention - Ministry of Health **China Center for Disease Control and Prevention** 155 Changbai Road Changping District Beijing 102206 **People's Republic of China**	*tel:* +86 10 58900213 *fax:* +86 10 58900346 *e-mail:* liangxf@hotmail.com

Professor Elizabeth Miller Head, Immunisation Department **Health Protection Agency, Centre for Infections** 61 Colindale Avenue Colindale London NW9 5EQ **United Kingdom of Great Britain & Northern Ireland**	*tel:* +44 208 327 7430 (direct) *fax:* +44 208 327 7404 *e-mail:* Liz.Miller@hpa.org.uk
Professor Terence Nolan Head, Department of Public Health **Melbourne School of Population Health** **The University of Melbourne** Level 5 207 Bouverie Street Carlton Victoria 3010 **Australia**	*tel:* +613-8344-9351 *fax:* +613 9347 6929 *e-mail:* t.nolan@unimelb.edu.au
Dr Katherine L. O'Brien Associate Professor **Department of International Health** **John Hopkins Bloomberg School of Public Health** **Centre for American Indian Health & International Vaccine Access Center** 615 North Wolfe Street Baltimore 21205 MD **United States of America**	*tel:* +1 410 955 6931 *fax:* +1 410 955 2010 *e-mail:* klobrien@jhsph.edu
Dr Paba Palihawadena Chief Epidemiologist Epidemiological Unit **Ministry of Healthcare and Nutrition** 231, De Saram Place Colombo 10 **Sri Lanka**	*tel:* +94 11 284 1536 *e-mail:* paba@health.gov.lk
Professor Helen Rees (Chair) Executive Director Reproductive Health and HIV Research Institute **Wits Institute** Hugh Solomon Building Corner Esselen and Klein Streets Hillbrow 2038 Johannesburg, Gauteng **South Africa**	*tel:* +27 11 358 5344 *fax:* +27 86 639 4305 *e-mail:* scornell@rhru.co.za; hrees@rhru.co.za;
Professor Claire-Anne Siegrist Head, WHO Collaborating Centre for Neonatal Vaccinology Department of Pediatrics & Pathology-Immunology **Centre Médical Universitaire** 1 rue Michel Servet 1211 Genève 4 **Switzerland**	*tel:* +41 22 379 5778 *fax:* +41 22 379 58 01 *e-mail:* claire-anne.siegrist@unige.ch
Dr Piyanit Tharmaphornpilas Senior Medical Officer **Ministry of Public Health** Tiwanon Road Taladkwan Muang Nonthaburi 11000 **Thailand**	*tel:* +66-89 969 0852 *fax:* +66 2 590 3196 *e-mail:* piyanit@live.com
Professor Oyewale Tomori Vice Chancellor **Redeemer's University** KM 46 Lagos-Ibadan Express Road 3005 Redemption City Ogun **Nigeria**	*tel:* +234 1 791 3890 *fax:* +263 4 746 867 *e-mail:* oyewaletomori@yahoo.com; tomorio@run.edu.ng

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.

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.

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

Working Group 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 is particularly complicated and could not be addressed by existing standing WHO advisory committees.

The need and creation for a Working Group is discussed and agreed during SAGE meetings.

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 meeting leading to the establishment of the Working Group.

TORs and proposed related expertise to serve on the Working Group are developed jointly by the SAGE member serving as Working Group Chair and the Lead WHO technical staff. Final decision is taken jointly by the SAGE Chair 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 Groups 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 terms of reference of the Working Group and indication of the desirable expertise. SAGE members, regional offices, WHO staff and key partner organization will also be approached for potential nominations. From the pool of nominees, the Working Group Chair 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.

Individuals other than SAGE members and organization representatives may participate in SAGE Working Groups meetings only by secretarial invitation in consultation with either Chairs of SAGE or of the Working Group. Occasionally the Working Group Chair, in consultation with the Lead WHO staff and the SAGE Chair, may request the participation of additional disease / vaccine experts who are not members of the Working Group. These may include SAGE members, organization representatives, industry representatives/experts, public health officials and faculty of academic institutions. Other experts, including representatives of vaccine manufacturers may be asked to provide information to the Working Groups on an ad hoc basis and as needed.

WHO staff perform, coordinate, or identify scientific studies and outbreak investigations to address questions that arise regarding appropriate vaccine policy decisions; conduct analysis of data addressing efficacy, effectiveness, safety, feasibility, and economic aspects of immunization policy.

Modus Operandi

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 the 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 terminating in development of group consensus and recommendations must occur in the open public forum of SAGE meetings.

Working Group Process.

Effective communication and a strong working collaboration between the Working Group Chair and the Lead WHO staff are significant determinants of the effectiveness of a Working Group. The development of a brief (1-2 pages) summary of each Working Group meeting by one of these people will facilitate the function of the Working Group. Summaries should be provided to the SAGE Executive Secretary so that IVB senior staff, immunization Regional Advisers and SAGE members can be informed in real time of progress and issues.

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 scheduled in association with SAGE meetings and should be anticipated at least two months in advance of the SAGE meeting. WHO routinely supports travel costs for the duration of SAGE meetings for SAGE members, chairs of regional technical advisory groups, WHO Regional Advisers and any experts invited to present at SAGE. WHO may support travel for additional persons for the purpose of a WG meeting. Such requests should be brought to the SAGE Executive Secretary for consideration on a case by case basis, with justification for the increased costs.

As issues mature, proposals for presentation to the SAGE should be submitted to the SAGE Executive Secretary at least 10 weeks ahead of each SAGE meeting for circulation to SAGE members and to WHO staff. At this stage, formal interaction between the SAGE Working Group Chair, lead WHO staff, SAGE Executive Secretary and the SAGE Chair should occur allowing for a briefing on the issue at hand and ensuring that areas of potential conflict are recognized prior to the meeting itself.

Decision to proceed with tabling the issue at the next SAGE meeting will then be taken jointly by the Chair of SAGE and IVB Director after consideration of issues raised during the consultative process.

Management of Conflict of Interest / Undue Influence

When a SAGE Working Group is formed, and at the start of each Working Group meeting, participants should respond to a request to report conflicts of interest relevant to the focus of the Working Group. This is done using the DOI. SAGE members, organization representatives or WHO staff who have conflicts of interest may not participate in the Working Group. Persons who serve as consultants, may participate in the Working Group despite conflicts of interest if, in the judgment of the SAGE Chair, SAGE Executive Secretary, Working Group Chair and lead WHO staff they bring specific expertise that is essential to the efforts of the Working Group. However, conflicts, both personal and those of their liaison organization (in the case of liaison representatives), must be declared and recorded at the beginning of each Working Group meeting. Participation of all persons with declared conflicts will be restricted by the Working Group Chair and lead WHO staff to that necessary for the Working Group to benefit from the expertise provided by the consultant. No person with an identified conflict of interest should participate in drafting policy options or policy recommendations.

All consultants participate in Working Groups at the discretion of the Working Group Chair and lead WHO staff. The value and impact of SAGE recommendations and WHO policies and recommendations are critically dependent upon public trust in the integrity of the process. Thus, participation of any consultant may be curtailed, even in the absence of a declared conflict of interest, if in the judgment of the Working Group Chair and the lead WHO staff a potential for the appearance of undue influence exists.

World Health Organization

CURRENT SAGE WORKING GROUPS

1. 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, United Kingdom
- Jon Abramson, Wake Forest University School of Medicine, United States of America
- Art Reingold, University of California, United States of America. (Joined the Working Group after the SAGE meeting in November 2010)
- Claire-Anne Siegrist, University of Geneva, Switzerland

Experts

- William Kwabena Ampofo, Noguchi Memorial Institute for Medical Research, Ghana
- Joseph Bresee, Centers of Disease Control, United States of America
- Janet Englund, Seattle Children's Hospital, United States of America
- 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, United Kingdom
- Barry Schoub, National Institute for Communicable Diseases, South Africa

WHO Secretariat

- John Tam
- Philippe Duclos
- Cuauhtémoc Ruiz-Matus
- Nahoko Shindo, replaced by Anthony Mounts in October 2011

2. 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, United Kingdom
- 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

WHO Secretariat

- Bruce Aylward
- Rudi Tangermann
- Roland Sutter
- Tracey Goodman
- Philippe Duclos

3. SAGE Working Group on vaccination in humanitarian emergencies (June 2011)

Terms of Reference

Develop a framework for public health decision-making for vaccination in humanitarian emergencies, to be reviewed by SAGE in April 2012.

The specific question that needs to be addressed:

What key scientific, ethical, economic, public health, operational and political criteria should be part of a decision-making framework to guide the use of vaccines in emergencies?

The approach to address this question may include:

Reviewing experiences with vaccination in humanitarian emergencies, compile the available data, identify the information gaps, guide the work required to address the information and action gaps, and prepare for a SAGE review of the general guidance on vaccination in humanitarian emergencies.

Specific issues to review in support of this approach would be:

- Defining the scope of humanitarian emergencies;
- Review of vaccination experiences in humanitarian emergencies with particular focus over the last 10 years and with respect to the political, ethical, public health/scientific, operational and economic aspects:
    - Vaccine preventable disease (VPD) burden and other available interventions for the prevention and control of these diseases;
    - Public health/scientific issues (evidence for effectiveness; purpose individual protection and/or interruption of transmission)
    - Economic aspects
    - Opportunity costs (due to competing public health priorities);
    - Availability of vaccines and acceptability range of cost per person immunized;
    - Operational/Programmatic Feasibility - supply availability, logistics need, procurement process and funding, human resources need and availability, cold chain space, training needs, supervision, injection safety, waste management, security, vaccine characteristics, regimens, regulatory issues; etc.
    - Ethical issues.

Composition

SAGE Members

- Helen Rees, Chair of Working Group. University of Witwatersrand, South Africa
- Zulfiqar Bhutta, The Aga Khan University, Pakistan
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia
- Xiaofeng Liang, Chinese Center for Disease Control and Prevention, China
- Narendra Arora, International Clinical Epidemiology Network, India

Experts

- Brenton Burkholder (Member until November 2011. In December 2011, Dr Burkholder was recruited by WHO and as such is no longer eligible to serve as a formal member of the working group).
- Jorge Castilla, Health Sector Expert, European Commission DG for Humanitarian Aid, Kenya
- Francesco Checchi, London School of Hygiene and Tropical Medicine, UK.
- Alejandro Cravioto, Executive Director, International Centre for Diarrhoeal Disease Research, Bangladesh.
- Rebecca Freeman Grais, Epicentre, France.
- Keymanthri Moodley, Bioethics Unit, Faculty of Health Sciences, University of Stellenbosch, South Africa.
- Gopinath Nair, Scientific and Administrative Head of National Institute of Cholera and Enteric Diseases, India (resigned for personal reasons in September 2011).
- Robin Nandy, Polio Eradication, UNICEF.
- Muhammad Ali Pate, National Primary Health Care Development Agency, Nigeria.
- Ronald Waldman, Global Health Bureau, Avian and Human Influenza Unit, US Agency for International Development, USA.

WHO Secretariat

- Peter Mala
- Peter Strebel
- Pem Namgyal
- Claire-Lise Chaignat
- Michelle Gayer

4. SAGE working group on yellow fever vaccines (established September 2011)

Terms of reference

Review the evidence and prepare recommendations related to the use of yellow fever vaccines and contained in the 2003 WHO position paper for SAGE review, and subsequent publication of an updated vaccine position paper.

The questions particularly to be addressed include the following:

1. Reconsider the need for booster doses every 10 years including for travellers in the context of the International Health regulations;
2. Review the impact of routine vaccination versus outbreak control;

3. Review the impact of the combined vaccination strategy (routine immunization and preventive campaigns);
4. Review the safety profile of the vaccines and update the recommendations in the context of safety issues including in particular with respect to immunization of HIV infected populations and immunocompromised, in pregnant or lactating women, people over 60 years old and in context of viscerotropic and neurological diseases;
5. Review of interference between yellow fever and other vaccines and co-administered vaccination.

Composition

SAGE Members

- Claire-Anne Siegrist, University of Geneva, Switzerland
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Thailand
- Oyewale Tomori, Chair of Working Group. Redeemer's University, Nigeria

Experts

- Chantal Akoua-Koffi, Virologist Head, Department of Biology, University of Bouake, Côte d'Ivoire
- Alan Barrett, Virologist, Director, Sealy Center for Vaccine Development, USA
- Li Dexin, Director, National Institute of Viral Diseases Control and Prevention, Centers for Disease Control, China
- Eduardo Gotuzzo, Clinician and Yellow Fever specialist, Department of Medicine, Universidad Peruana Cayetano Heredia, Peru
- Dede Kusmiaty, National Agency of Drug and Food Control, Indonesia
- Maryanne Neill, Retired, Monitoring Officer, Immunizations UNICEF, USA
- Matthias Niedrig, Virologist, Robert Koch Institute, Germany
- Jennifer Staples, Epidemiologist Centers for Disease Control and Prevention, USA
- Pedro Vasconcelos, Virologist and Epidemiologist, Instituto Evandro Chagas, Brazil

WHO Secretariat

- Sergio Yactayo
- Joachim Hombach
- Philippe Duclos

5. 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
- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia
- Peter Figueroa, Chair of Working Group. University of the West Indies, Jamaica
- Helen Rees, University of Witwatersrand, South Africa

Experts

- Hyam Bashour, Department of Family and Community Medicine, Damascus University, Syria
- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom
- 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

WHO Secretariat
- Alya Dabbagh
- Robert Perry
- Peter Strebel

6. SAGE working group on communication and 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
- Arthur Reingold, University of California at Berkeley, U.S.A.

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, U.S.A.
- Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa
- Heidi Larson, London School of Hygiene and Tropical Medicine, England
- Noni MacDonald, Dalhousie University, Canada
- Mahamane Laouali Manzo, Ministry of Health, Niger
- 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

WHO Secretariat

- Philippe Duclos

7. SAGE Working Group on Varicella and Herpes Zoster Vaccines (Establishment – 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).

The formulation of recommendations will be evidence-based and follow the principles set in the Guidance For The Development Of Evidence-Based Vaccine Related Recommendations

Guidance For The Development Of Evidence-Based Vaccine Related Recommendations
pdf

Composition

SAGE Members

- Jon Abramson, Chair of Working Group, Department of Paediatrics, Wake Forest University School of Medicine, U.S.A.
- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

Experts

- Marc Brisson, Département de Médecine Sociale et Préventive, Laval University, Canada
- Sin Yun Cheah, Health Sciences Authority, Singapore
- Philip LaRussa, Division of Pediatric Infectious Diseases, Department of Pediatrics, Columbia University, U.S.A.
- 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, U.S.A.
- Claudia Vujacich, Foundation for Infectious Diseases, FUNCEI, Argentina
- Dapeng Yin, National Immunization Programme, Chinese CDC, China

WHO Secretariat

- Philippe Duclos

Strategic Advisory Group of Experts on Immunization (SAGE) - November 2012
06 - 08 November 2012
Geneva, Switzerland

List of Participants

SAGE member

Abramson, Dr Jon Department of Pediatrics Wake Forest Baptist Health, Chair Medical Center Boulevard 27157 Winston-Salem, NC United States of America	email: jabrams@wakehealth.edu mobile: 1-336-418-1241 tel: 1-336-716-2512 fax: 1-336-716-9699
Almazrou, Dr Yagob Secretary General Council of Health Services 2650 King Abdulaziz Road 12431 Riyadh Saudi Arabia	email: yalmazrou@chs.gov.sa mobile: +966505472060 tel: +96612154906 fax: 96612936769
Arora, Professor Narendra Kumar (Vice-Chair) Executive Director The INCLEN Trust International F-1/5, Second Floor Okhla Industrial Area, Phase I 110020 Delhi, Delhi India	email: nkarora@inclentrust.org mobile: +91-9810110376 tel: +91-11-47730000
Eskola, Professor Juhani Deputy Director General National Institute for Health and Welfare (THL) Mannerheimintie 166 FI-00270 Helsinki Finland	email: juhani.eskola@thl.fi mobile: +358 29 524 6006 tel: +358 29 524 6006
Figueroa, Professor Peter Department of Community Health & Psychiatry University of the West Indies Gibralter Camp Road, Mona Kingston 7 Jamaica	email: peter.figueroa10@gmail.com mobile: +876-434-4789 tel: +876-970-6542
Liang, Dr Xiaofeng Deputy Director-General Chinese Center for Disease Control and Prevention 27 Nan Wei Road Xuan Wu District 100050 Beijing The People's Republic of China	email: liangxf@hotmail.com mobile: +13501080273 tel: +86-10-58900213 fax: +86-10-58900346
Miller, Professor Elizabeth Head Immunisation Department Health Protection Agency, Centre for Infections 61 Colindale Avenue Colindale NW 5EQ London United Kingdom of Great Britain and Northern Ireland	email: liz.miller@hpa.org.uk tel: +44 208 327 7430

Nolan, Professor Terry Head, Department of Public Health, Head, School of Population Health Melbourne School of Population Health The University of Melbourne L5/207 Bouverie St 3010 Carlton, Victoria Australia	email: t.nolan@unimelb.edu.au mobile: +61 4 1933 8383 tel: +61 3 8344 9351
O'Brien, Professor Katherine L. Professor Department of International Health Johns Hopkins Bloomberg School of Public Health 621 N. Washington Str. 21205 Baltimore, MD United States of America	email: klobrien@jhsph.edu mobile: +41 79 559 3165 tel: +1 410 955 6931
Palihawadana, Dr Paba Chief Epidemiologist Epidemiological Unit Ministry of Health Government of the Democratic Socialist republic of Sri Lanka 231, de Saram Place 01000 Colombo 10 Sri Lanka	email: paba@health.gov.lk mobile: +94 773291441 tel: +94 11 474.0491/269.5112 fax: +94 11 268.1548
Rees, Professor Helen Chair Executive Director Wits Reproductive Health and HIV Institute Hugh Solomon Building Corner Esselen and Klein Streets Hillbrow 2001 Johannesburg, Gauteng South Africa	email: hrees@wrhi.ac.za mobile: +27 82 572 2057 tel: +27 11 358 5344 fax: +27 86 639 4305
Siegrist, Professor Claire-Anne Pediatrics University of Geneva CMU, 1 rue Michel-Servet 1211 Geneva 4 Switzerland	email: claire-anne.siegrist@unige.ch mobile: +41 79 213 92 90 tel: +41 22 379 5778
Tharmaphornpilas, Dr Piyanit Senior Medical Advisor Disease Control Ministry of Public Health Muang, Nonthaburi, 11000 11000 Nonthaburi Thailand	email: piyanit@live.com mobile: +66 899 690 852 tel: +66 225 903 196
Tomori, Professor Oyewale Professor of Virology Department of Microbiology Redeemer's University KM 46 Lagos-Ibadan Express Road 3005 Redemption City, Ogun Nigeria	email: oyewaletomori@yahoo.com mobile: +234 8034996524 tel: +234 1 7742265

Chairs of WHO Regional Technical Advisory Groups

Hall, Dr Robert Senior Lecturer School of Public Health and Preventive Medicine Monash University 99 Commercial Rd 3004 Melbourne, Victoria Australia	email: robert.hall@monash.edu mobile: +61 4 0705 3061 tel: +61 3 9903 0452

Martins, Professor Helder Advisor of the Ministry of Health Faculty of Health Ministry of Health and Social Welfare Rua de França 32 00310 Maputo Mozambique	email: helderfbm921@gmail.com tel: +25823198360
Mendis, Professor Lalitha President Sri Lanka Medical Council 31, Norris Canal Road Colombo 10 10 Colombo Sri Lanka	email: sirikotha@yahoo.com tel: +94(0)777 323 716
Mohamed, Dr Ali Chair of Regional Technical Advisory Group P.O. Box 803 Ruwi, PCM 112 Muscat Oman	email: Jalalimerani@gmail.com mobile: +96899335681 tel: +96824562424 fax: +96824565454
de Quadros, Dr Ciro Executive Vice-President Sabin Vaccine Institute 2000, Pennsylvania Avenue, NW, Suite 7100 20016 Washington, DC, DC United States of America	email: ciro.dequadros@sabin.org mobile: +1 202-390-0626 tel: +1 202-265-6515 fax: +1 202-842-7689
van Damme, Professor Pierre Chair member Professor, Faculty of Medicine Vaccine & Infectious Disease Institute University of Antwerp, Campus Drie Eiken Universiteitsplein 1 2610 Antwerpen Belgium	email: pierre.vandamme@ua.ac.be tel: +32 3 265 2523 fax: +32 3 265 2640

Chairs of other Immunization Advisory Committees

Deeks, Dr Shelley Chair of IPAC Medical Director Immunization and Vaccine Preventable Diseases Public Health Ontario 480 University Avenue, Suite 300 M5G 1V2 Toronto, Ontario Canada	email: shelley.deeks@oahpp.ca mobile: + 1 647 284 6739 tel: + 1 647 260 7417
Griffiths, Dr Elwyn Chair, WHO Expert Committee on Biological Standardization Director General Biologics and Genetic Therapies Directorate Retired , Health Canada 3 The Farthings KT2 7PT Kingston upon Thames, Surrey United Kingdom of Great Britain and Northern Ireland	email: elwyn.griffiths2011@btinternet.com mobile: +44 79 72 590 211 tel: +44 208 549 1255
Hinman, Dr Alan Director for Programs Center for Vaccine Equity, Task Force for Global Health Task Force for Global Health 325 Swanton Way 30030 Decatur, Georgia United States of America	email: ahinman@taskforce.org mobile: +1 404 456 4666 tel: +1 404-687-5636

Wharton, Dr Melinda Deputy Director National Center for Immunization & Respiratory Diseases Centers for Disease Control and Prevention 1600 Clifton Road Mailstop A27 30333 Atlanta, Georgia United States of America	email: mew2@cdc.gov mobile: 001 404 917 7371 tel: 001 404 639 8755

Other participants

Aguado de Ros, Dr Teresa Consultant 56 Grand Montfleury 1290 Versoix Switzerland	email: aguado.deros.t@gmail.com mobile: +41 79 475 55 37 tel: +41 22 755 59 39
Aung, Dr Khin Devi Project Officer Vaccine Implementation, Country Programmes GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: kaung@gavialliance.org mobile: +41787319598 tel: +41229092974 fax: +41 22 909 6550
Bachy, Mrs Catherine Deputy International Vaccination Coordinator Medical Medecins Sans Frontieres Rue Leon Theodor, 85 1090 Bruxelles Belgium	email: catherine.bachy@msf.org mobile: +32496547937 tel: +3224753695
Bergsaker, Dr Marianne A Riise Deputy Director Department of Vaccines Norwegian Institute of Public Health Lovisenberggt 6/ P.O. Box 4404 Nydalen 0403 Oslo Norway	email: marianne.bergsaker@fhi.no mobile: +4791554997 tel: +4721076697
Berkley, Dr Seth Chief Executive Officer GAVI Alliance 2 chemin des Mines 1202 Geneva Switzerland	email: sberkley@gavialliance.org tel: +41 22 909 6500
Biellik, Dr Robin Consultant Epidemiologist Tranchepied 10 1278 La Rippe Switzerland	email: rbiellik@gmail.com mobile: +41 78 890 4577 tel: +41 22 367 2002
Bjorvatn, Professor Bjarne Consultant Moland 4994 Akland Norway	email: Bjarne.Bjorvatn@cih.uib.no tel: +47 37 03 38 49
Brooks, Dr Alan GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: abrooks@gavialliance.org tel: +41 22 909 2960
Castilla, Dr Jorge ECHO POB 49991-00100 Nairobi Kenya	email: jorge.castilla.echenique@gmail.com tel: +254725232760

Cernuschi, Ms Tania GAVI Alliance Senior Manager - HPV - Vaccine Implementation Team Policy and Performance GAVI Alliance Secretariat Chemin des Mines 2 1202 Genève Switzerland	email: tcernuschi@gavialliance.org tel: +41 (22) 909 7167
Checchi, Dr Francesco London School of Hygiene and Tropical Medicine Keppel Street London United Kingdom of Great Britain and Northern Ireland	email: francesco.checchi@lshtm.ac.uk tel: +447832987548
Cochi, Dr Stephen Senior Advisor Global Immunization Division Centers for Disease Control and Prevention Mailstop A-04 1600 Clifton Road, NE 30333 Atlanta, GA United States of America	email: scochi@cdc.gov mobile: +1-770-331-6643 tel: +1-404-639-8723
Cronin, Mrs Anne Senior Programme Manager GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: acronin@gavialliance.org mobile: 0041 79 745 1568 tel: 0041 22 909 7169 fax: 0041 22 909 6554
Curry, Mr David Executive Director Medical Ethics Center for Vaccine Ethics and Policy/University of Pennsylvania c/o The Wistar Institute 3601 Spruce Street Suite 242 19104 Philadelphia, Pennsylvania United States of America	email: david.r.curry@centerforvaccineethicsandpolicy.org mobile: +01 267 251 2305 tel: +01 267 251 2305
Cutts, Dr Felicity Consultant Self-employed Boulevard Louis Bernard La Londe les Maures France	email: felicity.cutts@lshtm.ac.uk tel: +33 677 292863
Dietterich, Ms Amy (Marion) Coordinator, GAVI CSO Constituency GAVI Civil Society Constituency CFP and Board Adviser Health Department International Federation of Red Cross and Red Crescent Societies Chemin des Crets 17 Petit-Saconnex 1211 Geneva Switzerland	email: amy.dietterich@ifrc.org mobile: +41 79 251 8017 tel: +41 22 730 4527 fax: +41 22 733 0395
Dochez, Dr Carine Programme Manager Epidemiology and Social Medicine Network for Education and Support in Immunisation (NESI), University of Antwerpen University of Antwerpen, Campus Drie Eiken Universiteitsplein 1 2610 Antwerpen Belgium	email: carine.dochez@ua.ac.be tel: +32 3 265 2891

Fine, Dr Paul London School of Hygiene and Tropical Medicine Keppel Street WC1E 7HT London United Kingdom of Great Britain and Northern Ireland	email: paul.fine@lshtm.ac.uk tel: +44 20 7927 2219
Furrer, Ms Eliane Senior Programme Officer, Policy & Market Shaping Policy and Performance GAVI Alliance Secretariat Chemin des Mines 2 1202 Geneva Switzerland	email: efurrer@gavialliance.org tel: +41 (22) 909 2958
Gandhi, Dr Gian Senior Health Specialist (Policy & Partnerships) UNICEF UNICEF House, 3 UN Plaza, Room 834 New York, NY 10017 United States of America	email: ggandhi@unicef.org tel: +1 212 326 7798
Gay, Ms Andrea Executive Director, Children's Health United Nations Foundation 1800 Massachusetts Avenue NW Suite 400 20036 Washington, DC United States of America	email: agay@unfoundation.org mobile: +1 202 459 1218 tel: +1 202 887 9040
Gellin, Dr Bruce Deputy Asst. Secretary for Health, National Vaccine Program Office National Vaccine Program Office Department of Health and Human Services 200 Independence Avenue SW Room 715-H 20201 Washington, DC United States of America	email: bruce.gellin@hhs.gov mobile: +1 202-841-6293 tel: +1 202-690-5566 fax: +1 202-690-4631
Gonçalves, Mr Paulo Partner The Boston Consulting Group, S.L. Avda. Diagonal 640-4 A 08017 Barcelona Spain	email: goncalves.paulo@bcg.com mobile: +34 629 045 265 tel: +34 93 363 47 18
Greco, Mr Michel Chair Measles Aerosol Product Development Group independent vaccine expert/chair Stop TB New Vaccines WG 41 quai Fulchiron c/o Parteurop 69005 Lyon France	email: grecomi@wanadoo.fr mobile: +33 6 07 31 75 43 tel: +33478426389
Harris, Ms Margaret Consultant 540 Route des Champees, Mijouet, 74250 Fillinges, Haute Savoie France	email: mharrisenator@gmail.com tel: +33 450 31 7445
Kandimaa Matterson, Mrs Anna-Carin Senior Programme Officer Policy Policy & Performance GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: amatterson@gavialliance.org mobile: +41 79 220 91 50 tel: +41 22 909 2949 fax: +41 22 909 6551

Keith, Ms Jacqueline Senior Advisor Strategy XXI Partners 1520 Spruce Street (#902) 19102 philadelphia, Pennsylvania United States of America	email: jkeith1@nyc.rr.com tel: +01 484 802 5366
Kelly, Mr Paul Director Country Support GAVI Alliance 2 chemin des Mines 1202 Geneva, Geneva Switzerland	email: pkelly@gavialliance.org mobile: +41 79 3008378 tel: +41 22 909 6534 fax: +41 22 909 6554
Khatib-Othman, Ms Hind Managing Director Country Programmes GAVI Secretariat 2 Chemin des Mines 1202 Geneva, Geneva Switzerland	email: hkhatib@gavialliance.org mobile: +41 79 745 2002 tel: +41 22 22 909 7133 fax: +41 22 909 6554
Kline, Mrs Sarah Independent Consultant Flat 3 61 Ramsden Road London United Kingdom of Great Britain and Northern Ireland	email: klinesarahe@gmail.com tel: +447786938008
Laforce, Dr F. Marc Clinical Professor of Medicine New York University School of Medicine Langone Medical Center 550 First Avenue OBv-A606 10016 New York United States of America	email: fmarclaforce@gmail.com mobile: +1-703-3433088 tel: +1-703-5342770
Landry, Dr Steve Deputy Director Global Health Program Bill & Melinda Gates Foundation 1432 Elliott Ave W 98119 Seattle, WA United States of America	email: steve.landry@gatesfoundation.org mobile: +1 206-619-9540 tel: +1 206-709-3164
Low, Professor Nicola Institute of Social and Preventive Medicine University of Bern Finkenhubelweg 11 3012 Bern Switzerland	email: low@ispm.unibe.ch tel: +41 30 631 3092
Madrid, Ms Yvette Program Officer Strategic Vaccine Supply, AVI PATH 207 Rte de Ferney Grand Saconnex 1218 Geneva Switzerland	email: ymadrid@path.org mobile: +41 79 126 47 53 tel: +41 22 747 10 54
Mahmood, Dr Kutub Scientific Director Vaccine Development Global Program PATH 2201 Westlake Avenue Suite 200 98121 Seattle, Washington United States of America	email: kmahmood@path.org mobile: +1-206-747-1062 tel: +1-206-285-3500 fax: +1-206-285-6619

Malvolti, Mr Stefano Director Vaccine Implementation GAVI Alliance 2 Chemin de Mines Geneva Switzerland	email: smalvolti@gavialliance.org tel: +41 79 8263126
Manevska, Ms Suzana Head Department for Communicable Diseases Sector for Preventive Health Care Ministry of Health 50th Division 6 1000 Skopje The former Yugoslav Republic of Macedonia	email: suzanamanevska@yahoo.co.uk tel: +38975402261
Martin, Dr Rebecca Center for Disease Control and Prevention 1600 Clifton Road Atlanta, GA 30329 Atlanta United States of America	email: rtm4@cdc.gov tel: 404-639-6232
Martinez, Dr Carla Senior Country Officer Country Programmes GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: cmartinez@gavialliance.org mobile: +41 79 745 4563 tel: +41 22 909 7146
McKinlay, Dr Mark Director Center for Vaccine Equity The Task Force for Global Health 325 Swanton Way 30030 Decatur, GA United States of America	email: mmckinlay@taskforce.org mobile: 6107155676 tel: 4046875617 fax: 4043710415
McKinney, Ms Susan Senior Advisor for Immunization Bureau for Global Health USAID 1300 Pennsylvania Ave, NW 20523 Washington, DC United States of America	email: smckinney@usaid.gov tel: +1 202 712 0614
Miller, Dr Mark Division Director DIEPS FIC/NIH 16 Center Drive, room 202 20892 Bethesda, MD United States of America	email: millemar@nih.gov tel: 301-496-0815
Mitchell, Ms Violaine Deputy Director Routine Immunization Bill & Melinda Gates Foundation 500 5th Ave N Seattle, WA United States of America	email: violaine.mitchell@gatesfoundation.org mobile: 206.6610819 tel: 206.709.3221
Moïsi, Dr Jennifer Program Leader, Meningitis and Pneumonia Agence de Médecine Préventive 13 chemin du Levant, Immeuble JB Say 01550 Ferney-Voltaire France	email: jmoisi@aamp.org tel: +33689069472

Nguyen, Ms Aurelia Policy Director Policy & Performance GAVI Alliance 2 ch. des mines 1202 Geneva Switzerland	email: anguyen@gavialliance.org tel: 41 (22) 909 6537
Nguyen Tran, Professor Hien (NITAG Chair) Director National Institute of Hygiene and Epidemiology 1 Yersin Street 10,000 Hanoi Viet Nam	email: ngtrhien@yahoo.com mobile: +84913352524 tel: 84-4-38212416 fax: 84-4-39723130
Ogden, Dr Ellyn USAID Worldwide Polio Eradication Coordinator USAID 1300 Pennsylvania Ave. NW Cube 5.07.052 20520 Washington DC United States of America	email: eogden@usaid.gov tel: +1 202 257 73 08
Palmier, Mrs Catherine Counsellor Canada Permanent Mission to the UN in Geneva 5 avenue de l'Ariana 1202 Geneva Switzerland	email: catherine.palmier@international.gc.ca tel: +41 22 919 9245 fax: +41 22 919 92 27
Pandak, Dr Carol Director PolioPlus Rotary International 1560 Sherman Ave. 60201 Evanston United States of America	email: carol.pandak@rotary.org tel: + 1 847 866 3304
Pariyo, Dr George Senior Manager, Monitoring Monitoring and Evaluation/Policy and Performance GAVI Alliance Chemin des Mines 2 1202 Geneva Switzerland	email: gpariyo@gavialliance.org mobile: +41 79 327 3470 tel: +41 22 909 6546
Pearman, Mr Jonathan Senior Advisor, Vaccines Country Programmes GAVI Alliance 2 chemin des Mines 1202 Geneva Switzerland	email: jpearman@gavialliance.org mobile: 41 79 331 6596 tel: 4122 909 2924
Preaud, Mr Jean-Marie Senior Technical Officer, Pharmaceutical operations ARVAC project Program for Appropriate Technology in Health PATH Bâtiment Avant-Centre 13 chemin du Levant 01210 Ferney-Voltaire France	email: jpreaud@path.org mobile: +33 473 790 437 tel: +33 450 280 835 fax: +33 450 280 407
Robert Juarez, Ms Maria Magdalena Director DoVC project Instituto de Salud Global de Barcelona Calle Roselló, 132, 7º 08036 Barcelona Spain	email: magda.robert@isglobal.org mobile: +41 794755506 tel: +41 794755506

Sanderson, Dr Colin Reader and health services research London School of Hygiene and Tropical Medicine (LSHTM) Keppel Street WC1E 7HT London United Kingdom of Great Britain and Northern Ireland	email: Colin.Sanderson@lshtm.ac.uk tel: +44 207 927 2231
Santosham, Professor Mathuram Professor Johns Hopkins University Department of International Health 621 N Washington St Baltimore MD 21205 21205 Baltimore United States of America	email: msantosh@jhsph.edu tel: +1 410 955 6931
Schmitt, Ms Sarah Consultant Route de Benex Dessus 1B 1197 Prangins Switzerland	email: schmitt_sl@hotmail.com mobile: +91 98 71 78 06 27 tel: +91 11 46 56 49 91
Schuchat, Mrs Anne Director National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention 1600 Clifton Road N.E. MS A-27 30333 Atlanta, Georgia United States of America	email: ACS1@CDC.GOV mobile: 404-538-9130 tel: 404-639-1540
Schwalbe, Ms Nina Managing Director - Policy and Performance Policy and Performance GAVI Alliance Secretariat Chemin des Mines 2 1202 Geneva Switzerland	email: nschwalbe@gavialliance.org mobile: +41793008212 tel: +41 (22) 909 6510
Scott, Ms Pippa Institute of Social and Preventive Medicine University of Bern Finkenhubelweg 11 3012 Bern Switzerland	email: pscott@ispm.unibe.ch tel: +41 (0)31 631 3555
Scott, Dr Robert S. Chairman The International PolioPlus Committee Rotary International 239 Queen Street K9A 1N4 Cobourg, Ontario Canada	email: bobscott@eagle.ca tel: 1 905 372 5078 (home)
Seale, Mr Andy Director, Advocacy and Communication PATH 207 Rte de Ferney Grand Saconnex 1218 Geneva Switzerland	email: aseale@path.org tel: +41 022 747 10 44
Shen, Dr Angela Senior Advisor Global Health Bureau US Agency for International Development 1300 Pennsylvania Ave, NW-Rm 3.7-106 20523 Washington, DC United States of America	email: ashen@usaid.gov mobile: 1-571-228-2058 tel: 1-202-712-0257

Shengelia, Dr Bakhuti Director Technical Support Country Programmes GAVI Alliance 2 Chemin des Mines 1202 Geneva Switzerland	email: BShengelia@gavialliance.org tel: +41 (79) 550 0722
Shirey, Ms Meredith Contracts Manager Chief UNICEF UNICEF Supply Division Oceanvej 10-12 2100 Copenhagen Denmark	email: mshirey@unicef.org tel: +45 3527 3033
Sosler, Dr Stephen Head - Regional Team Country Programmes GAVI Alliance 2 Chemin des Mines 1201 Geneva Switzerland	email: ssosler@gavialliance.org tel: +41 22 909 6591
Steffen, Dr Christoph Programme leader Agence de Médecine Préventive (AMP) 13 chemin du Levant 01210 Ferney Voltaire France	email: csteffen@aamp.org mobile: +33619664980 tel: +33 4 50 40 05 32
Thompson, Professor Kimberly Professor of Preventive Medicine and Global Health College of Medicine University of Central Florida Health Sciences Campus at Lake Nona 6850 Lake Nona Blvd. 32827-7408 Orlando, FL United States of America	email: kimt@kidrisk.org mobile: +1 617 680 2836 tel: +1 407 266 7037
Vandelaer, Dr Jos Chief, Immunization Health Section, Programme Division UNICEF 3 United Nations Plaza 10017 New York, NY United States of America	email: jvandelaer@unicef.org mobile: 1-917-214-5010 tel: +1-212-326-7612 fax: +1-212-824-6460
Wairagkar, Dr Niteen Senior Program Officer Global Health, Pneumonia Bill & Melinda Gates Foundation 500 5th Avenue North 98109 Seattle, WA United States of America	email: niteen.wairagkar@gatesfoundation.org mobile: +1 (206) 953-4376 tel: +1 (206) 770-1525 fax: 206-494-7039
Waldman, Dr Ron Presenter Professor Department of Global Health George Washington University 2175 K St. NW Suite 200 20037 Washington, DC United States of America	email: ronwaldman@gwu.edu tel: +1 202 374 2364

Wenger, Dr Jay Deputy Director Polio Program, Global Development Bill & Melinda Gates Foundation PO Box 23350 98102 Seattle, WA United States of America	email: kimberly.macnichols@gatesfoundation.org mobile: +1 206-673-6019 tel: +1 206-709-3450 fax: +1 206-494-7042
Werner, Ms Laurie Decade of Vaccines Collaboration/PATH 2201 Westlake Ave Suite 200 98133 Seattle, WA United States of America	email: lwerner@path.org tel: +1-206-351-6019
Wichmann, Dr Ole Director of Immunization Unit Robert Koch Institute DGZ-Ring 1 13086 Berlin Germany	email: WichmannO@rki.de tel: +49 30 18754 3468 fax: +49 30 18754 3514
Xeuatvongsa, Dr Anonh (NITAG Chair) Manager National Immunization Program Ministry of Health Simeuang Road Vientiane Lao People's Democratic Republic	email: anonhxeuat@gmail.com tel: +856 21 312352
de Chaisemartin, Mr Adrien Head of Performance Management Policy & Performance GAVI Alliance 2 chemin des Mines 1202 Geneva Switzerland	email: adechaisemartin@gavialliance.org tel: +41229092922 fax: +41229096551

Industry representatives

Abedi Kiasari, Dr Bahman Senior Advisor Razi Vaccine & Serum Research Institute Shaheed Beheshti St. Hesarak, Alborz Iran (Islamic Republic of)	email: int@rvsri.ir tel: +982634581009 fax: +982634581009
Azhari Zahri, Dr Adriansjah Quality Control Manager PT Bio Farma (Persero) Jl. Pasteur 28 40161 Bandung Indonesia	email: adriansjah@biofarma.co.id mobile: +628122375846 tel: +62222033755 fax: +62222041306
Benson, Dr Joan Executive Director International Organizations and Partnerships Merck & Co. Inc. 770 Sumneytown Pike P.O. Box 4 19486 West Point, PA United States of America	email: joan_benson@merck.com tel: +1 215 652 1815
Bigger, Dr Laetitia IFPMA Chemin Louis-Dunant 15 1211 Geneva Switzerland	email: L.Bigger@ifpma.org tel: +41223383251

Bodarky, Ms Lynn Sr. Director Pfizer Global Vaccines Pfizer 500 Arcola Road 19426 Collegeville, PA United States of America	email: lynn.bodarky@pfizer.com mobile: +1 908 392 7323 tel: +1 484 865 9659
Calmet, Dr Joel Senior Director, Vaccination Policy and Advocacy sanofi pasteur 2 avenue Pont Pasteur 69367 Lyon Cedex 7 France	email: joel.calmet@sanofipasteur.com tel: +33 4 37 37 70 06
Deschamps, Mrs Isabelle Director, Vaccination Policy & Advocacy Vaccination Policy & Advocacy sanofi pasteur 2, avenue Pont Pasteur 69367 Lyon Cedex 7 France	email: isabelle.deschamps@sanofipasteur.com mobile: +33 6 03 10 09 55 tel: +33 4 37 37 51 59
Hoa, Dr le Kim Vice Director, QC & QA, R&D/Head of QA Institute of Vaccine and Medical Biologicals 9 Pasteur Street Nha Trang Khanh Hoa Province Viet Nam	email: lekimhoa@dng.vnn.vn tel: +08 49 035 04198
Ibarra de Palacios, Dr Patricia Clinical Development & Medical Affairs Crucell Rehhagstrasse 79 3018 Bern Switzerland	email: patricia.ibarradepalacios@crucell.ch mobile: 41 (0)79 876 0834 tel: +41 (0)31 980 6583 fax: 41 (0)31 980 6772
Ibrahim, Dr Raed Shurky Chairman VACSERA 51 Wezaret El Zeraa St. Agouza Giza Egypt	email: Ceo@Vacsera.com mobile: +201223940940 tel: +20237611111 fax: +20237609177
Jadhav, Dr Suresh Executive Director Quality Assurance & Regulatory Affairs Serum Institute of India Ltd. 212/2, Hadapsar, 411028 Pune, Maharashtra India	email: ssj@seruminstitute.com mobile: +919823022248 tel: +912026602378 fax: +912026993945
Kuter, Dr Barb Executive Director Medical Affairs Merck Merck & Company 770 Sumneytown Pike WP-97A-345 19486-0004 West Point, PA United States of America	email: barbara_kuter@merck.com mobile: (610) 246-4050 tel: 215-652-4090 fax: (215) 993-1848
Leurquin, Mr Yves Head Vaccine Market Access Vaccine Business Division Takeda Thurgauerstrasse 130 8152 Zurich, Zurich Switzerland	email: yves.leurquin@takeda.com mobile: +41796428011 tel: +41796428011

Miranda, Mrs Eunice GlaxoSmithKline Vaccines Avenue Fleming 20 1300 Wavre Belgium	email: eunice.miranda@gskbio.com tel: +32 1085 8754
Modi, Dr Rajiv Managing Director Cadila Pharmaceuticals Ltd Cadila Corporate Campus, Sarkhej Dholka Road,Bhat 382210 Ahmedabad, Gujarat India	email: rimodi@cadilapharma.co.in tel: +912718225001
Pagliusi Uhe, Dr Sonia Executive Secretary Developing Countries Vaccine Manufacturers Network International chemin du Canal 5 1260 Nyon Switzerland	email: s.pagliusi@dcvmn.org tel: +41 22 363 9127
Poonawalla, Mr Adar Cyrus Member of Board of Governing Council, Trustee Serum Institute of India Research Foundation 212/2 Hadapsar Pune, Maharastra 411028 India	email: acp@seruminstitute.com tel: 91 20 2699 3939/3900
Popova, Dr Olga Govt. Affairs & Global Vaccine Policy Crucell Rehhagstrasse 79 3018 Bern Switzerland	email: olga.popova@crucell.com mobile: +41-79-5811582 tel: +41-31-9806316 fax: +41-79-9806472
Raw, Professor Isaias President of the Technical Scientific Committee, Instituto Butantan Butantan Foundation Av. Vital Brazil 1500 05503-900 São Paulo Brazil	email: iraw@butantan.gov.br tel: +55 11 2627 9367
Riedel, Mr Thomas Director, International Commercial Operations Novartis Vaccines and Diagnostics Emil-Von-Behring Strasse 76 35041 Marburg Germany	email: thomas.riedel@novartis.com tel: +496421393288
Soubeyrand, Dr Benoit Executive Director Medical Affairs Sanofi pasteur MSD 8 rue Jonas Salk 69007 Lyon France	email: skather@spmsd.com mobile: +33607582783 tel: +33437284032
Stohr, Dr Klaus Vice President Head, Global Vaccines Policy Novartis Vaccines and Diagnostics 350 Massachusetts Avenue 02139 Cambridge, Massachusetts United States of America	email: klaus.stohr@novartis.com tel: +1 617 871 7872
Suhardono, Dr Mahendra Production Director Bio Farma Jl. Pasteur 28 40161 Bandung Indonesia	email: mahendra@biofarma.co.id mobile: +62816624219 tel: +62 22 203 3755 fax: +62 222041306

Ueda, Dr Norihito Senior Director Vaccine Business Strategy Department Daiichi Sankyo 3-5-1, Nihonbashi Honcho, Chuo-ku 103-8426 Tokyo Japan	email: ueda.norihito.yv@daiichisankyo.co.jp mobile: +81 80 1310 8671 tel: +81 3 6225 1197

WHO staff

Aylward, Dr Raymond Bruce J. World Health Organization Polio, Emergencies and Country Collaboration	email: aylwardb@who.int mobile: +41 79 2173438 tel: +41 22 79 14419 fax: +41 22 791 1571
Banerjee, Dr Kaushik World Health Organization Immunization, Vaccines and Biologicals/EPI	email: banerjeek@who.int mobile: +41 79 500 65 31 tel: +41 22 791 32 93 fax: +41 22 791 41 93
Bentsi-Enchill, Dr Adwoa Desma World Health Organization Immunization, Vaccines and Biologicals/IVR	email: bentsienchilla@who.int tel: +41 22 79 11154
Bustreo, Dr Flavia World Health Organization Family, Women's and Children's Health Cluster	email: bustreof@who.int tel: +41 22 791 3309
Chang Blanc, Ms Diana World Health Organization Immunization, Vaccines and Biologicals/EPI	email: changblancd@who.int tel: 41 22 791 5070
Cherian, Dr Thomas World Health Organization Immunization, Vaccines and Biologicals/EPI	email: cheriant@who.int tel: +41 22 79 14460
Dellepiane de Rey Tolve, Dr Nora World Health Organization Immunization, Vaccines and Biologicals/QSS	email: dellepianen@who.int tel: +41 22 79 14788
Diorditsa, Dr Sergey Regional Office for the Western Pacific Expanded Programme on Immunization (EPI)	email: diorditsas@who.int tel: +63 2 528 9745
Duclos, Dr Philippe World Health Organization Immunization, Vaccines and Biologicals	email: duclosp@who.int tel: +41 22 79 14527
Fournier-Caruana, Dr Jacqueline World Health Organization Immunization, Vaccines and Biologicals/QSS	email: fourniercaruanaj@who.int mobile: +41794755519 tel: +41 22 79 12974
Freeman, Mr Andrew World Health Organization Polio Eradication Initiative	email: freemana@who.int tel: +41 22 791 1076
Gayer, Dr Michelle World Health Organization Emergency Risk Management and Humanitarian Response	email: gayerm@who.int mobile: +41 79 473 1386 tel: +41 22 79 13913
Goodman, Ms Tracey S. World Health Organization Immunization, Vaccines and Biologicals/EPI	email: goodmant@who.int tel: +41 22 791 2947
Henao Restrepo, Dr Ana Maria World Health Organization Immunization, Vaccines and Biologicals/Initiative for Vaccine Research	email: henaorestrepoa@who.int tel: +41 22 79 13402
Hombach, Dr Joachim Maria World Health Organization Immunization, Vaccines and Biologicals	email: hombachj@who.int tel: +41 22 79 14531

Hutubessy, Dr Raymond Christian W. World Health Organization Immunization, Vaccines and Biologicals/IVR	email: hutubessyr@who.int mobile: +41 79 79 39 582 tel: +41 22 79 13253
Jafari, Dr Hamid Syed World Health Organization Polio Eradication Initiative	email: jafarih@who.int tel: +41 22 791 2070
Kaddar, Mr Miloud World Health Organization Immunization, Vaccines and Biologicals/EPI	email: kaddarm@who.int tel: +41 22 79 11436
Kamara, Mrs Lidija World Health Organization Immunization, Vaccines and Biologicals	email: kamaral@who.int tel: +41 22 79 12145
Lam, Ms Jennifer World Health Organization Immunization, Vaccines and Biologicals	email: lamj@who.int tel: +41 079 6829143
Mala, Dr Peter World Health Organization Global Alert and Response/DCE	email: malap@who.int tel: +41 79 621 5286
Mantel, Dr Carsten Frithjof World Health Organization Immunization, Vaccines and Biologicals/EPI	email: mantelc@who.int mobile: +41 79 33 25480 tel: +41 22 79 13830
Martin, Dr Stephen World Health Organization HSE/Pandemic and Epidemic Diseases	email: martins@who.int tel: +41 22 79 11520
Mayers, Mrs Gillian F. World Health Organization Immunization, Vaccines and Biologicals/EPI	email: mayersg@who.int mobile: +41.79.249.3548 tel: +41 22 79 14674
Mir, Dr Tahir World Health Organization Polio Eradication (POL), EMRO	email: mirt@emro.who.int mobile: +201006019309 tel: +20222765255 fax: +20222765413
Mohsni, Dr Ezzeddine WHO Regional Office for the Eastern Mediterranean (EMRO) Communicable Diseases Division	email: mohsnie@emro.who.int mobile: +20 1005710284 tel: +202 2276 5267 fax: +202 22765414
Mosina, Dr Liudmila Regional Office for Europe (EURO) Vaccine Preventable Diseases and Immunization	email: mol@euro.who.int tel: +45 39 17 15 03
Murray, Ms Jillian World Health Organization Immunization, Vaccines and Biologicals	email: murrayji@who.int tel: +41 78 926 7835
Nishioka, Dr Sergio Andrade World Health Organization Immunization, Vaccines and Biologicals/QSS	email: nishiokas@who.int tel: +41 22 79 15579
Nshimirimana, Dr Déo Regional Office for Africa Immunization Vaccines Development	email: nshimirimanad@who.int tel: GPN 39203
Okwo-Bele, Dr Jean-Marie World Health Organization Immunization, Vaccines and Biologicals	email: okwobelej@who.int tel: +41 22 79 12779
Ott, Dr Joerdis Jennifer World Health Organization Immunization, Vaccines and Biologicals	email: ottj@who.int tel: +41 22 79 12805
Perry, Dr Robert World Health Organization Immunization, Vaccines and Biologicals	email: perryr@who.int mobile: +41 79 484 3195 tel: +41 22 791 3389

Pfeifer, Dr Dina Regional Office for Europe Vaccine Preventable Disease and Immunization (VPI)	email: dpf@euro.who.int mobile: +45 21 83 23 18 tel: +45 39 17 15 34
Popoola, Dr Victor World Health Organization Immunization, Vaccines and Biologicals	email: popoolav@who.int mobile: +41 77 940 9089 tel: +41 77 940 9089
Portnoy, Ms Allison World Health Organization Immunization, Vaccines and Biologicals	email: portnoya@who.int tel: +41 78 904 6764
Preziosi, Dr Marie-Pierre World Health Organization Immunization, Vaccines and Biologicals/IVR	email: preziosim@who.int mobile: +41 79 516 5978 tel: +41 22 79 13744
Riveros de Laurie, Ms Ximena World Health Organization Immunization, Vaccines and Biologicals/IVR/IMR	email: lauriex@who.int tel: +41 22 79 15082
Ruiz Matus, Dr Cuauhtemoc Regional Office for the Americas (AMRO) Immunization/Family and Community Health	email: ruizcuau@paho.org mobile: +1 202 701 8356 tel: +1 202 974 3945
Schmitz, Dr Julia World Health Organization Immunization, Vaccines and Biologicals/IVR	email: schmitzj@who.int tel: +41 22 79 13047
Schuster, Dr Melanie World Health Organization Immunization, Vaccines and Biologicals	email: Schusterm@who.int tel: +41 762404054
Scudamore, Mrs Caroline E. World Health Organization Immunization, Vaccines and Biologicals	email: scudamorec@who.int tel: +41 22 79 12337
Strebel, Dr Peter World Health Organization Immunization, Vaccines and Biologicals/EPI	email: strebelp@who.int tel: +41 22 791 1338
Tangermann, Dr Rudolf H. World Health Organization Polio Eradication Initiative/SAM	email: tangermannr@who.int tel: +41 22 79 14358
Teleb, Dr Nadia Regional Office for the Eastern Mediterranean Vaccine Preventable Diseases and Immunization	email: telebn@emro.who.int mobile: +201005710228 tel: +20222765252
Thapa, Dr Arun Regional Office for South-East Asia SE/IVD Immunization and Vaccine Development	email: thapaa@who.int tel: +911123370804
Thinley, Dr Sangay Regional Office for South-East Asia Family Health and Research	email: thinleys@who.int mobile: +91 9810504671 tel: +91 11 43040320
Wood, Dr David World Health Organization Immunization, Vaccines and Biologicals/QSS	email: woodd@who.int tel: +41 22 791 4050 fax: +41 22 791 4971
Zaffran, Mr Michel Jose World Health Organization Immunization, Vaccines and Biologicals	email: zaffranm@who.int mobile: +41 79 210 4501 tel: +41 22 791 5409
Zuber, Dr Patrick Louis F. World Health Organization Immunization, Vaccines and Biologicals/QSS	email: zuberp@who.int tel: +41 22 79 11521

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Meeting of the Strategic Advisory Group of Experts on immunization, April 2012 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 10–12 April 2012 in Geneva, Switzerland.[2] This report provides a summary of the discussions, conclusions and recommendations.

Report from the Department of Immunization, Vaccines and Biologicals

Building on input from all 6 WHO Regional Offices, the Director of the Department of Immunization, Vaccines and Biologicals presented a global report on immunization. The report included an update on: the Decade of Vaccines (DoV), Global Vaccine Action Plan (GVAP); Region-specific challenges and activities; progress towards measles elimination goals; World Immunization Week; the establishment of a cholera vaccine stockpile; the roll out of the Global Vaccine Safety Blueprint; implementation research priority setting; and SAGE processes and future agenda items.

The proposed GVAP-related resolution to be submitted to the World Health Assembly (WHA) recommends that member states apply the vision and strategies according to their epidemiologic situation, allocate adequate resources and report annually to Regional Committees on progress, constraints and actions taken to overcome challenges. It requests the Director-General to foster alignment and coordination of global immunization

[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 10–12 April 2012 together with summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2012/april/en/index.html; accessed in May 2012.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2012 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 10 au 12 avril 2012 à Genève (Suisse).[2] Le présent rapport fournit un résumé des discussions, ainsi que des conclusions et des recommandations auxquelles il est parvenu.

Rapport du Département Vaccination, vaccins et produits biologiques

En s'appuyant sur les contributions des 6 bureaux régionaux de l'OMS, le Directeur du Département Vaccination, vaccins et produits biologiques de l'OMS a présenté un rapport mondial sur la vaccination. Ce rapport comprenait un point sur les sujets suivants: plan d'action mondial pour les vaccins (GVAP) de la Décennie de la vaccination (DoV); difficultés et activités spécifiques aux régions; progrès vers les buts en matière d'élimination de la rougeole; Semaine mondiale de la vaccination; constitution d'un stock de vaccins contre la choléra; lancement du Plan pour la sécurité vaccinale dans le monde; fixation des priorités pour la recherche; et opérations et points à l'ordre du jour du SAGE.

Le projet de résolution liée au GVAP qui sera soumis à l'Assemblée mondiale de la Santé (AMS) recommande aux Etats Membres d'appliquer la vision et les stratégies en fonction de leur situation épidémiologique, d'affecter des ressources suffisantes et de faire rapport chaque année aux comités régionaux sur les progrès accomplis, les contraintes et les mesures prises pour surmonter les difficultés. Il prie le Directeur général de favoriser l'harmonisation et la coordination des efforts

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

[2] La série complète des communications et documents de travail de la réunion du SAGE tenue du 10 au 12 avril 2012, ainsi que les résumés des déclarations d'intérêts fournies par les membres de ce groupe sont disponibles à l'adresse: http://www.who.int/immunization/sage/meetings/2012/april/en/index.html; documents consultés en mai 2012.

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efforts, identify resources for technical support and monitoring of impact, and report every year to the WHA using the proposed accountability framework after a SAGE review of global progress.

Four ongoing areas of work will sustain the momentum of the Decade of Vaccines after the WHA: (i) the development of companion documents, including tools and guidance for translation and implementation of GVAP by different stakeholders and the countries to be published by December 2012 as a journal supplement; (ii) the development of the monitoring and evaluation framework and the finalization of indicators with mention of data sources, targets, baseline and detailed monitoring process; (iii) the development of detailed engagement plans for the spearheading agencies (WHO, UNICEF, Bill &Melinda Gates Foundation, GAVI Alliance, and the US National Institutes of Health) and a vigorous outreach strategy to attract other support and funding commitments for GVAP roll-out; (iv) a DoV communications strategy.

SAGE noted that the DoV presented an outstanding opportunity to expand immunization benefits and highlighted the central role of regional and national technical advisory groups on immunization for the implementation of GVAP. Country ownership being fundamental, SAGE urged WHO, GAVI and partners to work to generate and support country leadership and to make sure that national programmes are fully driven by the countries themselves with detailed country planning and budgeting. SAGE noted the necessary emphasis on routine immunization and equity and welcomed UNICEF's move to more closely monitor progress on reducing the equity gap using some of the established indicators. SAGE requested consideration of the establishment of a SAGE standing working group to monitor GVAP implementation.

Only 2 Regions are on track to achieve measles elimination, the Region of the Americas and the Western Pacific Region, and despite considerable effort, other Regions are unlikely to meet their goals. Complacency and vaccine hesitancy, weak infrastructure and limited resources threatened progress towards elimination, with a funding gap of US$ 32 million for the implementation of supplementary immunization activities in 2012. In addition to campaigns, routine immunization, surveillance, outbreak response and operational research all required strengthening. SAGE reiterated that elimination of measles and rubella was more cost-effective than disease control. SAGE noted that some 60 countries still needed to integrate rubella into routine immunization and stressed that there was a need to match high quality campaigns with strong routine vaccination systems. SAGE was concerned about the European situation and the need to identify and target previously unimmunized adult populations. Excellent opportunities for bolstering efforts are provided through the renewed commitment of spearheading partners, the signing of a global measles-rubella strategic plan, GAVI support for measles-rubella vaccination campaigns for under-15 year-olds in 50 countries introducing rubella vaccine, and a potential

mondiaux dans le domaine de la vaccination, de déterminer les moyens nécessaires au soutien technique et au suivi de l'impact et de faire rapport chaque année à l'AMS en utilisant le cadre de responsabilisation proposé, rapport qui sera précédé d'un examen par le SAGE des progrès à l'échelle mondiale.

Les travaux en cours dans les 4 domaines suivants soutiendront la dynamique de la Décennie de la vaccination après l'AMS: 1) élaboration de documents d'accompagnement, dont des outils et des orientations pour la transposition et la mise en œuvre du GVAP par les différentes parties prenantes et les pays, devant être publiés d'ici décembre 2012 sous forme de supplément au journal; 2) mise au point du cadre de suivi et d'évaluation et finalisation des indicateurs avec mention des sources de données, des cibles, des références et des procédures de suivi détaillées; 3) mise au point de plans d'engagement détaillés pour les institutions directrices (OMS, UNICEF, Fondation Bill & Melinda Gates, Alliance GAVI et National Institute of Health des Etats-Unis), d'une stratégie dynamique reposant sur des actions de proximité pour attirer l'aide et les engagements en faveur du lancement du GVAP et, 4) d'une stratégie de communication pour la DoV.

Le SAGE a pris note de l'occasion extraordinaire que représente la DoV pour étendre les bénéfices de la vaccination et a souligné le rôle central des groupes consultatifs techniques régionaux et nationaux sur la vaccination pour la mise en œuvre du GVAP. La prise en main par les pays étant cruciale, le SAGE a invité instamment l'OMS, l'Alliance GAVI et leurs partenaires à œuvrer pour provoquer et appuyer une prise en main par les pays et s'assurer que les programmes nationaux sont totalement pilotés par les pays eux-mêmes, avec une planification et un budget détaillés de leur part. Il a aussi pris note de l'importance à donner nécessairement à la vaccination systématique et à l'équité et s'est félicité de la démarche de l'UNICEF pour suivre plus étroitement les progrès vers la réduction des insuffisances en matière d'équité à l'aide de certains des indicateurs établis. Il a également demandé que soit envisagée la mise en place d'un groupe de travail permanent pour suivre la mise en œuvre du GVAP.

Seules 2 Régions sont en voie de parvenir à éliminer la rougeole (à savoir la Région des Amériques et celle du Pacifique occidental) et, malgré des efforts considérables, il est peu probable que les autres régions atteignent les buts qui leur sont fixés. L'excès de confiance et les réticences face à la vaccination, la faiblesse des infrastructures et la rareté des ressources ont menacé les progrès vers l'élimination, avec des besoins financiers restant à combler de 32 US$ millions pour les activités de vaccination supplémentaires en 2012. En plus des campagnes, l'ensemble des activités de vaccination systématique, de surveillance, de riposte aux flambées et de recherche opérationnelle doivent être renforcées. Le SAGE a rappelé que l'élimination de la rougeole et de la rubéole était d'un meilleur rapport coût/efficacité que la lutte contre ces maladies. Il a pris note du fait que quelque 60 pays doivent encore intégrer le vaccin contre la rubéole à leur calendrier de vaccination systématique et a souligné que la solidité des systèmes de vaccination systématique devait être à la hauteur de la qualité des campagnes. Le SAGE s'est dit préoccupé par la situation européenne et par la nécessité d'identifier et de cibler les populations adultes jusqu'à présent non vaccinées. L'engagement renouvelé des partenaires principaux, à travers la signature d'un plan stratégique mondial contre la rougeole et la rubéole, le financement par l'Alliance GAVI de campagnes de vaccination contre ces

GAVI specific allocation to measles activities. The measles-rubella SAGE working group has begun reviewing progress towards 2015 global measles control targets and regional measles and rubella elimination goals, and will provide regular updates to SAGE from November 2012.

maladies chez les <15 ans dans 50 pays introduisant le vaccin antirubéoleux et l'affectation potentielle par l'Alliance d'une aide spécifique en faveur des activités contre la rougeole, ont fourni de magnifiques occasions de renforcer les efforts. Le groupe de travail du SAGE sur la rougeole et la rubéole a commencé à examiner les progrès vers les cibles mondiales à l'horizon 2015 en matière de lutte contre la rougeole et vers les buts régionaux concernant l'élimination des 2 maladies et fera régulièrement le point sur la situation à l'intention du SAGE à partir de novembre 2012.

The first World Immunization Week was celebrated in the 6 WHO Regions during 21–27 April with expected participation by >180 countries, providing a unique communication opportunity.

La première Semaine mondiale de la vaccination a été célébrée dans les 6 Régions de l'OMS du 21 au 27 avril, avec la participation de >180 pays, fournissant une occasion unique de communiquer.

SAGE warned that disruption of vaccine supplies threatened success, and highlighted the importance of better procurement strategies at national and regional level, and improved market shaping exercises. SAGE stressed the importance of WHO's ongoing work with national regulatory authorities (NRA) to improve overall regulatory oversight of vaccine registration and safety, and to reduce the possibility of prequalification delisting because of NRA failure, with particular focus on emerging vaccine manufacturers.

Le SAGE a averti qu'un problème au niveau des approvisionnements en vaccins menacerait le succès des efforts et a souligné l'importance de meilleures stratégies d'achat au niveau national et régional et d'interventions plus efficaces pour façonner le marché. Il a mis en avant le rôle des travaux en cours de l'OMS avec les autorités nationales de réglementation (ANR) pour améliorer la supervision de l'homologation et de la sécurité des vaccins et réduire les risques de retrait de certains vaccins de la liste de préqualification du fait d'un échec auprès des ANR, en particulier dans le cas des fabricants de vaccins émergeants.

An initial consultation in September 2011 concluded that a short-term emergency stock of at least 2 million cholera vaccine doses should be established within the following 12 months, and WHO has begun work on setting up an oral cholera vaccine stockpile. A starter fund is needed and it is hoped that GAVI will contribute. A technical consultation took place in April 2012 to: review criteria for determining when to vaccinate against cholera in outbreak situations and how best to target vaccination; determine the optimal size of a cholera vaccine stockpile; and review how to manage the transition from short term cholera outbreak response activities to the long term strategy for endemic and epidemic control.

A l'issue d'une consultation initiale, menée en septembre 2011, il a été conclu qu'un stock d'urgence à court terme de 2 millions de doses de vaccin anticholérique au moins devrait être constitué dans les 12 mois suivant et l'OMS a commencé à rassembler un stock de vaccin anticholérique oral. Un financement de départ est nécessaire et on espère que l'Alliance GAVI y contribuera. Une consultation technique a eu lieu en avril 2012 afin: d'examiner les critères permettant de déterminer quand vacciner contre le choléra dans les situations de flambée et des moyens de cibler au mieux les activités de vaccination; de définir la taille optimale du stock de vaccins anticholériques; et d'étudier les modalités de transition entre les activités à court terme de riposte contre les flambées de choléra et les stratégies à long terme de lutte contre la maladie à l'état endémique et contre les épidémies.

Implementation research is an important component of WHO's work. To further strengthen this area of work the Quantitative Immunization and Vaccines Related Research Advisory Committee (QUIVER) has expanded its terms of reference and membership to provide advice on implementation research and changed its name to Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC). A time-limited working group of technical experts will assist in developing the implementation research agenda prior to discussion by IVIR-AC. Such a research agenda will ultimately feed into the technical and policy review functions of IVIR-AC and SAGE itself to strengthen WHO's ability to develop evidence-based policies. WHO is proposing to develop a prioritized global research agenda to inform partner organizations equipped to conduct or sponsor this type of research. WHO will provide a platform for researchers to share results and use findings to formulate vaccine policies and practices, coordinate efforts to build scientific consensus and develop best practices and guidelines for research; and in some cases, mobilize the necessary resources to conduct or initiate research activities. SAGE applauded the focus

La recherche sur la mise en œuvre des programmes est une composante importante de l'activité de l'OMS. Pour renforcer encore ce domaine de travail, le Comité consultatif sur la Vaccination quantitative et la Recherche liée aux Vaccins (QUIVER) a élargi son mandat et s'est adjoint des membres supplémentaires afin de délivrer des conseils en matière de recherche sur la mise en œuvre. Il a également changé de nom pour devenir le Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC). Un groupe de travail constitué d'experts techniques ayant un mandat limité dans le temps aidera à l'élaboration d'un programme pour la recherche sur la mise en œuvre avant sa discussion par l'IVIR-AC. Ce programme de recherche nourrira finalement les capacités d'examen technique et politique de l'IVIR-AC et du SAGE lui-même pour renforcer la capacité de l'OMS à formuler des politiques reposant sur des éléments factuels. L'OMS propose d'élaborer un programme mondial de recherche, avec des priorités bien définies, pour informer les organisations partenaires dotées des moyens de mener ou de parrainer le type de recherche correspondant. Elle offrira aux chercheurs une plate-forme leur permettant de partager leurs résultats et de les utiliser pour définir des politiques et des pratiques vaccinales, de coordonner les efforts pour parvenir à un consensus scientifique, de mettre au point les meilleures

on implementation research and stressed the importance of WHO's major coordinating role in ensuring alignment of research partners.

A SAGE working group dealing with vaccine hesitancy has been established with a wide range of expertise and it will work over the next 12 months to generate recommendations on addressing vaccine hesitancy and its determinants.

SAGE reiterated its concern that many countries receiving polio eradication funding are now reliant on these funds for their broader immunization programmes. SAGE noted that recent funding cuts in some countries may threaten the overall integrity of the immunization programme. SAGE highlighted the need for additional resources to address the critical and expanding areas of immunization programme management, supply chains, surveillance, implementation research, pharmacovigilance and communication.

Report from the Global Advisory Committee on Vaccine Safety

SAGE was presented with a report of the December 2011 GACVS meeting.[3] SAGE noted that the work on vaccine safety during pregnancy and lactation had been initiated and that the Global Vaccine Safety Initiative had been launched as the implementation mechanism of the Global Vaccine Safety Blueprint. A planning group composed of representatives from interested organizations has been established to steer the initiative, which is administered by WHO. SAGE highlighted the importance of enhancing vaccine safety monitoring in all countries.

Polio eradication

SAGE was updated on the status of the Global Polio Eradication Initiative (GPEI) Global Emergency Action Plan together with updates from senior government representatives on the national emergency action plans developed in Afghanistan, Nigeria and Pakistan. A report was presented on the impact of the current funding gap on implementation of the global plan, and a prioritization process for funding activities. SAGE also received a report from the SAGE polio working group regarding a switch from trivalent oral poliovirus vaccine (tOPV) to bivalent OPV (bOPV types 1 and 3) and related policy and technical issues, and proposed recommendations for consideration by SAGE.

SAGE was seriously alarmed by the polio eradication funding gap for 2012–2013 which has already led to cancellation of previously planned activities, particularly given the declaration of the WHO Executive Board that completing polio eradication was a public health emergency of the highest priority, and the heightened po-

pratiques et des lignes directrices pour la recherche et, dans certains cas, de mobiliser les ressources nécessaires pour conduire ou mettre en route les activités de recherche. Le SAGE s'est félicité de l'attention accordée à la recherche sur la mise en œuvre et a souligné l'importance du rôle de coordonnateur principal qu'exerce l'OMS dans la recherche d'une collaboration entre les partenaires dans la recherche.

Un groupe de travail du SAGE chargé de la réticence face à la vaccination a été mis en place avec une large gamme de compétences. Il œuvrera au cours des 12 prochains mois à l'élaboration de recommandations pour répondre à cette réticence et à ses déterminants.

Le SAGE a réaffirmé sa préoccupation en constatant que de nombreux pays qui bénéficiaient d'un financement pour l'éradication de la poliomyélite, sont maintenant dépendants de ces fonds pour leurs programmes de vaccination plus larges. Il a pris note de la menace que font peser les coupes budgétaires pratiquées dans certains pays sur l'intégrité globale du programme de vaccination. Il insiste sur la nécessité de ressources supplémentaires pour répondre aux besoins des domaines d'activité critiques ou en développement que sont l'administration des programmes de vaccination, les chaînes d'approvisionnement, la surveillance, la recherche sur la mise en œuvre, la pharmacovigilance et la communication.

Rapport du Comité consultatif mondial de la sécurité vaccinale

Le SAGE s'est vu présenter un rapport de la réunion de décembre 2011 du GACVS.[3] Il a noté avec intérêt que le travail sur la sécurité vaccinale pendant la grossesse et l'allaitement avait été mis en route et que l'Initiative mondiale pour la sécurité vaccinale avait été lancée en tant que mécanisme de mise en œuvre du Plan pour la sécurité vaccinale dans le monde. Un groupe de planification composé de représentants d'organisations intéressées a été mis en place pour piloter l'Initiative, administrée par l'OMS. Le SAGE a insisté sur l'importance d'une amélioration de la surveillance de la sécurité des vaccins dans tous les pays.

Eradication de la poliomyélite

Le SAGE a été informé de l'avancement du Plan d'action d'urgence de l'initiative mondiale pour l'éradication de la poliomyélite (GPEI), ainsi que des faits nouveaux concernant les plans d'urgence nationaux mis sur pied en Afghanistan, au Nigéria et au Pakistan, par les responsables des représentations des gouvernements. Un rapport sur l'impact des besoins financiers non satisfaits actuellement sur la mise en œuvre du plan mondial et un processus d'affectation de priorités pour les activités de financement ont été présentés. Le SAGE a également reçu de la part de son groupe de travail sur la poliomyélite un rapport concernant le passage du vaccin antipoliomyélitique oral trivalent (VPOt) au VPO bivalent (VPOb des types 1 et 3), la politique et les questions techniques associées et des propositions de recommandations qu'il devra examiner.

Le SAGE s'est fortement alarmé du déficit de financement pour l'éradication de la poliomyélite sur la période 2012-2013, qui a déjà conduit à annuler des activités planifiées antérieurement, au vu notamment de la déclaration du Conseil exécutif de l'OMS affirmant que l'achèvement de l'éradication de cette maladie était une urgence de santé publique extrêmement prioritaire et

[3] See No. 87, 2012, pp. 53–60.

[3] Voir Nº 87, 2012, pp. 53-60.

litical commitment of the Governments of Afghanistan, Nigeria and Pakistan. Noting that the number of polio cases and polio affected countries is now at the lowest level ever recorded, it would be tragic and an unacceptable waste of the massive investment already made in polio eradication if this opportunity to finally eradicate polio were not grasped. SAGE emphasized that the global initiative was at serious risk of failure because adequate resources are not available to cover essential activities. While accepting the logic of the prioritization process due to lack of funding, SAGE considered any reduction in essential activities to be unacceptable and a major threat to the overall global vaccine programme. SAGE urged all governments and partners to act immediately to fill the funding gap in order to ensure the success of global polio eradication.

de l'engagement politique à un niveau accru des gouvernements de l'Afghanistan, du Nigéria et du Pakistan. Sachant que le nombre de cas de poliomyélite et de pays infectés par cette maladie sont au niveau le plus bas jamais atteint, ce serait tragique et un gaspillage inacceptable des investissements massifs déjà consentis que de laisser passer l'occasion d'en finir avec l'éradication de la poliomyélite. Le SAGE a insisté sur le fait que l'Initiative mondiale était sérieusement menacée d'échec en raison de l'indisponibilité de ressources suffisantes pour couvrir ses activités essentielles. Tout en acceptant la logique de l'affectation de priorités aux interventions en raison du manque de financement, le SAGE a considéré toute réduction de ses activités essentielles comme totalement inacceptable et comme une menace majeure pour le programme mondial de vaccination dans son ensemble. Il a invité instamment tous les gouvernements et les partenaires à agir immédiatement pour combler ce déficit de financement afin d'assurer le succès de l'éradication de la poliomyélite à l'échelle mondiale.

SAGE welcomed the Global Emergency Action Plan and noted definite progress in the development and implementation of national plans in Afghanistan, Nigeria and Pakistan – including operational strategies, innovations and quality assurance measures – aimed at overcoming challenges associated with chronically missed children, and well-articulated processes for accountability at all levels. SAGE emphasized that close monitoring of implementation is essential in the coming months to ensure that the plans become reality and that the maximum impact is achieved. SAGE welcomed the synergy between polio eradication activities and strengthening of routine immunization. While the Afghanistan plan articulates this connection well, for both Nigeria and Pakistan SAGE considered that the linkages and governance mechanisms could be more clearly delineated. SAGE acknowledged GAVI inputs in key countries for health systems strengthening with particular emphasis on routine immunization, and potential support for injectable polio vaccine for the polio endgame, and urged that the Global Emergency Action Plan outline mechanisms to realize the synergies between polio eradication and strengthening of routine immunization.

Le SAGE a accueilli favorablement le Plan d'action mondial d'urgence et pris note des progrès tangibles dans la mise au point et l'application des plans nationaux en Afghanistan, au Nigéria et au Pakistan, et notamment des stratégies opérationnelles, des innovations et des mesures d'assurance de la qualité – destinées à surmonter les défis que représentent les enfants régulièrement laissés de côté – ainsi que de procédures de responsabilisation bien huilées à tous les niveaux. Le SAGE souligne qu'un suivi étroit de la mise en œuvre est indispensable dans les mois à venir pour s'assurer que les plans deviennent réalité et que l'impact obtenu est maximum. Il s'est félicité de la synergie entre les activités d'éradication de la poliomyélite et le renforcement de la vaccination systématique. Si le plan afghan fait bien apparaître ces connexions, le SAGE a eu l'impression que les liens et les mécanismes de gouvernance pouvaient être définis plus clairement dans les plans du Nigéria et du Pakistan. Le SAGE a reconnu la contribution de l'Alliance GAVI au renforcement des systèmes de santé et tout particulièrement de la vaccination systématique, dans un certain nombre de pays clés, ainsi que son soutien potentiel en faveur du vaccin antipoliomyélitique injectable pour le dernier assaut contre la poliomyélite. Il a également insisté pour que le Plan d'action mondial d'urgence définisse, dans leurs grandes lignes, des mécanismes pour dégager des synergies entre l'éradication de la poliomyélite et le renforcement de la vaccination systématique.

Wild polio virus type 2 was eliminated in 1999 but the continued use of tOPV contributes to ongoing type 2 vaccine-associated paralytic poliomyelitis and vaccine-derived poliovirus outbreaks (cVDPV2). The SAGE working group on polio recommended a switch from tOPV to bOPV to remove the threat of cVDPV2, and to accelerate the elimination of wild polio types 1 and 3 as bOPV is a more immunogenic vaccine. The working group stressed that prior to OPV2 cessation the following conditions must be met: ongoing transmission of cVDPV2 in Nigeria stopped; no persistent type 2 outbreaks of cVDPV for a minimum of one year; surveillance for timely cVDPV detection and capacity for prompt control of new cVDPV2 emergences in place; adequate supplies of bOPV and an affordable inactivated poliovirus vaccine (IPV) vaccine available, and the stockpile of monovalent OPV type-2 (mOPV2) in place; and an international agreement to stop delivery of tOPV formulations globally. SAGE reaffirmed its position that WHO should pursue a pre-eradication switch

Le poliovirus sauvage de type 2 a été éliminé en 1999, mais la poursuite de l'utilisation du VPOt participe à la survenue de poliomyélite paralytique et à des flambées de poliomyélite dérivée dues au type 2 (PVDV2c). Le Groupe de travail du SAGE sur la poliomyélite a préconisé le passage du VPOt au VPOb afin d'éliminer la menace de PVDV2c et d'accélérer l'élimination des poliovirus sauvages de types 1 et 3 dans la mesure où le VPOb est un vaccin plus immunogène. Il a insisté sur la nécessité, avant de stopper l'utilisation du VPO2, de réunir les conditions suivantes: arrêt de la transmission en cours des PVDV2c au Nigéria, absence de flambée persistante de PVDVc de type 2 pendant au moins 1 an, surveillance permettant la détection en temps utile des PVDVc, présence d'une capacité d'endiguement rapide des émergences de nouveaux PVDV2c, disponibilité d'approvisionnements suffisants en VPOb et en vaccins antipoliomyélitiques inactivés (VPI) abordables et existence d'un stock de VPO monovalent de type 2 (VPOm2) et d'un accord international pour arrêter la délivrance des formulations de type VPOt à l'échelle mondiale. Le SAGE a réaffirmé sa position selon laquelle l'OMS devait organiser, avant l'éradication, un

from tOPV to bOPV for routine immunization in a globally synchronized manner that minimized the risk of cVDPV2 emergence.

SAGE noted that while the risk of cVDPV emergence following OPV2 cessation is likely to be very low it cannot be ruled out and the use of IPV would mitigate the consequences of an emergence. SAGE noted the unaffordability of the current intramuscular (IM) IPV for many low and middle income countries. SAGE stressed the importance of having a low cost IPV option that is affordable for developing countries so that all OPV-using countries could introduce 1 dose of IPV in their vaccination schedule in advance of OPV2 cessation, in order to boost mucosal immunity prior to a tOPV→bOPV switch and to provide a foundation for rapidly establishing broad population immunity against type 2 in the event of emergence of cVDPV2 following OPV2 cessation. SAGE noted that the development of an affordable intramuscular (IM) or intradermal (ID) IPV at a cost of less than US$ 0.50 cents should be prioritized, and that studies of a fractional intradermal IPV dose appeared very promising. However, in many countries IM is expected to be preferred to ID because of operational challenges associated with ID injections and lack of registration of a fractional IPV dose. 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. SAGE also recommended that WHO/GPEI continue to work with GAVI to ensure financing for any GAVI-eligible countries wishing to introduce a low-cost IPV option as part of their vaccination schedule. SAGE recognized that some countries, particularly those with weak immunization systems and particularly poor coverage, may opt to switch from tOPV to bOPV without introducing IPV but that this approach would lead to an increase in population susceptibility to poliovirus type 2. Thus the stockpile of mOPV2 must be available for use in the event of a cVDPV2 outbreak following OPV2 cessation.

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. 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. 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. SAGE requested that WHO/GPEI draft a 'GPEI Strategic Plan/Budget for 2013-2018' by November 2012 that incorporates OPV2 cessation and eventual bOPV cessa-

passage du VPOt au VPOb, synchronisé à l'échelle mondiale, de manière à minimiser le risque d'émergence de PVDV2c.

Le SAGE a noté que si le risque d'émergence de PVDVc après l'arrêt du VPO2 était probablement très faible, il ne pouvait être exclu et que l'utilisation de VPI devrait atténuer les conséquences d'une telle émergence. Il a pris note de l'inaccessibilité économique du VPI par voie intramusculaire (IM) actuel pour de nombreux pays revenu faible ou intermédiaire. Il a insisté sur l'importance de disposer d'une version à faible coût du VPI, à la portée des pays en développement, de manière à ce que tous les pays utilisant le VPO puissent introduire 1 dose de VPI dans leur calendrier de vaccination préalablement à l'arrêt du VPO afin de stimuler l'immunité mucosale avant le passage du VPOt au VPOb et de fournir une base à la constitution rapide d'une large immunité contre le poliovirus de type 2 parmi la population dans la perspective de l'émergence de PVDV2c après l'arrêt du VPO2. Le SAGE a enregistré que la priorité devait être donnée à la mise au point d'un VPI par voie intramusculaire (IM) ou intradermique (ID) coûtant <0,50 US$ cents et que les études portant sur une dose fractionnaire de VPI intradermique semblaient très prometteuses. Néanmoins, on s'attend à ce que, dans beaucoup de pays, les formulations IM soient préférées aux formulations ID en raison des difficultés opérationnelles associées aux injections ID et du manque d'homologation du VPI sous forme de dose fractionnaire. Le SAGE a recommandé que l'OMS et la GPEI collaborent avec les fabricants de vaccins pour développer les 2 options et avec les autorités de réglementation pour lancer immédiatement une procédure d'examen accéléré pour le VPI ID, afin de s'assurer de la disponibilité d'une version du VPI à faible coût d'ici un an. Le SAGE a également recommandé que l'OMS et la GPEI continuent de collaborer avec l'Alliance GAVI pour garantir le financement de tout pays susceptible de bénéficier de son aide et souhaitant introduire une version du VPI à faible coût dans son calendrier de vaccination. Il a aussi reconnu que certains pays, notamment ceux dont les systèmes de vaccination sont peu robustes et dont la couverture vaccinale est particulièrement insuffisante, pourraient opter pour un passage du VPOt au VPOb sans introduction du VPI, mais que cette façon de procéder entraînerait une plus grande susceptibilité de leur population au poliovirus de type 2. Il faut donc que le stock de VPO2m soit disponible pour servir en cas de flambée de PVDV2c se produisant après l'arrêt du VPO2.

Le SAGE a recommandé de fixer un calendrier serré pour l'achèvement des différentes étapes nécessaires au passage du VPOt au VPOb. De même, des plans d'urgence doivent être en place pour la mise au point d'un VPI à faible coût et pour son introduction par les pays qui choisissent d'appliquer cette stratégie. Pour les pays qui prévoient d'introduire le VPI, y compris sa version à faible coût, une planification similaire doit s'effectuer. Le SAGE a préconisé que l'OMS et la GPEI poursuivent leur collaboration avec l'Agence GAVI pour s'assurer de la disponibilité dans les 18 mois d'un financement pour tout pays susceptible de bénéficier de l'aide de l'Alliance et souhaitant introduire un VPI à faible coût dans sa stratégie de transition entre les vaccins. Il a prié l'OMS et la GPEI d'entreprendre des consultations plus approfondies avec les pays et les régions pour rassembler des éléments sur les incidences politiques et programmatiques de l'introduction d'une dose de VPI (IM ou ID) dans le cadre de la stratégie de passage du VPOt au VPOb et faciliter la prise de décisions individuelles par les pays. Le SAGE a prié l'OMS et la GPEI de rédiger d'ici à novembre 2012 un projet de plan stratégique/budget de la GPEI pour la période

tion, 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.

Seasonal influenza vaccine

The working group on influenza vaccines and immunization presented SAGE with a comprehensive review of the influenza disease burden, vaccine performance, and safety in populations of all ages and at-risk groups, incorporating available data from low and middle-income country settings. Based on the review, the working group proposed specific recommendations with the objective of revising the 2005 WHO position paper on influenza vaccines.

SAGE recommended pregnant women as the most important risk group for inactivated seasonal influenza vaccination. Other risk groups to be considered, in no specific priority order were: health-care workers, children aged 6–59 months, the elderly and those with high-risk conditions. SAGE recommended that countries with existing influenza vaccination programmes targeting any of these groups should continue to do so and should incorporate immunization of pregnant women into such programmes. Countries should decide which other risk groups to prioritize for vaccination based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations.

The priority accorded to pregnant women was based on compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high. Additional considerations for targeting this group included operational feasibility and the opportunity to prioritize and strengthen maternal immunization programmes.

Health-care workers are recognized as a target group for whom vaccination would protect not only the individual but also vulnerable patients, and for whom a vaccination programme is an important element of infection control and pandemic preparedness. It was suggested that immunization of health-care workers should be considered as part of a broader infection control package for health-care facilities.

Children aged 6–23 months experience a high burden of severe disease. Protection in this immunologically naïve group requires 2 doses of vaccine, and vaccine effectiveness is particularly dependent on the matching of vaccine strains to circulating viruses. Children aged 2–5 years also have a high burden of disease, although less than the burden in those <2 years of age, and may respond better than younger children to influenza vaccines, both trivalent inactivated vaccines (TIV) and live-attenuated influenza vaccines.

Increasing evidence demonstrates that vaccines may be less effective in the elderly than in younger adults. However elderly persons have the highest risk of severe disease and mortality associated with influenza and they continue to be the main focus of influenza vaccine policies in many countries.

2013-2018, intégrant l'arrêt du VPO2 et éventuellement celui du VPOb, avec pour le moment différents scénarios d'introduction du VPI pendant la période de transition VPOt - VPOb et pour l'utilisation à long terme du VPI après l'arrêt complet du VPO.

Vaccin contre la grippe saisonnière

Le groupe de travail sur les vaccins antigrippaux et la vaccination a présenté au SAGE un bilan complet de la charge de morbidité due à la grippe, des performances des vaccins et de leur innocuité chez des populations de tous âges et chez des groupes à risque, intégrant les données disponibles concernant les pays à revenu faible ou intermédiaire. Sur la base de ce bilan, le groupe de travail a proposé des recommandations spécifiques dans l'objectif de réviser la note de synthèse de l'OMS sur les vaccins antigrippaux datant de 2005.

Le SAGE a recommandé de considérer les femmes enceintes comme le groupe à risque le plus important pour la vaccination par le vaccin antigrippal saisonnier inactivé. Les autres groupes à risque à prendre en compte, sans que leur ordre de citation définisse une priorité, sont le personnel soignant, les enfants de 6-59 mois, les personnes âgées et celles atteintes de pathologies à haut risque. Il a également recommandé aux pays disposant déjà de programmes de vaccination contre la grippe ciblant l'un de ces groupes de poursuivre ces programmes en y intégrant la vaccination des femmes enceintes. Les pays doivent décider quels autres groupes à risque devront être vaccinés en priorité, en fonction de la charge de morbidité, du rapport coût/efficacité, de la faisabilité et d'autres considérations pertinentes.

La priorité accordée aux femmes enceintes se fonde sur des preuves convaincantes de l'existence d'un risque substantiel de maladie grave pour ce groupe et de l'innocuité et de l'efficacité du vaccin antigrippal saisonnier pour prévenir l'apparition de maladies chez ces femmes et leurs jeunes enfants, qui sont aussi lourdement touchés. Parmi les autres considérations motivant le ciblage de ce groupe figurent la faisabilité opérationnelle et l'occasion de renforcer les programmes de vaccination maternelle et de leur donner une plus grande priorité.

Le personnel soignant est reconnu comme un groupe cible dont la vaccination devrait non seulement protéger les membres pris individuellement, mais aussi leurs patients vulnérables, et pour lequel un programme de vaccination est un élément important de la lutte contre l'infection et de la préparation à une pandémie. Il a été proposé de considérer la vaccination du personnel soignant comme faisant partie d'un ensemble plus large de mesures de lutte contre l'infection dans les établissements de soins médicaux.

Les enfants de 6 à 23 mois supportent une forte charge de maladies graves. La protection dans ce groupe immunologiquement naïf nécessite 2 doses de vaccin et si l'efficacité vaccinale est particulièrement tributaire d'un bon appariement entre les souches vaccinales et les virus circulants. La charge de morbidité est également importante pour les enfants de 2 à 5 ans, mais moindre que pour les enfants de <2 ans, et la réponse aux vaccins antigrippaux trivalents inactivés (VTI) et vivants atténués peut aussi être meilleure chez ces enfants plus âgés.

Il existe de plus en plus de preuves d'une moindre efficacité des vaccins chez les personnes âgées que chez les adultes plus jeunes. Ce sont pourtant les personnes d'âge avancé qui courent le plus grand risque de maladie grave et de décès liés à la grippe et cette tranche d'âge continue d'être la principale cible des politiques de lutte contre la grippe dans de nombreux pays.

Persons with specific chronic medical conditions, who are also at high risk for severe influenza illness and often targeted for vaccination, continue to be an appropriate target group. However, identification of these individuals in many settings is often challenging and may require considerable ongoing investment. In the 2009 pandemic, some indigenous populations were identified as important high-risk groups with higher rates of predisposing chronic conditions and higher rates of severe influenza disease and complications. Indigenous populations are often identifiable and accessible for vaccination programmes and should be considered a priority.

SAGE provided additional suggestions for these recommendations, including inclusion of relevant safety data for the targeted populations, particularly for pregnant women, and a clear delineation of recommended vaccine types for each target group (e.g. TIV for pregnant women). Clarification was also requested for the possible indirect benefits of vaccinating health-care workers on patients at risk of severe disease, the indirect effects of vaccinating children aged 6 months to 5 years at community-level, and the potential for influenza vaccine to improve childhood survival through prevention of secondary bacterial pneumonias. Finally, quadrivalent influenza vaccines that could potentially provide wider protection against influenza B viruses are becoming available and recommendations should not be limited to trivalent vaccine formulations.

SAGE recommended that the prioritization of specific target groups, local implementation timelines and target coverage goals should be determined at regional and country levels, as influenza immunization programmes are dependent on country-specific epidemiology, capacity and resources. SAGE noted that strengthening seasonal influenza programmes would assist in programmatic preparedness for pandemic vaccine introduction.

Successful introduction of influenza vaccines to healthy younger populations, including pregnant women and young children, would require educational programmes and social messaging. Year-round availability of influenza vaccines, including both northern and southern hemisphere formulations, is another critical element of programme implementation for pregnant women. Modeling of the potential impact of influenza vaccine introduction on morbidity and mortality and its economic consequences in the recommended risk groups, particularly in developing countries, should be pursued.

Impact of introduction of new vaccines on immunization and health systems

The ad hoc working group on the impact of new vaccine introductions (NVI) on immunization and health systems presented a synopsis of major themes emerging from 5 studies conducted by members of the group: a published literature review, a grey literature review, in-depth interviews with regional and country immunization staff, an in-depth study of recent vaccine introductions in 3 countries, and a statistical analysis of the impact of NVI on DTP3 coverage. The WHO Health

Les personnes atteintes de pathologies chroniques spécifiques, pour lesquelles le risque de contracter une forme grave de la grippe est également important, continuent d'être un groupe à cibler. Toutefois, l'identification de ces individus est souvent difficile dans de nombreux contextes et peut nécessiter en permanence des investissements considérables. Lors de la pandémie de 2009, certaines populations indigènes ont été repérées comme des groupes à risque importants, avec des taux plus élevés de pathologies chroniques prédisposantes et également des taux plus importants de formes sévères et de complications de la grippe. Ces populations indigènes sont souvent identifiables et atteignables par les programmes de vaccination et doivent être considérées comme prioritaires.

Le SAGE a formulé des suggestions supplémentaires pour ces recommandations, dont l'inclusion de données d'innocuité pertinentes concernant les populations cible, en particulier les femmes enceintes, et d'une définition claire des types de vaccins préconisés pour chaque groupe cible (VTI pour les femmes enceintes, par exemple). Des éclaircissements ont également été demandés sur les bénéfices indirects potentiels de la vaccination du personnel soignant pour les patients exposés à un risque de maladie grave, les effets indirects de la vaccination des enfants âgés de 6 mois à 5 ans à l'échelle de la collectivité et la capacité du vaccin antigrippal à améliorer la survie des enfants à travers la prévention des pneumonies bactériennes secondaires. Enfin, des vaccins antigrippaux quadrivalents, susceptibles de fournir une protection plus large contre les virus grippaux du groupe B, deviennent disponibles et les recommandations ne doivent pas se limiter aux formulations vaccinales trivalentes.

Le SAGE a recommandé que le classement par priorités des différents groupes cible, les chronologie de mise en œuvre locale et les buts en matière de couverture des groupes cibles soient déterminés aux niveaux régional et national, dans la mesure où les programmes de vaccination contre la grippe dépendent de l'épidémiologie, des capacités et des ressources dans le pays concerné. Le SAGE a noté que le renforcement des programmes contre la grippe saisonnière faciliterait la préparation programmatique à l'introduction du vaccin pandémique.

L'introduction avec succès de la vaccination antigrippale chez des populations plus jeunes et en bonne santé, dont les femmes enceintes et les jeunes enfants, nécessiterait des programmes éducatifs et des messages sociaux. La disponibilité tout au long de l'année des vaccins antigrippaux, y compris les formulations couvrant l'hémisphère nord et celles couvrant l'hémisphère sud, est un autre aspect critique de la mise en œuvre des programmes à l'intention des femmes enceintes. Il convient de poursuivre la modélisation de l'impact potentiel de l'introduction du vaccin antigrippal sur la morbidité et la mortalité et de ses conséquences économiques chez les groupes à risque qu'il est recommandé de viser, tout particulièrement dans les pays en développement.

Incidence de l'introduction de nouveaux vaccins sur la vaccination et les systèmes de santé

Le groupe de travail spécial sur l'incidence de l'introduction de nouveaux vaccins (INV) sur la vaccination et les systèmes de santé a présenté un résumé des grands thèmes qui se dégagent des 5 études menées par des membres du groupe, à savoir une revue de la littérature publiée, une revue de la littérature grise, des entretiens approfondis avec le personnel de vaccination à l'échelon régional et national, une étude poussée des introductions récentes de vaccins dans 3 pays et une analyse statistique de l'incidence des INV sur la couverture par le DTC3. On a fait

System Framework Building Blocks were used to organize the analysis of potential areas of impact of new vaccine introduction on health systems. While reductions in disease burden and improvements in disease and adverse events surveillance, training, cold chain and logistics capacity and injection safety were commonly documented as beneficial impacts, opportunities for strengthening the broader health system were consistently missed during NVI. Weaknesses in planning for human and financial resource needs as well as the diversion of effort towards NVI and away from the routine immunization system were highlighted as a concern. Where positive impacts on systems following NVI occurred, these were often in areas where detailed technical guidance or tools and adequate financing were available. SAGE supported the working group's conclusion that future NVI should explicitly consider and plan to optimize and document the impact of vaccine introduction on broader health systems.

Specific knowledge gaps that SAGE noted as worthy of further investigation were: assessment of which health interventions are most appropriate for integration with immunization programmes, and under what circumstances; whether there is redirection of resources from other health programmes to finance vaccine introductions; the actual costs of NVI (including collateral costs); methods for increasing equity with NVI; the health systems determinants of successful vaccine introduction; and measures of successful vaccine introduction from a broad health system perspective.

SAGE endorsed the following revised principles for adding a vaccine to a national immunization system while strengthening the immunization and health systems. Optimal new vaccine introduction that strengthens health systems benefits from:

1) A strong country-led, evidence-based decision-making, planning, and prioritization process that is accountable and coordinated with other components of the health system.

2) A well-performing or improving and responsive immunization programme.
3) Seizing the opportunity to achieve:
   - A well-trained and motivated health workforce
   - Quality education and communication about the new vaccine for the health workforce and community
   - Functional cold storage, logistics and vaccine management systems
   - Safe immunization practices and monitoring of adverse events
   - High-quality monitoring and evaluation, including disease surveillance and immunization coverage monitoring
   - Resource, performance, and management accountability.
4) Maximizing opportunities to deliver vaccines as integral components of comprehensive health pro-

appel aux blocs de construction des systèmes de santé de l'OMS pour organiser l'analyse des domaines d'impact potentiels de l'introduction des nouveaux vaccins sur les systèmes de santé. Si des réductions de la charge de morbidité et des améliorations concernant la surveillance de la maladie et des manifestations indésirables, la formation, les moyens logistiques, les capacités de la chaîne du froid et la sécurité des injections ont été clairement attestées en tant qu'impacts bénéfiques, les occasions de renforcer le système de santé dans un sens plus large ont été régulièrement manquées pendant les INV. Les faiblesses de la planification des besoins en ressources humaines et financières, ainsi que le détournement au profit des INV des efforts devant bénéficier au système de vaccination systématique ont été pointés comme préoccupants. Lorsque des INV ont produit des effets positifs sur les systèmes, ces effets concernaient souvent des domaines dans lesquels des instructions techniques détaillées et des outils, ainsi qu'un financement suffisant, étaient disponibles. Le SAGE a souscrit à la conclusion du groupe de travail selon laquelle les futures INV devraient explicitement envisager et prévoir d'optimiser et de documenter l'impact de l'introduction du ou des vaccins concernés sur les systèmes de santé au sens large.

Parmi les lacunes en matière de connaissances dont le SAGE a noté qu'elles justifiaient des études plus poussées, figurent les interventions sanitaires et les circonstances se prêtant le mieux à une intégration avec la vaccination; l'existence éventuelle d'un détournement des ressources qui bénéficiaient à d'autres programmes sanitaires pour financer l'introduction des nouveaux vaccins; les coûts réels des INV (y compris les coûts collatéraux); les méthodes pour obtenir une plus grande équité dans les INV; les déterminants au niveau des systèmes de santé du succès de l'introduction des vaccins; et les mesures de ce succès du point de vue plus large des systèmes de santé.

Le SAGE a approuvé les principes révisés suivants pour l'adjonction d'un vaccin dans le système de vaccination national tout en renforçant la vaccination et les systèmes de santé. Les conditions énumérées ci-après contribueront à ce que l'introduction d'un nouveau vaccin s'opère de manière optimale et renforce les systèmes de santé:

1) Procédures solides, dirigées par les pays, pour la prise de décision à partir d'éléments factuels, la planification et la détermination des priorités; elles s'assortissent de l'obligation de rendre des comptes et se font en coordination avec les autres composantes des systèmes de santé.
2) Programme de vaccination performant ou en cours d'amélioration et réactif.
3) Exploitation de cette occasion pour obtenir:
   - des professionnels de santé suffisamment formés et motivés
   - une éducation et une communication sur les nouveaux vaccins de grande qualité à l'intention du personnel de santé et de la collectivité;
   - des systèmes fonctionnels pour la logistique, le stockage au froid et la gestion des vaccins;
   - des pratiques vaccinales sans risque et le suivi des manifestations indésirables;
   - un suivi et une évaluation de grande qualité, notamment pour la surveillance de la maladie et de la couverture vaccinale;
   - une capacité à rendre des comptes sur les ressources, les résultats et la gestion.
4) Optimisation des possibilités de délivrer les vaccins en tant que composantes des efforts globaux pour promouvoir la

motion and disease prevention and control efforts so that vaccines are delivered as part of a package of effective, feasible, and affordable interventions based on national contexts.

5) Sufficient allocation of human and financial resources to introduce the new vaccine and sustain its use without adversely affecting other programmes and services.
6) A safe and efficacious vaccine that is appropriate for local use and is available with an uninterrupted, sufficient supply.

SAGE endorsed the working group's proposal that the 2005 WHO Vaccine Introduction Guidelines be updated to assist decision-makers and the managers of the Expanded Programme on Immunization with identifying and taking opportunities to strengthen the health system throughout the process of NVI, from decision-making to planning, implementation, and evaluation. SAGE recommended that the updated guidance be framed as considerations for strengthening the health system that could be flexibly applied to suit local contexts rather than as requirements or obstacles to vaccine introduction. Furthermore, opportunities for improving integration of delivery of services, commodities, and messages with other parts of the health system should be actively sought with the recognition that integration is a bidirectional process.

To avoid the gaps in planning for NVI that can compromise existing immunization programmes and the broader health system, SAGE recommended that donors and partners provide sufficient and timely support to facilitate country planning and evaluation of NVI impact on health systems.

Vaccination in humanitarian emergencies

SAGE was presented with an update from the SAGE working group on vaccination in humanitarian emergencies including the outcome of a literature review, lessons learnt from 5 case studies conducted by the working group targeting a range of recent emergencies in China, the Fiji Islands, Haiti, Pakistan, and Somalia, and an ethical perspective to guide the use of vaccination in humanitarian emergencies. SAGE was presented with a draft proposed framework for assisting decision-making which includes a comprehensive definition of an acute emergency. The basic decision-making process comprises 3 steps aimed at determining whether (i) a vaccine-preventable disease poses an important risk to the affected population (ii) an effective vaccination response could be implemented (iii) a vaccination response would be appropriate given other public health priorities.

The case studies provided important insights into the decision-making process in different contexts, including the role of contextual factors, the limited consideration of ethical factors, the influence of vaccine availability, limited consideration of epidemiological factors, and reluctance to apply existing guidelines as they were considered insufficient to support decision-making. Useful lessons learnt from the case studies will be used to complement the literature review findings.

Remaining work includes: the specification of variables and their relative importance in the decision-making

santé et prévenir et combattre les maladies, afin qu'ils soient administrés dans le cadre d'un ensemble d'interventions efficaces, faisables et abordables, au niveau national.

5) Affectation de ressources humaines et financières suffisantes pour introduire le nouveau vaccin et appuyer son utilisation sans que cela nuise aux autres programmes et services.

6) Utilisation d'un vaccin sûr et efficace, adapté aux conditions locales et disponible grâce à un approvisionnement suffisant et ininterrompu.

Le SAGE a approuvé la proposition du groupe de travail de mettre à jour les directives de l'OMS pour l'introduction des vaccins de 2005 afin d'aider les décideurs et les administrateurs du Programme élargi de vaccination à identifier et à saisir les occasions de renforcer le système de santé tout au long du processus d'INV, de la prise de décisions à la planification, à la mise en œuvre et à l'évaluation. Il a recommandé que les directives actualisées soient formulées comme des considérations visant à renforcer le système de santé et pouvant être appliquées de manière flexible pour s'adapter aux contextes locaux plutôt que comme des exigences ou des obstacles freinant l'introduction des vaccins. En outre, il convient de rechercher activement les occasions d'améliorer l'intégration de la délivrance des services, des biens et des messages avec d'autres composantes du système de santé, en reconnaissant que l'intégration est un processus bidirectionnel.

Pour éviter des lacunes dans la planification des INV pouvant compromettre le dispositif des programmes de vaccination et le système de santé au sens plus large déjà en place, le SAGE a recommandé que les donateurs et les partenaires apportent un soutien suffisant et en temps utile pour faciliter la planification et l'évaluation par les pays de l'impact de l'INV sur les systèmes de santé.

Vaccination dans les situations d'urgence humanitaire

Le groupe de travail sur la vaccination dans les situations d'urgence humanitaire a informé le SAGE des faits les plus récents, avec notamment les résultats d'un examen de la littérature, les enseignements tirés des 5 études de cas qu'il a faites sur une série de situations d'urgence en Chine, aux Îles Fidji, à Haïti, au Pakistan et en Somalie, et les aspects éthiques devant guider les actions de vaccination dans ces situations. Il s'est également vu proposer un projet de cadre pour aider à la prise de décisions incluant la définition complète d'une situation d'urgence aiguë. Le processus de prise de décisions de base comprend 3 étapes visant à déterminer si: 1) une maladie évitable par la vaccination représente un risque important pour la population touchée; 2) une réponse efficace par la vaccination pourrait être mise en œuvre; et 3) si une telle réponse serait appropriée compte tenu des priorités de la santé publique.

Ces études de cas ont donné un bon aperçu du processus de prise de décisions dans différents contextes et notamment du rôle des facteurs contextuels, de la prise en compte limitée des facteurs éthiques, de l'influence de la disponibilité des vaccins, de la prise en considération restreinte des facteurs épidémiologiques et de la réticence à appliquer les directives existantes dans la mesure où elles sont considérées comme insuffisantes pour appuyer la prise de décisions. Des enseignements utiles qui seront utilisés pour compléter les résultats de la revue de la littérature ont été tirés de ces études.

Il reste notamment à: spécifier les variables et leur importance relative dans l'outil de prise de décisions; grader/pondérer les

tool and scoring/weighting vaccine-specific characteristics; formal presentation of the case studies; development of worksheets for each vaccine-preventable disease; developing a «tool book»; and field testing the tool.

SAGE warned that while ethical considerations were pivotal to decision-making, ethical guidance should be crafted in such a way that decision-making is facilitated rather than delayed by debate. While the concept of "do no harm" is a basic principle of ethical health care, it must always be weighed against the possible implications of not taking action, as non-action may also cause harm. When autonomy of individuals is restricted due to emergencies, the dignity of individuals should still be respected. The importance of vaccination of children and pregnant women was considered a particular priority. As the vaccines used were generally safe, with potential benefits far outweighing risks, clear communication to this effect was essential.

While research was considered important to answer questions on the most effective management during emergencies, the guiding public health principle of saving lives first, followed by research, should be reflected appropriately in the guideline. However, there will be some research questions such as implementation research that can only be answered during an emergency. Should research be justified then additional teams dedicated to the research programme might be required to avoid diverting relief workers from life-saving interventions. Ethical clearance for research should be done preferably by a local ethics committee or in its absence by an international committee.

SAGE asked the working group to consider how a broader awareness among agencies of the Siracusa principles,[4] particularly the balance between individual and community rights, could be communicated.

It was noted that during the decision-making process, some managers may find that requests from political seniors could be in conflict with the course of action directed by their professional role. For this reason the question of dual loyalty should be addressed explicitly in the framework. The framework should also make reference to the WHO/UNICEF vaccine donation guidelines.

SAGE supported the approach taken for the framework. It is designed to accommodate regional and national differences, focusing on epidemiological and health service considerations. The framework is expected to be used to facilitate decision-making in any given emergency. The decision-making authority may be a national government (if functional) or the health cluster mechanism under the leadership of the UN designated humanitarian coordinator where there is no functional government. The framework allows assessment of the potential use of all appropriate vaccines during a spe-

caractéristiques spécifiques aux vaccins; présenter formellement les études de cas; mettre au point des feuilles de calcul pour chaque maladie évitable par la vaccination; élaborer un «manuel outil»; et à tester sur le terrain cet outil.

Le SAGE a averti que si les considérations éthiques étaient essentielles dans la prise de décisions, les recommandations dans ce domaine devaient être rédigées de manière à faciliter les décisions plutôt qu'à les retarder par le débat. Si «ne pas nuire» est un principe fondamental pour délivrer des soins de santé conformément à l'éthique, il doit toujours être mis en balance avec les conséquences possibles de l'absence d'action dans les cas où un manque d'action pourrait nuire. Lorsque l'autonomie des individus est restreinte par la situation d'urgence dans laquelle ils se trouvent, il convient de continuer de respecter leur dignité. La vaccination des enfants et des femmes enceintes a été considérée comme particulièrement prioritaire. Comme en général les vaccins utilisés étaient sûrs et comme leurs bénéfices potentiels compensaient largement les risques, une communication claire sur ce point était indispensable.

Si la recherche est considérée comme importante pour déterminer les mesures les plus efficaces pour gérer les situations de crise, la directive doit convenablement refléter la priorité à donner, sur la recherche, au principe directeur de la santé publique intimant de sauver des vies. Néanmoins, certaines des questions explorées comme la recherche sur la mise en œuvre ne peuvent trouver de réponse que dans les situations d'urgence. Si des activités de recherche se justifient, il pourrait être nécessaire de disposer d'équipes supplémentaires, affectées spécialement au programme de recherche, pour éviter de détourner des secouristes des interventions destinées à sauver des vies. Il est préférable que l'autorisation éthique pour ces activités de recherche soit donnée par un comité d'éthique local ou, en l'absence d'un tel comité, par un comité international.

Le SAGE a prié le groupe de travail d'envisager des moyens de sensibiliser plus largement les agences souscrivant aux Principes de Syracuse,[4] notamment à l'équilibre entre droits individuels et droits collectifs.

Il a été constaté qu'au cours du processus de prise de décisions, certains administrateurs trouvaient parfois que les requêtes des responsables politiques étaient en conflit avec les actions que leur rôle professionnel leur dictait. Pour cette raison, le problème de la double loyauté devra être explicitement envisagé dans le cadre. Celui-ci devra aussi faire faire référence aux principes directeurs OMS/UNICEF pour les dons de vaccins.

Le SAGE a appuyé la démarche suivie pour l'élaboration de ce cadre. Ce dernier est conçu pour s'adapter aux différences régionales et nationales portant sur des aspects relatifs à l'épidémiologie et aux services sanitaires. On attend de lui qu'il soit utilisable pour faciliter la prise de décisions dans une situation d'urgence donnée. L'autorité de prise de décisions peut être un gouvernement national (s'il est opérationnel) ou le groupe de responsabilité sectorielle santé, sous la direction du coordonnateur humanitaire désigné par les Nations Unies, lorsque le gouvernement n'est plus opérationnel. Le cadre permet d'évaluer les possibilités d'utilisation de tous les vaccins appropriés dans

[4] *Siracusa principles on the limitation and derogation provisions in the International Covenant on Civil and Political Rights* (United Nations, Economic and Social Council, 1985) http://www1.umn.edu/humanrts/instree/siracusaprinciples.html

[4] *Principes de Syracuse concernant les dispositions du Pacte international relatif aux droits civils et politiques qui autorisent des restrictions ou des dérogations* (Conseil économique et social des Nations Unies, 1985) http://wwwl.umn.edu/humanrts/instree/siracusaprinciples.html.

cific emergency and may be repeatedly applied as the emergency evolves.

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. SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies. SAGE requested that the finalized framework be presented to the November 2012 SAGE meeting for consideration.

Rotavirus immunization schedules

SAGE reviewed new evidence that afforded an opportunity to avert additional deaths from rotavirus disease, including systematic reviews of rotavirus disease burden and effectiveness of different immunization schedules, improved estimates of the benefits in different epidemiological settings, and additional data on the risk of intussusception after rotavirus vaccination. It was informed by separate reviews by both the GACVS and the Immunization Practice Advisory Committee.

The risk benefit analysis continues to favour early immunization but the current age restrictions for the first dose (≤15 weeks) and last dose (≤32 weeks) are preventing vaccination of many vulnerable children. By removing the age restrictions, programmes will be able to immunize children who are currently excluded from the benefits of rotavirus vaccines and this is likely to include some of the children most vulnerable to severe rotavirus disease. Many thousands more deaths would be averted, but with a small additional increase in intussusception cases.

SAGE also noted that in view of the age distribution of rotavirus disease, providing rotavirus vaccine to children older than 24 months of age will be of little benefit.

Considering the above, SAGE continues to recommend that the first dose of rotavirus vaccine be administered along with DTP, as soon as possible after 6 weeks of age as this maximizes disease protection.

SAGE recognized that countries have different burdens of disease and may or may not have introduced rotavirus vaccines. For this reason, countries should develop country-specific plans on how the removal of age restrictions on vaccine administration can be introduced in a manner that supports existing programmes. SAGE requests WHO to develop tools to support country decision-making and where possible National Immunization Technical Advisory Groups (NITAGs) and Regional Technical Advisory Groups (RTAGs) should assist this process.

Given the small risk of intussusception after rotavirus vaccine administration, caregivers should be informed

le cadre d'une situation d'urgence donnée et peut être appliqué de manière répétée à mesure que cette situation évolue.

Le SAGE insiste sur l'intérêt de faire fonctionner le cadre dans le contexte de nouvelles urgences si l'occasion s'en présente dans les 6 mois qui viennent et rétrospectivement pour les situations d'urgence récemment rencontrées, y compris celles décrites dans les études de cas. La collaboration entamée avec des parties prenantes clés, dont des bureaux régionaux et des agences opérationnelles, devra être organisée par le Département Gestion des risques liés aux situations d'urgence et action humanitaire de l'OMS et le groupe global de responsabilité sectorielle pour la santé. Le SAGE a également suggéré que la démarche appliquée à la prise de décisions dans le cadre soit adoptée pour d'autres interventions sanitaires en situation d'urgence. Il a demandé à ce que le cadre finalisé soit présenté pour examen lors de sa réunion de novembre 2012.

Calendriers des vaccinations antirotavirus

Le SAGE a étudié de nouveaux éléments suggérant des possibilités d'éviter des décès supplémentaires par des maladies à rotavirus et notamment ceux fournis par l'examen systématique de la charge de morbidité due aux rotavirus et de l'efficacité des différents calendriers de vaccination, des estimations améliorées des bénéfices dans différents contextes épidémiologiques et des données supplémentaires sur le risque d'invagination intestinale suite à la vaccination antirotavirus. Il a été informé par des examens menés séparément par le GACVS et le Comité consultatif sur les pratiques vaccinales.

L'analyse risque/bénéfice continue d'être en faveur d'une vaccination précoce, mais les restrictions portant actuellement sur l'âge d'administration de la première dose (≤15 semaines) et de la dernière (≤32 semaines) empêchent la vaccination de nombreux enfants vulnérables. En éliminant ces restrictions relatives à l'âge, les programmes seraient en mesure de vacciner des enfants actuellement privés des bénéfices des vaccins antirotavirus, parmi lesquels se trouvent probablement certains des enfants les plus vulnérables aux maladies à rotavirus graves. Plusieurs milliers de décès supplémentaires pourraient être évités moyennant un faible accroissement additionnel du nombre de cas d'invagination intestinale.

Au vu de la distribution en fonction de l'âge des maladies à rotavirus, le SAGE a également constaté qu'administrer le vaccin antirotavirus à des enfants de >24 mois n'apportait guère de bénéfice.

En tenant compte des considérations précédentes, le SAGE continue de recommander l'administration de la première dose de vaccin antirotavirus en même temps que le vaccin DTC, et cela dès que possible après l'âge de 6 semaines, car une vaccination précoce maximise la protection obtenue contre la maladie.

Le SAGE a reconnu que les pays étaient différemment touchés par la maladie et pouvaient avoir ou non introduit des vaccins antirotavirus. De ce fait, les pays doivent élaborer des plans nationaux spécifiques sur la marche à suivre pour éliminer les restrictions portant sur l'âge d'administration des vaccins tout en soutenant les programmes existants. Il a prié l'OMS de mettre au point des outils pour appuyer la prise de décisions par les pays et, dans la mesure du possible, les groupes techniques consultatifs nationaux sur la vaccination (GTCV) et les groupes techniques consultatifs régionaux (RTAG) devraient apporter une aide dans ce processus.

En raison du faible risque d'invagination intestinale après l'administration du vaccin antirotavirus, les personnes qui s'oc-

of this risk and be adequately counselled to recognize early signs of intussusception, and encouraged to present cases immediately for medical attention.

SAGE encouraged all countries to establish or strengthen postmarketing surveillance which should focus on documenting any intussusception cases.

SAGE recognized that a comprehensive communication strategy that explains the reasons for this change of schedules should be developed and made available to all stakeholders including policymakers, programme managers, communities and parents, and requested WHO to develop appropriate tools. SAGE also stressed that vaccination is a dynamic field that will always be challenged by new data.

Evidence and recommendations for the use of single-dose inactivated hepatitis A vaccine

In November 2011, SAGE provided recommendations on the use of hepatitis A vaccines and recommended that a revised hepatitis A vaccine position paper be drafted. Based on information presented from a randomized controlled trial in Nicaragua and evaluation data from the national use of single-dose vaccine in Argentina, SAGE noted that a single-dose schedule might be an effective and cost-effective option for immunization programmes. However, given the limited evidence base presented, SAGE requested that the hepatitis A working group further review and carefully consider all data on single-dose use of inactivated hepatitis A vaccine, particularly with regard to long-term immunogenicity and seroprotection, including protection against hepatitis A-related disease and fulminant hepatitis.

The working group presented a comprehensive review and assessment of publicly available data on the long-term impact of single-dose hepatitis A vaccine administration on hepatitis A incidence, fulminant hepatitis and seroprotection. In addition Argentina presented detailed information on the monitoring of the impact of their single-dose hepatitis A vaccination programme including its impact on liver transplantation in children.

Results indicated that a single dose of inactivated hepatitis A vaccine can provide long-term seroprotection for up to 10.6 years with long-term protection against hepatitis A. An anamnestic response was documented for a period of up to 10 years, irrespective of the age of vaccinees. Six years after country-wide implementation of a one-dose schedule in children 12 months of age in Argentina, country-wide surveillance indicated a durable impact with an overall reduction in hepatitis A incidence and an absence of cases detected among vaccinees, whereas a number of cases continue to occur in the unvaccinated population, indicating continued exposure to hepatitis A virus.

SAGE concluded that while a 2-dose regimen of hepatitis A vaccines is currently in use in some countries, national immunization programmes may consider inclusion of single-dose inactivated hepatitis A vaccines

cupent des enfants doivent être informées de ce risque, convenablement conseillées pour reconnaître les signes précoces de ce problème et encouragées à présenter immédiatement les cas pour avis médical.

Le SAGE a encouragé tous les pays à mettre en place ou à renforcer une surveillance post-commercialisation, qui doit être axée sur l'enregistrement documenté des cas d'invagination intestinale.

Il a reconnu qu'une stratégie de communication détaillée expliquant les motifs de ce changement de calendrier devait être élaborée et mise à la disposition de toutes les parties prenantes, y compris les décideurs politiques, les administrateurs de programme, les collectivités et les parents et a prié l'OMS de mettre au point des outils appropriés. Il a également souligné le fait que la vaccination est un domaine en évolution rapide qui sera régulièrement remis en question par de nouvelles données.

Données et recommandations concernant l'utilisation d'une dose unique de vaccin inactivé contre l'hépatite A

En novembre 2011, le SAGE a émis des recommandations sur l'utilisation des vaccins anti-hépatite A et a recommandé l'élaboration d'une note d'information révisée sur ces vaccins. Sur la base des données tirées d'un essai contrôlé randomisé mené au Nicaragua et de celles fournies par l'évaluation de l'utilisation en Argentine, à l'échelle nationale, d'une dose unique de vaccin, le SAGE a noté qu'un schéma monodose pouvait constituer une option efficace et rentable pour les programmes de vaccination. Cependant, compte tenu de l'ampleur limitée du corpus de données présenté, il a prié le Groupe de travail sur l'hépatite A de continuer à examiner et de prendre soigneusement en compte toutes les données sur l'utilisation d'une dose unique de vaccin anti-hépatite A, en particulier pour ce qui concerne l'immunogénicité et la séroprotection à long terme, la protection contre les maladies liées à l'hépatite A et l'hépatite fulminante.

Le Groupe de travail a présenté un examen et une évaluation complets des données à la disposition du public sur l'impact à long terme de l'administration d'une dose unique de vaccin contre l'hépatite A sur l'incidence de cette maladie, l'hépatite fulminante et la séroprotection. En outre, l'Argentine a exposé des informations détaillées sur le suivi de l'incidence de son programme de vaccination par une dose unique de vaccin anti-hépatite A, notamment sur la transplantation hépatique chez les enfants.

Les résultats ont indiqué qu'une dose unique de vaccin inactivé anti-hépatite A pouvait apporter une séroprotection à long terme pouvant perdurer jusqu'à 10,6 ans, ainsi qu'une protection de longue durée contre l'hépatite A. Une réponse anamnestique a été attestée sur une période allant jusqu'à 10 ans, indépendamment de l'âge au moment de la vaccination. Six ans après la mise en place à l'échelle nationale en Argentine d'un schéma de vaccination monodose chez les enfants de 12 mois, la surveillance menée à la même échelle a repéré un impact durable, qui consistait en une réduction globale de l'incidence de la hépatite A et en l'absence de cas détectés parmi les enfants vaccinés, alors que des cas continuaient à survenir parmi la population non vaccinée, indiquant la poursuite de l'exposition au virus de l'hépatite A.

Le SAGE a conclu que, même si un schéma de vaccination par 2 doses de vaccin anti-hépatite A est actuellement en usage dans certains pays, les programmes nationaux de vaccination pourraient envisager d'inclure l'administration d'une dose unique

in immunization schedules. Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.

SAGE applauded Argentina for its innovative approach that generated valuable data in support of this potentially cost-effective one-dose schedule and encouraged the country to continue monitoring the impact of its single-dose hepatitis A vaccine programme and annual communication of information to WHO.

Off-label use of vaccines: During discussion on the use of a single-dose schedule for hepatitis A vaccination, the broader question of the off-label use of vaccines was also discussed. This issue had also been raised during discussion on the use of influenza vaccine in pregnant women, and on the removal of age restrictions for the use of rotavirus vaccine. 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.

Report from the GAVI Alliance

The GAVI Chief Executive Officer underlined the unprecedented demand for pneumococcal and rotavirus vaccines by eligible countries but indicated that the limited availability of fully prequalified vaccines, expansion of cold chain capacities and limited choice of preferred vaccines had delayed some planned country introductions. The roll out of yellow fever and meningitis vaccines in endemic countries continues. By the end of 2012, eligible countries will be able to apply for 2 new vaccines – rubella combined with measles (MR) for countries meeting the required criteria, and HPV. By 2015, 31 countries are expected to have introduced the MR vaccines in their national programmes. For HPV, GAVI will be supporting demonstration projects supported by a broader group of stakeholders, including those with adolescent, cancer and reproductive health expertise.

Policies under revision include GAVI's fragile states policy and the new vaccine introduction grant support to countries, with plans to include differential levels of support for routine, new and campaign vaccines. The Health Systems Funding Platform was being rolled out despite the current Global Fund funding challenges, and Performance-Based Financing mechanisms will be present in countries by the end of 2012. GAVI recognized the need for flexibility in future targeting of resources for its health system strengthening support in countries to achieve better immunization outcomes. Sixty countries had met their co-financing obligations with only 2 countries currently defaulting on payments. However,

de vaccin inactivé contre l'hépatite A dans leurs calendriers de vaccination. Les protections à long terme conférées par le schéma monodose et le schéma à 2 doses doivent être régulièrement suivies par les pays et examinées par le SAGE.

Le SAGE a félicité l'Argentine pour sa démarche innovante qui a généré des données précieuses à l'appui d'un bon rapport coût/efficacité de ce schéma monodose et l'a encouragé à poursuivre le suivi de l'impact de son programme de vaccination par une dose unique de vaccin anti-hépatite A et à communiquer des informations à ce sujet à l'OMS sur une base annuelle.

Emploi hors autorisation de mise sur le marché des vaccins: Au cours de la discussion sur l'utilisation du schéma monodose de vaccination contre l'hépatite A, la question plus large de l'emploi hors autorisation de mise sur le marché des vaccins a également été examinée. Cette question avait également été soulevée lors de la discussion sur l'utilisation du vaccin antigrippal chez les femmes enceintes et à propos de l'élimination des restrictions portant sur l'âge pour l'administration des vaccins antirotavirus. Le SAGE a demandé l'élaboration d'un article indiquant dans quelles circonstances l'utilisation hors autorisation de mise sur le marché d'un vaccin quelconque pouvait être recommandée, tout en explicitant les différences entre décisions réglementaires et recommandations de santé publique. Les implications sur le plan juridique et programmatique des recommandations d'utilisation hors autorisation de mise sur le marché et la nécessité d'une communication claire doivent être examinées.

Rapport de l'Alliance GAVI

L'Administrateur principal de l'Alliance GAVI a souligné la demande sans précédent en vaccins antipneumococciques et antirotavirus de la part des pays susceptibles de bénéficier de son aide, mais a indiqué que la disponibilité limité des vaccins ayant subi la totalité du processus de présélection, le développement des capacités de chaîne du froid et le choix restreint en vaccins préférés avaient retardé certaines des introductions nationales prévues. La mise en place de vaccins contre la fièvre jaune et contre la méningite dans les pays d'endémie de ces maladies se poursuit. D'ici fin 2012, les pays susceptibles de bénéficier de l'aide de l'Alliance pourront faire une demande pour 2 nouveaux vaccins: un vaccin antirubéoleux combiné à un vaccin antirougeoleux pour les pays remplissant les critères voulus et le HPV. D'ici à 2015, 31 pays devraient introduire des vaccins anti-rougeoleux-antirubéoleux dans leurs programmes nationaux. En ce qui concerne le HPV, l'Alliance GAVI appuiera des projets de démonstration bénéficiant du soutien d'un groupe plus large de parties prenantes, dont certaines auront des compétences sur la santé des adolescentes, le cancer et la santé génésique.

Parmi les politiques en cours d'examen figurent la politique de GAVI en faveur des Etats fragiles et l'aide par des subventions aux pays pour l'introduction de nouveaux vaccins, avec des projets de différenciation du niveau de l'aide pour la vaccination systématique, les nouveaux vaccins et les campagnes de vaccination. La plate-forme de financement des systèmes de santé a été établie, malgré les difficultés de financement rencontrées actuellement par le Fonds mondial et les mécanismes de financement en fonction des résultats seront en place dans les pays d'ici fin 2012. L'Alliance reconnaît la nécessité d'une certaine flexibilité dans l'affectation dans les pays de ses ressources pour le renforcement des systèmes de santé pour obtenir de meilleurs résultats en matière de vaccination.

the ability of countries to successfully graduate out of GAVI support remained a concern.

The April Board retreat will consider a range of potential issues in which GAVI could become involved including measles, Japanese encephalitis, typhoid, malaria, dengue, polio vaccines, the cholera vaccine stockpile, continued technology expansion, implementation research, support to low-middle income countries, and vaccine export capacities. Overall, the Alliance was looking to better define the roles and responsibilities of its partners and achieve better synergies across the Alliance and related programmes, while aiming to strengthen country ownership and leadership.

Information on vaccines for an Intergovernmental Negotiating Committee to prepare a global legally binding instrument on the use of mercury

At its 25th session in 2009, the Governing Council of the United Nations Environment Programme (UNEP) requested an Intergovernmental Negotiating Committee (INC) to prepare a global legally binding instrument on the use of mercury. A variety of mercury-containing products are used in health care including thiomersal, an organic form of mercury, used as a preservative in vaccines presented in multi-dose vials. The INC was specifically tasked by the UNEP Governing Council to address health issues in the proposed global mercury instrument, and including reduction of mercury use in products and processes as part of the overall strategy to reduce human and environmental risks from mercury. WHO provided independent authoritative health information to its 194 member state governments and during the third INC session (INC3) from 31 October to 4 November 2011, WHO advised countries that mercury quantities in thiomersal-containing vaccines were extremely small, and if vials and syringes are handled in an environmentally sound manner as hospital waste, there would be minimal environmental release of mercury. Countries requested information on alternative preservatives (e.g. 2-phenoxyethanol) for vaccines, and the economic, programmatic and manufacturing implications of moving (globally) to single-dose, preservative-free vaccines prior to INC4, scheduled for 27 June – 2 July 2012.

A WHO Informal Consultation from 3 to 4 April 2012 concluded that: replacement of thiomersal with an alternative preservative may affect the quality, safety and efficacy of vaccines; re-registration would be required by the National Regulatory Authority in each jurisdiction where a reformulated product was intended to be used; currently available alternative preservatives interacted in unpredictable ways with existing vaccines, and there are no consensus alternative preservatives for the near- or mid-term. There is insufficient existing manufacturing capacity to remove thiomersal and switch to single-use vials. Such a switch would have significant

Soixante pays se sont acquittés de leurs obligations de co-financement et 2 pays seulement sont actuellement en défaut de paiement. Néanmoins, la capacité des pays à réussir à s'affranchir de l'aide de l'Alliance GAVI reste préoccupante.

Dans le cadre de sa retraite d'avril, le Conseil abordera une série de questions dans lesquelles l'Alliance GAVI pourrait être impliquée, dont la rougeole, l'encéphalite japonaise, la typhoïde, le paludisme, la dengue, les vaccins antipoliomyélitiques, le stock de vaccins anticholériques, la poursuite du développement technologique, la recherche sur la mise en œuvre, l'aide aux pays à revenu intermédiaire faible et les capacités d'exportation des vaccins. Globalement, l'Alliance s'efforçait de mieux définir les rôles et les responsabilités de ses partenaires et de dégager de plus fortes synergies entre elle et les programmes associés, tout en visant un renforcement de l'appropriation et de la prise en main par les pays.

Informations sur les vaccins pour un Comité de négociation intergouvernemental chargé d'élaborer un instrument international juridiquement contraignant concernant l'utilisation du mercure

Lors de sa 25e session en 2009, le Conseil d'administration du Programme des Nations Unies pour l'environnement (PNUE) a prié un Comité de négociation intergouvernemental (CNI) d'élaborer un instrument international juridiquement contraignant concernant l'utilisation du mercure. Les soins de santé utilisent divers produits contenant du mercure, dont le thiomersal, une forme inorganique de cet élément utilisée comme agent conservateur dans les vaccins présentés en flacons multidoses. Le CNI a été spécifiquement chargé par le Conseil d'administration du PNU d'examiner le traitement des questions de santé dans l'instrument international sur le mercure proposé et d'y inclure la réduction des usages de cet élément dans les produits et les procédés, dans le cadre d'une stratégie globale pour diminuer les risques qu'il comporte pour l'homme et l'environnement. L'OMS a fourni à ce sujet des informations sanitaires indépendantes faisant autorité aux gouvernements de ses 194 Etats Membres et, à l'occasion de la troisième session du CNI (INC3) qui s'est tenue du 31 octobre au 4 novembre 2011, a indiqué aux pays que les quantités de mercure présentes dans les vaccins contenant du thiomersal étaient extrêmement faibles et que si les flacons et les seringues étaient manipulées de manière respectueuse de l'environnement en tant que déchets hospitaliers, les rejets de mercure dans l'environnement seraient minimaux. Les pays ont demandé des informations sur les agents conservateurs de substitution (2-phénoxyéthanol, par exemple) pour les vaccins et sur les incidences pour l'économie, les programmes et la fabrication du passage (à l'échelle mondiale) à des vaccins exempts d'agent conservateur et présentés en dose unique avant l'INC4, devant se dérouler du 27 juin au 2 juillet 2012.

Une consultation informelle organisée par l'OMS du 3 au 4 avril 2012 a conclu que le remplacement du thiomersal par un agent conservateur de substitution pourrait nuire à la qualité, à l'innocuité et à l'efficacité des vaccins; qu'une nouvelle homologation serait requise par l'autorité nationale de réglementation dans chaque juridiction où l'on aurait l'intention d'utiliser un produit reformulé; et que les agents conservateurs de substitution actuellement disponibles interagissaient de manière imprévisible avec les vaccins existants et ne faisaient l'objet d'aucun consensus à court et moyen termes. La capacité de production de vaccins existante est insuffisante pour procéder au retrait du thiomersal et passer aux flacons à usage unique. Une telle tran-

cold chain, storage, and waste management implications and would result in very large increases in costs for immunization programmes. There would be a clear risk (if reformulation with alternative preservatives or with no preservatives is required) that some products would become unavailable – particularly the current low-cost vaccines (tetanus toxoid, diphtheria-tetanus-whole cell pertussis, hepatitis B). There would be a high risk of serious disruption to routine immunization programmes and mass immunization campaigns if thiomersal-preserved multi-dose vials were not available for inactivated vaccines, with a predictable and sizable increase in mortality, for exceedingly limited environmental benefit.

SAGE was also informed of risks to vaccine access before the treaty negotiations have finished. As there are no technical justifications for alternatives, demand is limited and countries will likely face supply interruptions if they opt to introduce such a strategy. SAGE was also informed that environmental regulatory requirements are likely to increase if the treaty is ratified, creating potential future issues for access to thiomersal as a raw material in vaccine manufacture. Investment in a focused effort to identify additional preservatives and future preferred product presentations for multi-dose delivery of vaccines will thus be important.

SAGE was gravely concerned that current global discussions may threaten access to thiomersal-containing vaccines without scientific justification. SAGE reaffirmed that thiomersal-containing vaccines were safe, essential and irreplaceable components of immunization programmes, especially in developing countries, and that removal of these products would disproportionately jeopardize the health and lives of the most disadvantaged children worldwide. While SAGE supports global moves to minimize environmental mercury releases, it is essential that access to thiomersal-containing vaccines is not restricted under this global initiative. SAGE supported urgent global advocacy and communication efforts at the highest level of government and by other stakeholders to ensure continued availability of thiomersal-containing vaccines. SAGE supported ongoing dialogue between the health and environment sectors at global and national levels to facilitate a common understanding of the critical role of thiomersal-containing vaccines. Noting the potential threat to thiomersal-containing vaccines, 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. ■

sition aurait des conséquences importantes sur la chaîne du froid, le stockage et la gestion des déchets et entraînerait de très fortes augmentations des coûts pour les programmes de vaccination. Il y aurait clairement un risque (en cas de reformulation avec des agents conservateurs de substitution ou sans agent conservateur si nécessaire), que certains produits deviennent indisponibles – en particulier les vaccins actuels à bas coût (à base d'anatoxine tétanique, antidiphtérique-antitétanique-anticoquelucheux (à germes entiers), anti-hépatite B). Il y aurait aussi un fort risque d'interruption des programmes de vaccination systématique et des campagnes de vaccination de masse si les flacons multidoses conservés par du thiomersal n'étaient plus disponibles pour les vaccins inactivés, avec une augmentation prédictible et appréciable de la mortalité, dépassant les bénéfices limités pour l'environnement.

Le SAGE a aussi été informé des risques pour l'accès aux vaccins avant que les négociations du traité n'aient pris fin. Comme il n'existe aucune justification technique pour les produits de substitution, la demande est limitée et les pays seront probablement confrontés à des interruptions de l'approvisionnement s'ils optent pour cette stratégie. Le SAGE a également reçu l'information que les exigences réglementaires visant à protéger l'environnement seraient probablement accrues si le traité venait à être ratifié, d'où la possibilité de problèmes dans l'avenir pour accéder au thiomersal en tant que matière première dans la fabrication des vaccins. Il est donc important d'investir dans des efforts ciblés pour trouver d'autres agents conservateurs et des présentations futures préférables pour la délivrance sous forme multidoses des vaccins.

Le SAGE s'est dit gravement préoccupé de la menace que font peser les discussions actuelles au niveau mondial sur les vaccins contenant du thiomersal, sans qu'il y ait à cela de justification scientifique. Il a réaffirmé que les vaccins renfermant ce composé étaient des composants sûrs, essentiels et irremplaçables des programmes de vaccination, en particulier dans les pays en développement, et que le retrait de ces produits compromettrait de manière disproportionnée la santé et la vie des enfants les plus déshérités dans le monde entier. Si le SAGE est en faveur d'une démarche à l'échelle de la planète pour minimiser les rejets de mercure dans l'environnement, il est essentiel que l'accès aux vaccins contenant du thiomersal ne soit pas restreint au titre de cette initiative mondiale. Le SAGE s'est prononcé en faveur d'un plaidoyer urgent à l'échelle mondiale et d'efforts de communication au plus haut niveau des gouvernements et de la part d'autres parties prenantes pour garantir que les vaccins renfermant du thiomersal continuent d'être disponibles. Il a appuyé le dialogue en cours entre les secteurs de la santé et de l'environnement aux niveaux mondial et national en vue de faciliter une compréhension commune du rôle critique de ces vaccins. Prenant note de la menace potentielle pour les vaccins contenant du thiomersal, le SAGE a prié l'OMS de produire un rapport sur la sécurité de l'approvisionnement en vaccins économiquement accessibles et encouragé les donateurs à investir dans la mise au point de nouvelles technologies vaccinales facilitant la délivrance de vaccins efficaces et abordables aux populations les plus à risque. ■

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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.
General	SAGE requested that cold chain and vaccine management, thiomersal and the non-specific effects of vaccines also be discussed by SAGE in the future.	Agenda item	Nov 2011	Pending/Ongoing	A specific session Information on vaccines for an Intergovernmental Negotiating Committee to prepare a global legally binding instrument on the use of mercury took place at the April 2012 SAGE meeting. It discussed thiomersal and alternative preservatives and presentations. A session on the non-specific effects of vaccines is under preparation and tentatively slotted for April 2013. Other agenda items have been added on the master list of items to be discussed by SAGE and will be ready for discussion in the next 2 years.
General	SAGE recommended that new approaches, such as periodic intensification of routine immunization, be carefully evaluated prospectively to determine their effectiveness and cost-effectiveness.	Action	Apr 2009	Ongoing	Work with Immunization Basics to document country experiences is wrapping up. Mission to observe Zimbabwe Child Health Days which included routine catch up doses was undertaken in June 2009. Final report available (17 June 2010). Mission to Macedonia was undertaken in April/May 2010 to document the European Immunization Week (EIW) (draft report has been reviewed by WHO and will be finalized shortly). This topic has been referred to the WHO Immunization Practices Advisory Committee (IPAC) which has discussed it intensively at its meetings June and November 2010, particularly the issue of no longer being able to use the delivery strategy to reliably disinguish whether a dose is routine and supplementary. Jointly WHO & UNICEF prepared a Guidance Note outlining four criteria to determine if a given vaccination is a routine or supplemental dose. IPAC endorsed the Guidance Note at its meeting September 27-28, 2011. WHO/UNICEF are now proceeding to disseminate the criteria and consult with stakeholders regarding the consequences.
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	The WHO European Region inaugurated its Immunization Communication Working Group in December 2010. EURO is working to give countries tools to address vaccine hesitancy at the individual level. These include: 1. Development of the Tailoring Immunization Programs to Profile Susceptibles “TIPPS” 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 on the service/demand side. Best practices from other disease programs are included that can be adapted for country-specific issues. TIPPS was piloted in Sweden and Bulgaria The Toolkit is being further pilot tested and will hopefully be rolled out in more countries next year. 2. Strengthening the ability of member states to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication. It is currently under peer-review. This was done at the request of EPI managers. 3. Advocating through Immunization Week, which began in 2006. Activities are independent for each country. 4. Strengthening the use of new media. Well-ranked bloggers who write in Russian and English will be brought in to dialogue about how to better engage around vaccine confidence.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General	WHO to organize a special teleconference for SAGE to discuss action given by WHO in follow-up of SAGE recommendations.	Action	Nov 2011	Completed	Rather than organizing a specific teleconference, it was finally agreed with SAGE members that this would be featured in the second preparatory teleconference for the April 2012 SAGE meeting. During the conference as time was limited, it was proposed that the Chair and Vice-Chair of SAGE would review in detail the SAGE tracking sheet of action items and recommendations and would review if recommendations were given adequate follow-up and if not if these were high or low priorities in the context of the necessary prioritization of WHO activities in a context of limited resources. The Chair of SAGE will reported on this during the second preparatory teleconference for the November 2012 SAGE meeting and the very few areas for necessary additional attention were flagged.
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). 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. Expected early 2013.
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.
General	SAGE encouraged the Regional Office in EMRO to pay special attention to countries affected by political turmoil and requested specific monitoring for any adverse impacts on immunization programmes in GAVI graduating countries.	Action	Apr 2011	Ongoing	There are no GAVI graduating countries in the EMR. EMRO is working closely with and is paying special attention to the countries affected by political turmoil. During the past few months: EMRO provided extensive support to Libya for procuring vaccines for routine immunization to avoid stock out and drop in routine immunization coverage as well as to respond to the measles outbreak; EMRO has conducted 2 training workshops on vaccine management in Egypt, attended by officers from all governments (provinces) Effective vaccine management assessment in Egypt will be conducted in September 2011 with EMRO support; EMRO continues to provide extensive technical and financial support to Yemen for conducting outreach and mobile activities to maintain and improve the routine immunization coverage; EMRO is working closely with Syria and is currently providing the necessary technical support for evidence-based decision on new vaccines introduction, including supporting surveillance of new vaccines and provision of information on vaccine availability and vaccine prices.
General - GVAP	SAGE requested consideration of the establishment of a SAGE standing working group to monitor GVAP implementation.	Action	Apr 2012	Ongoing	Draft Terms of Reference for a SAGE DoV-GVAP standing working group have been drafted. They will be discussed at the November 2012 SAGE meeting. Following finalization of the group's ToRs we will proceed with a call for nominations and selection of working group members.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers	SAGE suggested to monitor gaps and opportunities and consecutively develop a systematic process to responds to these needs in collaboration with keys partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines.	Pending	Nov 2010	Pending	Activities to lead to better vaccine price information and vaccine pricing transparency are being considered and under discussion for funding. Contribution of WHO to the DoV work stream on global access. 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. IVB has launched a new project on vaccine product, price and procurement. The purpose of the project is to support GAVI graduating and lower 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.
Childhood mortality	SAGE noted the recommendation by QUIVER 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 QUIVER are hampered by the lack of primary data, and more efforts should be made to make such data readily available. Specically, for pertussis disease burden estimation QUIVER 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. QUIVER recommends that polio related data should be made available for multiple modeling groups to encourage comparison of results using different approaches.
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	Ongoing	A meeting on use of oral cholera vaccines in complex emergencies was held in early May 2011, and the WHA passed a resolution on mechanism for cholera control and prevention was passed in the May 2011 assembly. In addition, a meeting on cholera vaccine stockpile was held in Geneva from 6 to 7 September 2011. A meeting on the experience of Zanzibar to use cholera vaccine as a preventive tool was held in February and the Zanzibar Government is keen to use the vaccine island-wide if support is forthcoming. Further, in May meeting on the finalization of cholera stockpile was held and the building of a cholera vaccine stockpile is now a reality. In the meantime, cholera vaccine has been introduced as a pilot in Haiti as well as in Guinea. The preliminary reports from both appear highly encouraging on the utility of vaccine to prevent cholera.

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Decade of Vaccines	SAGE proposed stronger emphasis on consequences for non-delivery of programmes, and sustained funding for quality monitoring and surveillance. SAGE stressed the opportunity provided to use immunization programmes as the focus for health system strengthening and as a key pillar of primary health care. Specifically noted was the need to integrate vertical vaccination programmes and horizontal health care programmes to maximize the impact on improving health. SAGE supported the draft Global Vaccine Action Plan (GVAP) but sugguested that it needed to be more exciting and innovative, extending the benefits of immunization to populations beyond the traditional EPI childhood age group. SAGE felt that the DoVC should strongly address the emerging global challenge of vaccine hesitancy, which posed a major threat to immunization programmes worldwide. Innovative communication strategies and grassroots advocacy are required if community demand for immunization as a health right is to be mobilized. SAGE requested the planning teams to identify a few major “game-changers” which, if implemented, would have a significant impact.	Action	Nov 2011	Completed	All comments were taken into consideration in the revised version of the GVAP that was then used for the broad consultation process. Draft 3 was discussed during a SAGE extraordinary meeting in February 2012.
Decade of Vaccines	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. IVR leads on coordinating R&D agenda with partners agencies. Progress on establishing a vaccine research forum; progress on establishing R&D related indicators for the GVAP.
Feasibility of measles eradication	SAGE requested that progress towards meeting the 2015 global targets and regional elimination goals be monitored.	Action	Nov 2010	Ongoing	See update provided with respect to the measles rubella working group.
Feasibility of measles eradication	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	Ongoing	The working group on measles and rubella was formed in late 2011. Peter Figueroa is the chair of the working group and as of 27 September 2012, the group has held monthly conference calls and 2 face-to-face meetings (22 March and 20-21 September 2012). The working group is preparing for a session on measles and rubella at the November 2012 SAGE meeting. The session will include a report on progress, challenges, lessons learnt, and opportunities for achieving measles and rubella targets. In addition, there will a presentation on aeorsol measles vaccination and a brief update on the planned outputs from the working group in 2013.
Feedback from IPAC	IPAC update.	Information	Nov 2011	Ongoing	The last IPAC meeting was held in October 2012, and feedback will be provided on this meeting as well as the April 2012 meeting, to SAGE in November 2012. The next IPAC meeting will occur April 2013, one week prior to the SAGE meeting. Key topics on IPAC upcoming agenda include solar refrigeration guidance to countries, development of unvaccinated framework, health worker checklist piloting and controlled temperature chain (CTC) application with Meningococcal A vaccine MenAfriVac.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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. Some key areas of the study: What are the barriers/challenges that limit the rate of new vaccine adoption by LMICs? What are the potential options to address these rate limiting constraints? And what are the likely costs, benefits and implications of various options for supporting countries to address identified rate limiting constraints? Based upon these analyses the study will develop prioritized strategies and suggest practical measures at the global, regional, and national level to support non GAVI and LMICs in their decisions to adopt new vaccines. An Advisory Group for the study team was set up with representatives from WHO, BMGF, GAVI, UNICEF, NVI (Netherland Vaccine Institute) and vaccine manufacturers (IFPMA&DCVMN). The study began in November 2009 and was completed in March 2011. Finding and preliminary conclusions and recommendations were presented to the SAGE in November 2010. An operational plan to implement is under discussion with various agencies and donors - At regional level: EMRO is working with LMICs in the region to set up a pooled procurement system with the support of UNICEF and other partners. AFRO is conducting a feasibility study on regional pooled procurement. 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 et develop transition plans. 2 regional assessment were already conducted on GAVI graduating countries (EURO and PAHO), 2 others will be undertaken by the end of 2011. A full set of activities has been approved for 2012 to support countries transitioning from GAVI support. 6 countries are on the top of the list: Angola, Congo Rep, Bhutan, Sri Lanka, Moldova and Georgia. The establishment of a pooled procurement in EMRO is still on the agenda and technical development despite the unstable political situation in most of the concerned countries. New efforts are necessary in mid 2012. EMRO Regional Committee will discuss in the October 2012 session the official estalishment of a pooled procurement mechanism with the support of UNICEF. WHO and GAVI partners are conducting situation analysis in GAVI graduating countries and developing transition plan (6 countries are on the 2012 agenda). The challenges are financial but also link to pricing, procurement, reliable data and decision making processes.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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. Actionable activities will be then adopted and discuss with partners for implementation. Work is now underway to consider ways of addressing the potential obstacles and issues faced by the 16 graduating countries from GAVI support. 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 draft GVAP has partly addressed some the issues but more clarity and consistency is needed. A brainstorming meeting was organized on the lower-middle-income countries activity information and coordination on 12-13 March 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. We are planning to present the results of this consultation and others to follow at the November 2012 SAGE. A session is now planned on Middle income countries at the November SAGE meeting.
GRADing and review of evidence	SAGE emphasised that SAGE working groups should identify the specific questions for grading early for endorsement by SAGE. SAGE also noted the need for training of working group members on the review of evidence process.	Action	Apr 2011	Ongoing	This information has been communicated to the SAGE working groups. As an illustration special effort was made by the hepatitis A WG to validate the PICO questions for GRADing with SAGE members way ahead of the SAGE session to discuss the recommendations that took place in November 2011. Due to limited resources, and need to limit time investment for working group members, it is proposed that support be provided by the secretariat by the working groups. Training organized by WHO will be advertised and offered to staff and WG members. Brief video training sessions (2-4 hours)developed by WHO, the CDC and the Cochrane Collaboration were reviewed for their suitability and usefulness. As a result of further discussions with SAGE members and considering that these videos were not adequately targeted for our intended audience and sill long, SAGE requested the development of a brief video that could also be useful for other immunization related advisory groups. A 15 minutes and 20 seconds duration video was developed in the summer 2012 and the video has been circulated and posted on the SAGE website.
GRADing and review of evidence	SAGE endorsed the preparation of a shorter version of guidelines for peer-reviewed publication after incorporation of their guidance and using a few specific examples such as meningitis C conjugate vaccine.	Action	Apr 2011	Completed	Following the pilot testing of the guidance document (with conjugate meningococcal vaccines, measles, TBE and pertussis) and incorporation of resulting final adjustments, the guidance document has been circulated and posted on the website. A shorter version of this guidance was prepared with the GRADE discussion working group and published in Vaccine in early 2012. The general guidance document was also revised and version 2 posted on the SAGE website in March 2012.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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 hosts its first annual meeting in November 2012.
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: 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 - PWIDs) 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. 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 (ATD). 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. A written update will be provided on the progress of HIV-vaccine research for the April 2013 SAGE meeting.
Hepatitis A	SAGE recommended that a revised hepatitis A position paper should be drafted to guide countries on decisions on hepatitis A vaccine introduction, including reference to vaccine response of high-risk groups (e.g. HIV-positive individuals). SAGE requested the working group to carefully consider all data on the use of a 1-dose schedule, and whether this could be recommended in the revised hepatitis A position paper.	Action	Nov 2011	Completed	A specific session with focus on long term protection achieved by a single dose administration of hepatitis A vaccines took place at the April 2012 SAGE meeting. The updated vaccine position paper was published in July 2012 building on the SAGE recommendations from both the November 2011 and April 2012 discussions.
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	

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Hepatitis B	All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals.	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%. SEARO has a draft regional strategy and will convene two meetings in 2012 to finalize. AFRO has convened a regional hepatitis TAG and will bring their input to the Regional Committee in 2012. 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 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_BD a WHO/UNICEF "best estimate" in line with previous SAGE recommendations. 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.

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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	- 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) - 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 final administrative arrangements should be finalized in the coming weeks. - 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. Following this study a project proposal from GEF was submitted to the Gates Foundation Grant Challenge and granted (100,000 USD). This project will start with a pilot in one district. Used syringes will be collected and decontaminated by autoclave and supplied to a manufacture for recycling. As of today the project is waiting for the purchase of an autoclave.
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	Ongoing	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 will be presented at the November 2012 meeting.
Immunization schedules	Development of additional documents. 1. Guidance to countries on consideration for improving a national schedule, 2. Document on implementing vaccination programmes in older age groups; 3. Tool to help health workers avoid missed opportunities.	Action	Apr 2008	Completed	1. A "Users' Guide" to accompany the Summary Tables of WHO Recommendations for Immunization, has been finalized and is available on the WHO web site (http://www.who.int/immunization/policy/immunization_tables/en/index.html). This document outlines how countries can use the WHO recommendations to review their national immunization schedules. 2. As a first step existing WHO recommendations on delayed vaccination are being compiled from the position papers and summarized in a Table. 3. Discussions with IVR are on-going to explore revising the missed opportunities protocol and collaborating on a study of missed opportunities in 1-2 countries as part of the IVR EPI Schedules Optimization Project. A summary table of WHO Recommendations for Interrupted or Delayed Immunization has been posted on WHO's web site.

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Impact of the introduction of new vaccines on immunization and health systems	SAGE recommended that the ad-hoc working group work towards producing guidelines and tools for WHO to assist decision-makers and EPI managers contemplating the introduction of new vaccines, in order to take account of collateral effects inherent in introduction. The guidelines should provide a set of indicators that would enhance the potential positive effects, and reduce any potential negative effects, both on the immunization system and the health system. The guidelines should accommodate vaccines with different characteristics.	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 3 countries was conducted by LSHTM in 2011-12 to gather further information. 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, which is to be published after external review in early 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 which are to be published in early 2013 as a result of the proceedings of the ad hoc working group are being vetted by the partner agencies and will be endorsed by their senior personnel.
Influenza	SAGE approved the proposal from the Secretariat to update the WHO position paper on seasonal influenza vaccination as well as the establishment of a new working group on influenza vaccines and immunization.	Action	Apr 2010	Ongoing	During the last three face to face meeting of the SAGE WGIVI, the group had reviewed its workplan as outlined in the conceptual matrix and information on burden of disease, vaccine performance (vaccine effectiveness, safety), vaccine cost effectiveness and a number of operational issues. The group felt that there are sufficient information for updating the position paper on influenza vaccine. A background paper outlining evidence to support recommendations to update the position paper for influenza vaccine is included in the Yellow Book for the April 2012 SAGE meeting. Focus of the position paper is largely for low and middle income countries with consideration also be given to high income countries.
Influenza	SAGE requested that WHO report on the utilization of deployed vaccine, including by risk group, once data collection has been completed.	Action	Nov 2010	Ongoing	The results on the 2010 survey of countries on the utilization of deployed H1N1 pandemic vaccine was presented to the SAGE Working Group on Influenza Vaccines and Immunization (SAGE WGIVI) in their February 2011 meeting and to SAGE in the April meeting. The average vaccine utilization rate between WHO regions ranges from 15% to 73%. Vaccine coverage between WHO regions for targeted at risk populations ranged from 6% to 94% (results not available for EUR) representing 0.6% to 24% of general population of those regions. The report for the survey on the deployment of H1N1 pandemic vaccines is available at: http://whqlibdoc.who.int/publications/2012/9789241564427_eng.pdf.
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. 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 doses of H5N1 vaccine for 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 workplans are available 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 work by the SAGE Influenza working group will have to wait for the output from discussion in the PIP framework.

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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.
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 RO 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. WPR JE Lab workshop planned 2nd quarter 2013 in RO Korea. A paper summarizing the development of the JE LabNet has been delayed but planned for submission 4th quarter 2012.
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 planned that will comprise a review of immunization strategies.

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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 by end of 2011.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. 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 in supporting activities but they are still in the process to identify the best approaches. 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. 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. 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. The draft GVAP has partly addressed some the issues but more clarity and consistency is needed. A brainstorming meeting was organized on the lower-middle-income countries activity information and coordination on 12-13 March 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. We are planning to present the results of this consultation and others to follow at the November 2012 SAGE.EMRO is wotking with UNICEF SD to launch in 2013 the EMR Initiative on pooled procurement and contribute to the UNICEF pooled procurement for MIC focusing on new vaccines.
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE encouraged WHO to assist countries to use data from neighbouring countries and their region for decision-making. SAGE recognized that this required strengthening of the WHO country offices in lower-middle-income countries.	Action	Nov 2010	Ongoing	WHO is working at regional level and in particular with EURO and EMRO to promote intercountry exchanges and cross fertilization on burden of disease, immunization system strengthening, vaccine management and vaccine safety, prioritization and immunization planning, vaccine procurement and immunization financing. All opportunities are used to assist countries to know and potentially use data from neighboring countries. We are also working with PROVAC and SIVAC to develop their scope of work and consider more lower and middle income countries in their work plan and activities. Funding to support such activities is a big constraint. Those issues and questions are also being raised at the Decade of Vaccine working groups discussions. Recommendations are made to prioritize country ownership and intercountry mutual support. 16 countries are now graduating from GAVI support and requesting specific support to transition from external financial support to using their national resources and budget to pay for new vaccines and related supplies. This creating a strong push to consider support for lower middle income countries to sustain the introduction of new vaccines. Coherent and fair policies should be designed and implemented including vaccine supply and prices.

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Malaria	SAGE requested that it be kept informed of developments in the ongoing multi-country Phase 3 trial and indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur.	Action	Oct 2009	Ongoing	In March 2010, SAGE was provided with a summary of the unpublished results of a Phase 2 comparison of 0,1,2 month vs. 0,1,7 month schedule for RTS,S, conducted in Gabon, Ghana and Tanzania. The safety and immunogenicity results from this trial are now published in Journal of Infectious Disease (see ww.ncbi.nlm.nih.gov/pubmed/20735271). 511 infants were randomized to receive RTS,S/AS01(E) at 0, 1, and 2 months (in 3 doses with diphtheria, tetanus, and whole-cell pertussis conjugate [DTPw]; hepatitis B [HepB]; Haemophilus influenza type b [Hib]; and oral polio vaccine [OPV]), RTS,S/AS01(E) at 0, 1, and 7 months (2 doses with DTPwHepB/Hib+OPV and 1 dose with measles and yellow fever), or EPI vaccines only. The additional exploratory efficacy analyses from this trial were indicative that 3 doses of RTS,S are necessary for efficacy, and that 2 doses are insufficient. The Phase 3 trial of RTS,S/AS01E completed enrollment Jan 2011 with 15,460 infants enrolled in 11 sites in 7 African countries. The first of 3 analyses is of 12 months follow up data for safety and efficacy on the 5-17 month old without co-administration. This data was published in an NEJM article in October 2011. It reported 55% efficacy (95% CI 50-59) against all episodes of out-patient malaria, and 47% (95%CI 22-64) efficacy against severe, life-threatening malaria. There were no safety signals, although febrile seizure and meningitis will be further explored. The first data in the initial target population (6-14 week old infants in co-administration with pentavalent DTwP/HIb/Hep B and OPV) will become available to WHO in Q4 2012. This will include 12 month follow-up for both out-patient clinical malaria and in-patient severe malaria efficacy. The full trial results will be available in Q4 2014 and will include information on 30 month follow-up, the efficacy of an 18 month booster dose and site-specific clinical malaria efficacy. The Joint Technical Expert Group on malaria vaccines (JTEG) met in Feb 2012 and has advised that this 2014 data may support policy recommendation in 2015. 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. The dates for regulatory submissions remain unconfirmed, with a recent indication that GSK may defer their previously stated submission date of June 2013 until more data is available. An additional schedule study is underway in Malawi, including explorations of several different 3 dose schedules, some of which include a birth dose of RTS,S, or a dose at 6 months of age. A new Malaria Policy Advisory Committee (MPAC) has been convened for the first time by the WHO Global Malaria Programme in Q1 2012. An efficient process for JTEG presentation of candidate policy recommendations to both SAGE and MPAC will be determined. The policy recommendations are likely to occur during a planned joint SAGE/MPAC session in April 2015, if the data to become available to WHO in late 2014 supports this. The vaccine development partnership has been encouraged to fully explore optimal schedules and age groups for possible administration of this vaccine and additional schedule and co-administration studies are ongoing. A major issue for communication will be the clear need to consider RTS,S/AS01 as an addition to, not a replacement for, existing preventive measures, particularly long-lasting insecticidal nets and the need for ongoing availability of rapid diagnostic tests, and high quality safe and effective antimalarial drugs after any possible use of this vaccine in the future. Furthermore there will be a need to communicate what 50% efficacy means in this context (i.e. a reduced rate of malaria episodes). An additional schedule study is underway in Malawi, including explorations of several different 3 dose schedules, some of which include a birth dose of RTS,S, or a dose at 6 months of age. In 2014 data will emerge from the Phase 3 trial which will provide efficacy on a fourth dose given 18 months after the 3 dose primary immunization series.

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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	Ongoing	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.
Optimizing immunization schedules	SAGE requested that the models reflect operational realities – for example, delays in vaccine administration.	Action	Nov 2010	Postponed	Models to examine these factors have been developed. Their application to PCV was presented in Nov 2011. The implication of coverage and timeliness by age on rotavirus vaccine impact was presented at the April 2012 SAGE meeting.
Optimizing 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 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 vaccinesNov 2011 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 are proposed for SAGE consideration at the November 2012 meeting. For all: review of number of contacts during first years of life (ongoing); cost of contacts (planned); update on actual age at vaccination data (completed and used in conjunction with rotavirus epidemiology).
Optimizing pneumococcal conjugate vaccine (PCV) schedules	SAGE also suggested that schedules might need to be adjusted to ensure protection of special risk groups including HIV-positive infants and pre-term neonates, and suggested that specific guidance was needed for such groups.	Action	Nov 2011	Ongoing	Available evidence on special groups immunization was included in the revised PCV PP that was published in April 2012
Optimizing pneumococcal conjugate vaccine (PCV) schedules	SAGE requested that available evidence and guidelines to facilitate decision-making at country and regional level be posted on the WHO website.	Action	Nov 2011	Completed	A BETA version of the proposed approach to summarize the evidence and of the website will be presented to SAGE during the April 2012 meeting. Inputs from SAGE members and participants will be documented using a survey tool.
Pertussis	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	Pending	The initial offer of the pertussis strains made by Dr Nicole Guiso from the Institut Pasteur (IP) was not presented to the ECBS in 2010 due to the lack of information regarding the use of the strains and the related data. The proposal is currently subject to the official decision regarding the future of these strains that the Institut Pasteur needs to make. A possibility for maintaining the strains in the IP repository is one of the options under consideration but we are still expecting feedback on this from IP.
Pneumococcal Position Paper	Consolidate the two existing pneumococcal related position papers, i.e. that on PCV7 and that on PPV23 into one and only updated penumococcal vaccines position paper.	Action	Nov 2011	Done	It was initially envisioned that we could combine all recommendations and background information into one and only position paper on the use of conjugate and/or polysaccharide pneumococcal vaccines. The position paper on the use of PCV7 will indeed be phased out as soon as the updated position paper will be published. We have, however, decided to keep the position paper on the use of polysaccharide vaccine for reference on the web as it contains valuable background information that could not be sufficiently fitted in the new position paper on the use of pneumococcal vaccines. The key related recommendations are included in the new paper. When we further update the paper in 2-3 years we will then completely phase out the position paper on the use of polysaccharide pneumococcal vaccines and keep one and only accessible position paper on the use of pneumococcal vaccines. The updated paper was published on 6 April 2012.

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Polio	SAGE agrees with the proposal for recommendations on the use of IPV in low-income settings in the post-eradication era to be issued in April 2012.	Action	Nov 2010	Ongoing	Following the publication of the WHO position paper on routine pre-eradication polio vaccination in June 2010, the SAGE Working Group on IPV continued to review evidence towards finalizing its main remit of advising SAGE on eventual post-eradication polio vaccination policy recommendations. It had initially been anticipated that the WG's second remit, recommendations on post-eradication IPV policies, would be presented to SAGE in April 2011. However, SAGE decided to extend this timeline following the adoption of an additional third main remit for the WG, to provide guidance on all workstreams related to the 'new polio endgame', including to assess the utility and feasibility of type 2 OPV cessation in the pre-eradication era (i.e. prepare for a switch from tOPV to bOPV for routine immunization). The WG initiated work on this third TOR during their 3rd meeting in March 2011, and continued the review of relevant evidence during the fourth meeting in Feburary of 2012. Following the fifth SAGE Polio WG meeting in September 2012, it is anticipated that SAGE will review, by April 2012, the potential timeframe towards synchronouse OPV2 cessation, which is now targeted for 2015 or 2016, pending progress towards affordable IPV options and establishing other key pre-requisites for OPV2 cessation, including policies for longterm biocontainment policy and post-OPV outbreak response. The WG, recognizing the continued risks associated with eventual cessation of all OPV use (i.e. cessation of bOPV), recommended at their 5th meeting that countries should plan to continue IPV vaccination for at least 5 years after bOPV cessation. This issue will be reviewed as additional information becomes availabel, particularly the experience with OPV2 cessation.
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	Ongoing	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). 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.
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. The WHO PE research team continued to provide updates on ongoing studies conducted to inform the programme of work on the new polio endgame at the 4th and 5th SAGE Polio WG meetings in 2012.

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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 tOPVÕbOPV switch and longer term IPV uptake following complete OPV cessation.	Action	Apr 2012	Ongoing	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. 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. Further consultations towards finalization of the document will be held with the IMB in October and a during the polio session at the November 2012 SAGE meeting.
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	The financial requirements for the 'Endgame' are projected to be US$ 5.5 billion for the period 2013-2018; this reflects substantial work under various scenarios and is the consensus position of the core GPEI partners, in consultation with the relevant global, regional and country stakeholders. The proportion across key budget categories, which include the introduction of IPV, surveillance and laboratory costs, outbreak response capacity & vaccine stockpiles, as well as containment certification costs, will be adjusted as progress against key polio eradication milestones is evaluated. Adjusting the estimated year of interruption will increase/decrease costs accordingly. The financial needs of this plan will be met by implementing a resource mobilization, communications and advocacy strategy jointly developed by GPEI partners with the guidance of the relevant executive groups in the GPEI architecture, particularly the Polio Partners' Group and the Polio Emergency Steering Committee. Discussions with GAVI are ongoing to ensure financing for the introduction of a low-cost IPV option as part of OPV2 cessation for GAVI-eligible countries.
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	The SAGE Polio WG will, during the November 2012 SAGE meeting, report in detail on the outcome of discussions about the ongoing work towards achieving options for affordable IPV, including on the WGs direct interaction with four IPV manufacturers; discussions with regulatory authorities have started but will need to continue and be intensified as progress is made on this important issue with manufacturers.
Polio eradication	SAGE noted that the Inactivated Polio Vaccine (IPV) working group had revisited the issue of post-eradication IPV policy in low-income settings in the light of the new information on affordable IPV options and agreed that the group should now focus on further clarifying the criteria for IPV use (e.g. coverage and cVDPV risk) and the modalities of use (e.g. schedules and vaccine formulations) in the post-eradication era.	Action	Apr 2011	Ongoing	The Working Group has convened by teleconference in September 2011 to discuss the potential expansion of the remit of the Working Group to inform the development of a comprehensive new pre- and post-eradication 'polio endgame strategy'. Key strategic issues the Working Group will be asked to work on are a) a synchronized switch from tOPV to bOPV for routine immunization globally, and b) the early introduction of low-cost IPV, in advance of, or coinciding with, the tOPV-bOPV switch, and c) the synchronized cessation of all bOPVs for routine immunization globally. Since then, SAGE has renamed the group as 'SAGE Polio Working Group', and approved of the expanded remit to provide guidance on the 'new polio endgame', including the tOPV to bOPV switch.

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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	The Executive Board in January 2012 adopted a Resolution declaring the completion of polio eradication to be a programmatic emergency for global public health, requiring the application of appropriate vaccination recommendations for all travellers to and from areas infected with poliovirus. In response to the Independent Monitoring Board's report from February 2012, in its report to the World Health Assembly May 2012, the GPEI secretariat highlights that all approaches should be considered, including 'the possibility of using the International Health Regulations to limit the potential spread from affected countries.' Additionally, as in previous years, the World Health Organization will in 2012 update its International Travel and Health publication, providing vaccination recommendations to travellers based on the most up-to-date global polio epidemiology.
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	Ongoing	As a fundamental step in the polio endgame, the SAGE Polio Working Group recommends that synchronous OPV2 cessation should be targeted for the near-term (i.e. 2015 or 2016). The SAGE Polio WG, at their 5th meeting in September 2012, continued to review in detail progress towards preparing for the eventual cessation of OPV2 (i.e. the 'tOPV-bOPV switch'); this included direct interaction with four IPV manufacturers to elucidate options and timeframe for the availability of affordable IPV, as well as a detailed review of key pre-requisites for OPV2 cessation such as long-term policies for laboratory biocontainment of polioviruses and post-OPV outbreak response, as well as the status and sensitivity of surveillance for polioviruses. It is expected that by April 2013, SAGE will be presented with a more detailed time-frame on the evolution of the polio endgame, including the time-frame to prepare for OPV2 cessation by 2015 or 2016.
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.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of global public health resource and additional efforts 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	Ongoing	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.
Rotavirus immunization schedules	SAGE requests WHO to develop tools to support country decision-making and where possible National Immunization Technical Advisory Groups (NITAGs)and Regional Technical Advisory Groups(RTAGs)should assist this process.	Action	Apr 2012	Completed	Communication strategy, country summaries, global summaries and web site have been completed.
Rotavirus immunization schedules	SAGE recognized that a comprehensive communication strategy that explains the reasons for this change of schedules should be developed and made available to all stakeholders including policymakers, programme managers, communities and parents, and requested WHO to develop appropriate tools.	Action	Apr 2012	Completed	Communication strategy, country summaries, global summaries and web site have been completed.

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Thiomersal	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
Thiomersal	SAGE endorses the proposal for a scientific meeting on alternatives to thiomersal prior to the fourth session of the Intergovernmental Negotiating Committee to prepare a global legally binding instrument on Mercury (INC4), as this would support the aims of the INC and avert concerns that developing countries are using products no longer used in industrialized countries. SAGE asked GACVS to present a review of the safety of alternative preservatives. SAGE will also consider the broader implications of alternative preservatives for global immunization policy.	Action	Nov 2011	Completed	A scientific meeting was held on 3-4 April 2012 to develop further guidance on vaccines for the UNEP-convened Intergovernmental Negotiating Committee meeting 4, and the conclusions of this meeting were reported to SAGE on April 2012 for a specific session Information on vaccines for an Intergovernmental Negotiating Committee to prepare a global legally binding instrument on the use of mercury took place at the April 2012 SAGE meeting. It discussed thiomersal and alternative preservatives and presentations.
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	Pending	Written update will be provided for the November 2012 SAGE meeting.
Typhoid	Need for feedback from WHO's regional offices and countries to determine how countries could implement SAGE recommendations.	Action	Nov 2007	Ongoing	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 all stakeholders interested in typhoid and to develop a global agenda for the control and prevention of typhoid fever. WHO will work closely with Sabin in this process. Since typhoid vaccine is one of the 7 vaccines that GAVI listed as their priority vaccines for support, for the November 2011 meeting of the GAVI Board, a case was made for typhoid vaccine support. The GAVI Board finally 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 stand there is clearly no appepite for any donors to support ViPS typhoid vaccine. Thus all activities related to encouraging countries to consider ViPS are stopped. Focus is now on supporting the development of conjugate vaccine and strengthening surveillance in countries to generate better data on typhoid.

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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	The Coalition against Typhoid (CaT) grant from the Bill and Melinda Gates was approved and Sabin Vaccine Institute has received a three year grant to do this work. In collaboration with partners, CaT has now developed a detailed work plan for typhoid and partners need to mobilise resources to implement them. WHO prequalified the sanofi pasteur Vi polysaccharide vaccine which has been major step as it is the first typhoid vaccine to be WHO prequalified. [Update 27 Jan 2012]: Through a collaborative effort, revised technical document on advancing the use of existing typhoid vaccines was prepared and submitted to the GAVI Policy and Planning Committee in October 2011 for discussion by GAVI Board in November. The Board met and decided that GAVI will only open a typhoid vaccine support window when a WHO prequalified conjugate typhoid vaccine is available. This effectively dampens interest to use ViPS vaccine. And a conjugate typhoid vaccine is unlikely to be availabe in the next five years or so.
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 have been incorporated in the framework to reduce unvaccinated children. In addition a case study from India has also been included. The finalization of the framework is on-going. A follow-up meeting with the WHO regions and partners was scheduled on the 4th October 2012 to review the different approaches in progress.
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	Ongoing	The work has been prioritized. A framework to increase coverage has been drafted and was presented to a small group comprising of representatives from EURO (2), AFRO (1), HQ and Dr David Durrheim, member of SAGE. The draft from HQ as well as parallel work going on in EURO and AFRO was presented. A follow-up meeting with the WHO regions and partners was scheduled on the 4th October 2012 to review the different approaches in progress.
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 has been conceptualized. In addition to the work on the framework at HQ, the EURO, AMRO/PAHO and AFRO regional offices of WHO are working on operational guidelines and demand generation side documents respectively. A framework to increase coverage has been drafted and was presented to a small group comprising of representatives from EURO (2), AFRO (1), HQ and Dr David Durrheim, member of SAGE. The draft from HQ as well as parallel work going on in EURO and AFRO was presented. A follow-up meeting with the WHO regions and partners has been scheduled on the 4th October 2012 to review the different approaches in progress.
Vaccination in humanitarian emergencies	SAGE asked the working group to consider how a broader awareness among agencies of the Siracusa principles,4 particularly the balance between individual and community rights, could be communicated.	Action	Apr 2012	Ongoing	The draft has been circulated to all major agencies for review and comments are already being received. Further awareness raising efforts regarding Syracusa principles among agencies should occur through fora such as health cluster mechanisms, etc
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	ERM staff do consider that the framework approach for other health interventions in emergencies is a good recommendation from SAGE. There is currently a lack of staff to follow-up on this recommendation but ERM hopes to revisit this issue in the coming months.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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	Ongoing	Pilot testing ongoing in the Horn of Africa (completed); Pakistan; and South Sudan
Vaccination in humanitarian emergencies	SAGE requested that the finalized framework be presented to the November 2012 SAGE meeting for consideration.	Action	Apr 2012	Ongoing	Finalization of the draft is ongoing and the draft will be presented at the November 2012 SAGE meeting.
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 (details available from: www.gatesfoundation.org/vaccines/Pages/rfp-immunity-assessment-tool.aspx). Question to SAGE should WHO in parallel also support new research or should upon the development of this tools review the feasibility of incorporating this tools in existing survey methods.
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. As of September 2012: A consultant has been recruited to review currently available biomarkers and draft a guideline 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. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results will be discussed. Work in progress will 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.
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. As of September 2012: • Convened initial meeting 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, the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies.

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	Since the November 2011 SAGE session on VPD surveillance, WHO has conducted the following activities as aligned with SAGE recommendations: 1) clear objectives of the sentinel site surveillance network should be established. WHO has drafted a mission statement and objectives, which are currently being internally reviewed 2) WHO leadership in establishing minimal criteria for national surveillance management commitment; use of modern data collection and sharing processes. In December 2011, WHO began the dissemination five (5) agreed minimal criteria, as follows: • The country establishes a surveillance management team , consisting of: o Ministry of Health focal point; Sentinel hospital focal point; Sentinel hospital laboratory focal point, and Data manager focal point. • Countries that are conducting only Tier 1 meningitis surveillance enrol at least 100 suspect meningitis cases per year into the surveillance system and investigate cases according to the established surveillance protocols; • The country reports data regularly to WHO according to the schedule agreed with the WHO Regional Office; • The sentinel sites (if applicable) and/or national laboratories in the country participate in the WHO laboratory IB-VPD external quality assessment programme; and • Countries conducting only Tier 1 meningitis surveillance will meet the established quality indicators for Tier 1 before WHO provides funding for the country to establish Tier 2 (meningitis-pneumonia-sepsis) surveillance. 3) Developing methods to estimate the catchment population. WHO has drafted a methodology for determining a catchment population for IB-VPD Tier 1 sentinel surveillance which is currently being discussed with partners and will be piloted in March in Nepal. 4) Adequate funding and human resources for surveillance. Currently, WHO has no firm commitment from donors for 2013 funding for sentinel site surveillance. WHO has been discussing continued funding with GAVI. 5) Sustaining the global and regional reference laboratories for training, quality assurance, and PCR testing of culture negative specimens. WHO is in the process of contracting with global and regional reference laboratories and is working to ensure that regional reference laboratories conduct PCR testing of CSF specimens from sentinel sites. 6) Developing global standard operating procedures for clinical, laboratory and data management; and enhancing site capacity. A new laboratory manual for IB-VPD meningitis laboratory diagnostics was finalized in November 2011 and is available on the WHO website. (http://whqlibdoc.who.int/hq/2011/WHO_IVB_11.09_eng.pdf) An accompanying laboratory poster and clinical poster (on the process of obtaining CSF) is currently being printed and will also be provided to all sentinel sites.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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	Ongoing	A SAGE Working Group on vaccination in humanitarian emergencies was established in June 2011 http://www.who.int/immunization/sage/sage_wg_hum_emergencies_jun11/en/index.html Two face-to-face meeting of the working group took place on 20-21 September 2011 and on 16-17 February 2012. The group is holding regular teleconferences. Although it was initially envisoned that the working group would complete its work on time for a SAGE review of the conmplete framework for decision making on the use of vaccinations in humanitarian emergencies, the work is not yet complete and the working group requested some broad consulation with partners prior to submitting the framework to SAGE's review and approval. In April 2012 SAGE will then be provide with the outcome of the literature review and completed ethical perspective in support of the use of vaccination in humanitarian emergencies. It will be asked to discuss the proposed "Vaccination in acute humanitarian emergencies: a framework for decision-making" and advise on activities necessary to facilitate the further buy in and use of the framework. A review and definitive endorsement of the complete framework will then be sollicited in November 2012.
Varicella and Herpes Zoster vaccine Working Group	Establishment of a SAGE working group on the use of varicella and herpes zoster vaccine.	Action	Nov 2011	Completed	The establishment of a SAGE working group on the use of varicella and herpes zoster vaccine was slightly delayed to follow the establishment of the working group on dealing with vaccine hesitancy. Following a call for nominations, the working group was finally established in May 2012 and has since then held monthly teleconferences.

WHO/AFRO TASK FORCE ON IMMUNIZATION MEETING

SUMMARY REPORT

BURGERS PARK HOTEL, PRETORIA, SOUTH AFRICA
21 TO 22 JUNE 2012

Background

The Task Force on Immunization (TFI) serves as the principal advisory group to the WHO Regional Office for Africa (WHO/AFRO) for development of policies related to vaccines and immunization. TFI is charged with advising WHO on overall regional policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization services and linkages between immunization and other health interventions. The mandate of TFI is to provide strategic advice rather than technical input, and is not restricted to childhood vaccines and immunization but extends to the control of all vaccine-preventable diseases in the context of health systems strengthening.

In this light, the 21st TFI Members' Meeting convened at Burgers Park Hotel, Pretoria, South African, from 21 to 22 June 2012. Key objectives of this meeting were for TFI Members to be adequately briefed on progress made in implementing 2011 TFI recommendations as well as exchange on technical updates and recent scientific developments with a particular focus on:

- Strategic options for rubella control and congenital rubella syndrome (CRS) elimination in the African Region;
- Developing a regional communication strategy for immunization;
- Implementing research for immunization in the African Region;
- Assessing progress made in attaining the regional polio eradication goal; and
- Reviewing recent SAGE recommendations and their implications for the African Region.

Opening Session

The meeting was opened by the WR/South Africa *a.i.* who welcomed participants to Pretoria. He pointed out that the on-going WHO reform is essential to help the Organization adapt to the changing complexity of public health which will allow WHO to fulfil more effectively its

role as the world's leading public health agency and, at the same time, create a more flexible Organization which is better equipped to respond to the health needs of the 21st century. He then highlighted that the reform process itself has three overall objectives, namely: (1) Improved health outcomes, with WHO meeting the expectations of its Member States and partners in addressing agreed global health priorities, focused on the actions and areas where the Organization has a unique function or comparative advantage, and financed in a way that facilitates this focus; (2) Great coherence in global health, with WHO playing a pivotal role in enabling the many different actors to play an active and effective role in contributing to the health of all peoples; and (3) An Organization that pursues excellences – one that is effective, efficient, responsive, objective, transparent and accountable.

WR/South Africa then reviewed the proposed two-day programme-of-work and stated that topics to be covered would lead to the strengthening of immunization systems within the African Region and, moreover, positively impact on MDG-4 by contributing to the reduction of the child mortality rate within the Region. He emphasized that the recent World Health Assembly (WHA) resolution on the Decade of Vaccines and its associated Global Vaccine Action Plan; and the recent WHA resolution that declared polio a programmatic emergency for global public health, would guide recommendations made at this TFI Members' Meeting for the Regional Director's consideration.

Review of Implementation of December 2011 TFI Recommendations

The IVD Director informed TFI Members that of the 16 recommendations made in December 2011, 7 (44%) were fully achieved; 7 (44%) were in process of being implemented; and 2 (12%) were not achieved. TFI Members appreciated that political commitment to attain the polio eradication goal remains high; that polio emergency plans are being satisfactorily implemented; and that cross-border cooperation is being facilitated with supportive documents (such as declarations and reports) following meetings and visits. They took note that the polio risk assessment/prediction tool is in the process of being used in all countries in an attempt to mitigate risks and that polio surveillance is in the process of being further strengthened at the sub-national level in all countries to meet operational targets.

TFI Members took due note that the strategy document entitled *Reaching the unreached children with immunization services: strategy options for the African Region* was disseminated to all countries and partners within the African Region. They were informed that countries are in the process of developing plans to operationalize the proposed strategy options in order to reach the unreached children with full participation of their communities; and

although not yet achieved, WHO/AFRO would develop in the coming months, technical guidelines for the implementation of country plans based on proposed strategy options.

With regard to the successful 2012 African Vaccination Week (AVW), TFI Members were informed that countries did start preparations early to include the involvement of the media, private sector, civil society, opinion leaders and communities in planning, implementing and evaluating the initiative; and that WHO/AFRO did publish a leaflet on AVW as a tool to increase awareness. For future AVW initiatives, countries are in the process of developing medium-terms goals.

As recommended at the last TFI Members' Meeting, a draft document entitled *Strategic options for rubella control and congenital rubella syndrome (CRS) elimination in the African Region* was developed for review/discussion at the June 2012 TFI Members' Meeting. Concerning measles, implementation of the 3rd Regional Measles TAG recommendations are in process in an attempt to attain the pre-elimination targets for 2012 as a milestone towards the 2020 elimination goal.

Concerning Maternal & Neonatal Tetanus (MNT), TFI Members were informed that countries are in the process of developing strong programme linkages between the immunization programme and maternal & newborn health services, as well as other related programmes in order to accelerate the attainment of the MNT elimination goal. Furthermore, countries that have not yet completed TT SIAs, are in the process of scaling-up implementation of MNTE strategies in order to reach the MNTE goals. Although not yet achieved, WHO/AFRO will provide technical guidance/support to country that have already attained the validation of MNT elimination in order to assist them sustain/monitor progress regarding status of MNT elimination.

Annex 1 of report provides details of status of implementation of each recommendation.

Rubella Control & CRS Elimination

A number of presentations were made on rubella control and CRS elimination, ranging from a global perspective of rubella control & CRS elimination to the epidemiology of rubella & CRS in the African Region. Of the 130 countries that globally report rubella coverage[1], only 3 countries are located within the African Region – all of which are island nations[2] which may

[1] Coverage with the first dose of measles-containing vaccine used as proxy to calculate rubella coverage
[2] Cape Verde, Mauritius, Seychelles

not provide an accurate representation of rubella coverage. Moreover, the African Region currently does not have a defined goal on rubella control or CRS elimination. Noting that limited data is available on the epidemiology of rubella in the African Region, acquiring adequate evidence is imperative in order to inform decision-making related to the introduction of the rubella vaccine in a phased manner within the Region. Taking this into account, the importance of building national capacity to improve rubella and CRS reporting was highlighted as well as investigating and effectively documenting rubella outbreaks. Furthermore, supporting rubella sero-surveys in a number of selected countries was stressed as well as strengthening/scaling-up CRS sentinel surveillance and conducting retrospective record reviews for CRS cases.

Thereafter, WHO/AFRO presented to TFI Members the proposed AFR regional strategy option for rubella control and CRS elimination which included the following 3-step process, namely:

Prepare	Disseminate relevant background documents to countries and continue to present/discuss issues using opportunities as they arise.
	Support selected countries to conduct sentinel surveillance for CRS, especially following documented rubella outbreaks.
	WHO & UNICEF to continue to dialogue/advocacy with countries regarding the uptake of rubella vaccines according to approaches recommended for rubella/CRS elimination.
	Identify countries to prioritize for the introduction of RCVs through MR vaccination campaigns and routine immunization commencing 2013.
	Provide technical guidance & advocate with non-GAVI eligible countries to encourage them to introduce rubella containing vaccines according to recommended strategies.
	Support the investigation and documentation of rubella epidemics.
	Support CRS sentinel surveillance and retrospective reviews of clinical records and registers in speciality clinics.
Initiate	Intensify advocacy and technical support to countries to facilitate the country application to GAVI before end-2012.
	Support eligible countries to develop comprehensive plans for the implementation of rubella/CRS elimination strategies.
	Support operational research to determine the magnitude of the CRS problem and the communication barriers/behavioural gaps that be addressed to facilitate a successful introduction of rubella vaccine into the national immunization schedules.
Scale-up	Develop a regional strategy document and long-term plan for rubella/CRS elimination for possible discussion at the WHO Regional Committee.
	Assess the capacity of the measles/rubella surveillance & laboratory network to test increased numbers of specimens and introduce integrated measles/rubella surveillance.
	Continue to monitor impact as rubella vaccine is introduced in all countries.

Thereafter, TFI Members endorsed the proposed AFR regional strategy option for rubella control and CRS elimination with the understanding that the amendments, inclusions and comments they raised be included in final version of strategy.

Communication for Immunization

Two presentations on communication for immunization were made which highlighted the crucial role communication plays in increasing immunization coverage. The first presentation concentrated on monitoring & evaluation (M&E) for immunization communication which outlined how communication can be monitored & evaluated via mass media, print media, community level communication and advocacy; and what can be measured – namely:

Communication for Immunization – What can be Measured?	
Reach	Demographics and geography of those reached
	Frequency/intensity of reach (exposure levels)
	Who were not reached – further in-depth research required
Reception	Appropriateness (e.g. language, culture, format)
	Clarity and resonance of message
Effects	Knowledge about immunization efficacy, services adverse effects, rights to vaccines
	Changes in beliefs and social norms in relation to vaccinations (e.g. dispelling myths)

Presentation also emphasized how M&E can be used to assess the effectiveness of communication to increase community/individual understanding of the value of vaccines and their health rights to immunization, as well as how the development and implementation of communication strategies and plans can be monitored.

The second presentation concentrated on using communication for social change where it was highlighted that the key drivers of the change process include: dialogue & debate; action & reflection; social learning; and self & community efficacy. In order to develop quality communication materials, emphasis was placed on: understanding the complexity of human behaviour; seeking to understand target audience barriers to knowledge/adoption; using appropriate local languages and mediums; testing all communication material prior to delivery; using adequate time and resources; and ensuring on-going critical evaluation and monitoring.

Subsequently, TFI Members requested that WHO/AFRO develops a regional immunization communication strategy which takes into consideration the current communication strengthens and weaknesses within the region by country; the country needs for communication competencies; a plan for the development of in-country communication competency development; among others.

Recent 2012 SAGE Recommendations

WHO/HQ presented to TFI Members the conclusions and recommendations from the extraordinary meeting of SAGE held in February 2012, and the SAGE meeting held in April 2012. TFI Members were informed that the 65th WHA endorsed the Decade of Vaccines Global Vaccine Action Plan (GVAP) and that WHO's role in supporting the roll-out of GVAP would include: regular reports to WHO governance; supporting the translation of GVAP into regional and country strategies; and supporting the implementation and monitoring of GVAP at all levels. In addition, the 65th WHA designated the last week of April as World Immunization Week which would be used as the overarching framework to promote importance of vaccination across the life-course and ensure universal access to vaccination.

With regard to the April 2012 SAGE Meeting, topics covered included: establishing a global emergency oral cholera vaccine stockpile; switching from tOPV to bOPV (which will be further discussed at the next SAGE Meeting scheduled to take place in November 2012); use of seasonal influenza vaccines; vaccination in humanitarian emergencies; hepatitis A vaccine; impact of introduction of new vaccines on immunization and health systems; rotavirus vaccine – optimizing schedules; information on vaccines for an inter-governmental negotiating committee on mercury.

Annexes 2 & 3 of report provides tentative topics for discussion at the next SAGE meeting in November 2012 in addition to cross-cutting and strategic issues for discussion at future SAGE meetings scheduled for 2013 and 2014.

TFI Members were appreciative of information session on SAGE recommendations made to date in 2012 and requested that such information be sent to all EPI Managers and WHO Country Offices on a regular basis.

Implementation Research in support of Immunization

Two presentations on immunization implementation research were made; one on setting a prioritized global agenda; the other on implementation research in support of immunization within the African Region. TFI Members were informed of the process, scope and guiding principles in place to develop a global immunization research agenda that maximizes the impact of vaccines and immunization as well as defines and implements a transparent and collaborative process to take forward such an agenda. Additionally, TFI Members learnt about the role WHO would play once the global immunization research agenda is developed – namely:

WHO's Role – Implementation Research Agenda	
1	Serve as a catalyst to garner support
2	Provide platform to bring different stakeholders together
3	Take forward research products useful for policies through WHO established processes
4	Initiate research for critical research topics not taken up by any specific research groups
5	Explore similar initiatives at the regional level
6	Plan to keep agenda alive rather than a one-time process

With regard to implementation research in support of immunization within the African Region, TFI Members were briefed on steps taken by WHO/AFRO to conduct a rapid review of available peer reviewed literature and reports on this topic. Findings found that only 10% of publications were from African affiliations, and approximately 30% of published materials were written by WHO staff. TFI Members were also informed that a number of pertinent topics related to immunization implementation research were made through SAGE recommendations over the past years as well as by WHO at various immunization forums.

TFI Members then reviewed and endorsed the draft document proposed by WHO/AFRO to address implementation research on immunization within the region with the understanding that the amendments, inclusions and comments raised by each TFI Member be included in final version of document.

Polio Eradication

A number of presentations were made on polio eradication in terms of recent global and regional developments as well as progress made against major process indicators and data-derived insights. TFI Members were informed that, globally in the first four months of 2012, there have been substantially fewer cases (-58%) in fewer districts (-46%) of fewer countries (-67%) compared to the same period in 2011. However, due to the funding shortfall the Global

Polio Eradication Initiative faces in 2012 and beyond, a substantial number of planned 2012 polio campaigns within the African Region have been cancelled, and the trend is set to continue should funding constraints and OPV shortages prevail - which will jeopardise gains made to date. Moreover, TFI Members were briefed that in the four[3] polio priority countries, 1.84m children never received a single dose of OPV. TFI Members were then duly updated on recommendations of the most recent Polio Independent Monitoring Board Meeting (April 2012); SAGE recommendations related to polio (April 2012); and outcome of polio deliberations at the 65th WHA (May 2012).

In terms of country-specific key developments and key concerns/risks, the following information was shared with participants - namely:

	Major Developments	Major Concerns/Risks
Nigeria	▪ Presidential polio task force launched ▪ 2012 national emergency plan developed ▪ Strategies to deal with refusals executed ▪ Over 2,200 surge staff to be recruited ▪ GIS/GPS used to improve SIA quality ▪ Environmental surveillance expansion ▪ Accountability framework in place	▪ Prevailing insecurity in Northern Nigeria ▪ Inadequate political commitment at LGA level ▪ Sub-optimal quality of SIAs leading to increased number of missed children ▪ Weak RI coverage leading to increase in susceptibles and VDPV circulation
Angola	▪ Increased political commitment from central to provincial levels ▪ Improved SIA quality - except Luanda ▪ Environmental surveillance initiated ▪ On-going cross-border activities with DRC & Namibia ▪ HR surge capacity in Luanda	▪ Political commitment not always reflected at district level ▪ Increased trend of missed children in Luanda ▪ Surveillance gaps - particularly in Luanda ▪ Weak RI coverage at sub-national level
Chad	▪ Increased political commitment from central to provincial levels ▪ Polio emergency plan reviewed ▪ Strategies developed to reach the unreached children ▪ HR surge capacity implemented	▪ Political commitment not always reflected at district level ▪ High vulnerability of children living in Lake Chad Islands ▪ Sub-optimal quality of SIAs ▪ Very low RI coverage ▪ Surveillance gaps at sub-national levels
DRCongo	▪ EPI review conducted ▪ 6-month outbreak assessment conducted	▪ Recurrent insecurity in Eastern DRC ▪ Political commitment not always reflected at

[3] Angola (45,000); Chad (140,000); DRCongo (640,000); and Nigeria (610,000)

	▪ Reduction of missed children in some provinces ▪ LQAS implemented during SIAs ▪ Increased use of social data to improve SIAs	district level ▪ Surveillance gaps & low population immunity ▪ Sub-optimal quality of SIAs with persistent refusals

In terms of data derived insights, it was highlighted that a high proportion of children in Nigeria continue to be missed in many LGAs located in high-risk states as demonstrated by recent independent monitoring and LQAS data. Furthermore, in Angola (particularly in Luanda), up to 13% to 20% of children are being missed despite the overall improvement of SIAs in other areas; and that in DRCongo, poor quality of SIAs prevail despite many campaigns in Katanga, witnessing cVDPV oubreaks which confirms low population immunity. Finally, in Chad, there is an overall improvement in SIAs quality especially in Logone Oriental (the foci of transmission) and Tandjile (where nomadic population are located).

TFI Members welcomed this polio update and voiced their agreement with the recent SAGE and IMB polio recommendations made that adequate funds and OPV stocks be in place in a timely manner in order to conduct all planned polio emergency activities. TFI Members also raised concern that due attention is not being paid to urban settings where polio prevails and that GPEI should intensify focus on Northern Nigeria and ensure all planned polio activities in West Africa be implemented.

TFI Recommendations

Based on the latest detailed immunization information provided to TFI Members, the following TFI recommendations were made:

Rubella Control and CRS Elimination

Preamble:

The TFI has deliberated at length on the presentations made and on the proposed regional strategy option for rubella control and CRS elimination.

The July 2011 updated WHO position paper on rubella vaccines has provided the necessary guidance on the recommended strategies to attain the elimination of rubella and CRS, as shown in other Regions. The WHO position paper and available data from the African Region has indicated that there is adequate evidence of the epidemiological picture of rubella and CRS. However, TFI notes that there is a need to continue to generate more up-to-date scientific evidence relevant to the African Region.

TFI also notes the guidance that countries should attain and sustain at least 80% vaccination coverage in routine immunization and/or in SIAs so as to achieve and maintain CRS elimination over the long term.

TFI notes with appreciation the opening of the GAVI window to support countries to introduce rubella containing vaccines.

TFI endorses the strategic option document with the proposed amendments, inclusions and comments.

The TFI recommends that:

1. WHO/AFRO changes the designation of the Regional Measles TAG to Regional Rubella/Measles TAG.
2. The Regional Rubella/Measles TAG provides guidance to WHO to refine the strategies for Rubella/CRS elimination in the Region and to develop and propose interim goals, including for a pre-elimination stage.
3. The Rubella/Measles TAG recommendations be discussed by the TFI in June 2013.
4. An agenda item on Rubella/CRS elimination be included in the WHO Regional Committee Meeting for 2014.

5. Countries that have already achieved ≥80% MCV1 coverage should make efforts to introduce rubella vaccine, using the opportunity of the GAVI co-financing mechanism or through their own means.
6. WHO/AFRO and partners should support countries to conduct research and/or to set-up robust surveillance systems to better understand the epidemiology of rubella and CRS.
7. WHO/AFRO and partners should conduct advocacy with countries and provide technical and financial support to build evidence of disease burden, to forecast vaccine needs and scale-up the introduction of RCVs.

Indicators for measurement:

a. TAG has advised WHO/AFRO and partners on the development of a final strategy document and proposed interim goals for pre-elimination (before June 2013).
b. The Rubella/Measles TAG recommendations discussed by the TFI in June 2013.
c. An agenda item on Rubella/CRS elimination has been included in the WHO Regional Committee meeting for 2014.
d. Eligible countries have included rubella vaccine in their cMYPs.
e. Countries have been supported by WHO/AFRO and partners to conduct research and/or to set-up robust surveillance systems.
f. WHO/AFRO and partners have advocated with countries and provided technical support.

Communication for Immunization

Preamble:

Although there has been significant work done in the WHO African Region around communication for immunization, particularly in relation to the polio eradication initiative and efforts to reach all targeted populations, the Decade of Vaccines creates an opportunity to build on this work and develop a regional communications strategy for immunization that will build towards the following goal:

> To enable "*individuals and communities to understand the value of vaccines and demand immunization as both their right and responsibility"* (strategic objective 2, Global Vaccine Action Plan).

Communication is central in achieving the above goal and in sustaining programmes. Communication helps communities and individuals to:

- Understand the benefits and risks of immunization;

- Seek services;
- Make demands on the health system;
- Improve ownership of the planning and implementation of programmes locally;
- Build networks and communities of practice.

The TFI recognizes that good communication is based on a set of key values, a list of which is outlined (but not exhaustive) below:

- Is based on research and evidence (quantitative and qualitative);
- Is based on theoretical models for social and behaviour change;
- Is culturally sensitive;
- Is gender sensitive;
- Is focused on principles of equity and accessibility to information ensuring attention to highly vulnerable populations;
- Is based on human rights to include the fundamental elements of impartiality, neutrality and humanity;
- Builds local capacity, an on local skills, networks and traditions;
- Uses a mixture of tools (media/TV, radio, print, outdoor, mobile phones; community dialogues, community networks, events, etc.);
- Engages a mixture of stakeholders;
- Is of sufficient magnitude to have an impact;
- Is measured for progress, outcome and impact.

The TFI restates its previous recommendation of developing a regional immunization communication strategy and for that purpose

The TFI recommends that:

1. WHO/AFRO and other partners should initiate the process for the development of a regional immunization communication strategy. The first part of the process should be a situational analysis, using a tool to measure competences for health communication in the region at country, district and community levels.
2. Following the situational analysis, a group of experts (from many disciplines and cultural backgrounds) should meet to discuss the findings and provide relevant guidance for the development of a regional strategy.
3. A dedicated group should be tasked to develop the regional immunization communication strategy.

Indicators for measurement:

a. A country-level situational analysis on immunization communication is completed by end-November 2012;
b. A meeting of experts with multi-disciplinary background on communication is held at the December 2012 Annual Regional Conference on Immunization.
c. The draft strategy document on immunization communication presented to the TFI at its first meeting in 2013.

Implementation Research in support of Immunization

Preamble:

Research has been a main emphasis of TFI recommendations in the past and that this is being addressed by WHO/AFRO. TFI notes with satisfaction that a draft document has been prepared by WHO/AFRO in consultation with a TFI Working Group on Research, to address implementation research on immunization in the region.

TFI also acknowledges on-going efforts at the global level to develop an immunization implementation research agenda and notes that there are gaps in implementation of immunization programmes in the African region which can be addressed through research.

The TFI recommends that:

1. The document on implementation research in support of immunization within the African region should have a strong qualitative research component.
2. The document should be finalized taking into consideration a conceptual framework that includes recommendations from the various stakeholders and includes all areas relevant to immunization.
3. The document includes the following WHO/AFRO support to countries:
    a. Country research demands and ownership be enhanced;
    b. National research agendas be formulated;
    c. Capacity to access funding for research be built; and
    d. Partnerships be strengthened.
4. The regional implementation research document should be aligned with the WHO global implementation research agenda.

Indicators for measurement:

a. Revised document incorporated comments/amendments made by TFI Members at the June 2012 meeting and resubmitted to TFI Members for review by end-August 2012.
b. Comments from TFI Members received by WHO/AFRO by end-September 2012.
c. Document resubmitted after incorporation of comments received from TFI Members and tabled for formal endorsement in the TFI Members' Meeting in December 2012.

Polio Eradication

Preamble:

Since 2011, TFI acknowledges improvements made in the WHO African Region in terms of reducing wild poliovirus transmission. However, TFI is deeply concerned with:

- A 3-fold increase in WPV cases in Nigeria in 2012 compared to 2011 for the same period.
- A substantial number of polio SIAs and other polio eradication activities in the Region have been cancelled or scaled-down resulting in 1.84m children never received a dose of oral polio vaccine in the 4 polio priority countries mainly due to funding shortfalls, among other causes.
- AFP surveillance, routine immunization and quality of SIAs remain sub-optimal mainly at the sub-national level, with a potential high risk of failure to detect and interrupt WPV transmission, particularly in urban and peri-urban areas.
- On-going political and humanitarian crisis in West Africa, coupled with the high population movements in this sub-region, represents an important risk for on-going polio transmission.

Therefore, TFI strongly supports the SAGE and IMB polio recommendations to ensure that funds and vaccines are predictable and timely available in order to conduct all planned polio emergency activities. Special focus must be in urban and peri-urban settings. In addition, particular attention and increased efforts should be focused on Northern Nigeria and other West African countries.

The TFI recommends that:

1. Countries and WHO/AFRO should intensify their efforts to fully implement all previous TFI polio recommendations, the WHO/AFRO Regional Committee (RC) polio resolution (AFR/RC61.R4), and the 65th World Health Assembly (WHA) polio resolution, in order to complete the target of a polio-free African Region and recognizes that this is a good

opportunity for a massive advocacy endeavour to get countries and partners to commit themselves in this last effort towards polio eradication.

Indicator for measurement:

a. Number of countries that have implemented previous TFI polio recommendations and the recent RC and 65th WHA polio resolution.

Annexes

Annex 1 – Detailed status of implementation of December 2011 TFI recommendations

Annex 2 – SAGE November 2012: tentative topics for discussion

Annex 3 – SAGE Meetings in 2013 & 2014: Cross-cutting and strategic issues for discussion

Annex 4 – TFI Members' Meeting, June 2012: Programme-of-Work

Annex 5 – TFI Members' Meeting, June 2012: List of Participants

- FINAL REPORT-

TECHNICAL ADVISORY GROUP ON VACCINE-PREVENTABLE DISEASES
XX MEETING: "PAVING THE WAY FOR IMMUNIZATION"
Washington DC, 17-19 October 2012

Members 2012

Dr. Ciro A. de Quadros
Executive Vice President
Sabin Vaccine Institute
Washington, D.C., United States

President

Dr. Akira Homma
Chairman
Policy and Strategy Council, Bio -Manguinhos Institute
Rio de Janeiro, Brazil

Dr. Anne Schuchat
Director
National Center for Immunization and Respiratory Diseases (NCIRD)
Centers for Disease Control and Prevention
Atlanta, GA, United States

Dr. Arlene King
Chief Medical Officer
Ministry of Health and Long-term Care
Ontario, Canada

Dr. Jeanette Vega
Managing Director
Foundation Initiatives
The Rockefeller Foundation
New York, NY, United States

Dr. José Ignacio Santos Preciado
Senior Professor
Department of Experimental Medicine
School of Medicine, *Universidad Nacional Autónoma de México* (UNAM)
Mexico City, Mexico

Dr. Peter Figueroa (unable to attend)
Chief Medical Officer
Ministry of Health
Kingston, Jamaica

Dr. Ramiro Guerrero-Carvajal (virtual participation)
Director
Research Center for Social Protection and Health Economy (PROESA)
Cali, Colombia

Roger Glass
Director
Fogarty International Center, NIH/JEFIC-National Institutes of Health
Bethesda, MD, United States

Dr. Cuauhtémoc Ruiz Matus **Ad hoc Secretary**
Senior Advisor, Comprehensive Family Immunization
Pan American Health Organization
Washington, D.C., United States

Acronyms

AFP	Acute Flaccid Paralysis
aP	Acellular Pertussis vaccine
bOPV	Bivalent Oral Polio Vaccine
CDC	Centers for Disease Control and Prevention of the United States
CFR	Case Fatality Rate
CRS	Congenital Rubella Syndrome
cVDPV	(circulating) Vaccine-derived Poliovirus
DoV	Decade of Vaccines
DPT	Diphtheria-Pertussis-Tetanus vaccine
DPT3	Third dose of the Diphtheria-Pertussis-Tetanus vaccine
DTaP	Diphtheria, Tetanus and Acellular Pertussis vaccine (pediatric)
DT	Diphtheria-Tetanus vaccine (pediatric)
EPI	Expanded Program on Immunization
EW	Epidemiological Week
GACVS	Global Advisory Committee on Vaccine Safety
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan
Hib	*Haemophilus influenzae* type b
ICC	Interagency Coordinating Committee
IEC	International Expert Committee (for the documentation and verification of measles, rubella, and CRS elimination in the Americas)
IPV	Inactivated Polio Vaccine
MR	Measles-Rubella vaccine
NIP	National Immunization Program
NITAG	National Immunization Technical Advisory Group
NLN	National Laboratory Network
NNT	Neonatal Tetanus
NRA	National Regulatory Authority
OCV	Oral Cholera Vaccine
OPV	Oral Polio Vaccine
PAHO	Pan American Health Organization
PoA	Plan of Action
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
TAG	PAHO's Technical Advisory Group on Vaccine-preventable Diseases
tdap	Tetanus, Diphtheria, and Acellular Pertussis vaccine (adolescents/adults)
tOPV	Trivalent Oral Polio Vaccine
TT	Tetanus Toxoid vaccine
UNEP	United Nations Environment Program
UNICEF	United Nations Children's Fund
VAPP	Vaccine-associated Paralytic Poliomyelitis
WHO	World Health Organization
wP	Whole-cell Pertussis Vaccine

Introduction

The XX Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases of the Pan American Health Organization (PAHO) was held in Washington, D.C. on 16-18 October 2012.

The slogan for the meeting, "Paving the Way for Immunization", reflected the Region's global leadership in immunization.

The purpose of the meeting was to make recommendations on how to address current and future challenges facing immunization programs in the Americas.

The Deputy Director of PAHO, Dr. Jon Andrus, opened the meeting by welcoming the participants and providing introductory remarks.

Dr. Ciro de Quadros chaired the meeting and began by asking the participants to take a minute of silence in memory of Dr. Claudio Marcos da Silveira, who passed away on 28 August 2012. During his years in PAHO, he collaborated in the development and implementation of several immunization strategies that resulted in the regional control and elimination of various vaccine-preventable diseases, notably the regional elimination of polio and measles and the elimination of neonatal tetanus as a public health problem in most countries of the Americas.

The TAG recognized the contributions of the PAHO secretariat to the success of this meeting and thanked the headquarters for hosting it.

Polio Vaccines

The Global Polio Eradication Initiative (GPEI) continues to make progress towards eradication. Following the successful interruption of the circulation of polio in India in 2011, the virus is currently endemic in only three countries (Afghanistan, Nigeria and Pakistan). Nigeria is the only country in the world where the circulation of type 2 vaccine-derived poliovirus (cVDPV2) has circulated for over 5 years.

In 2011, wild polioviruses which originated in Nigerian and Pakistan caused epidemics in countries that had been polio-free, emphasizing the constant risk of importation or exportation of the virus to areas where polio had already been eliminated.

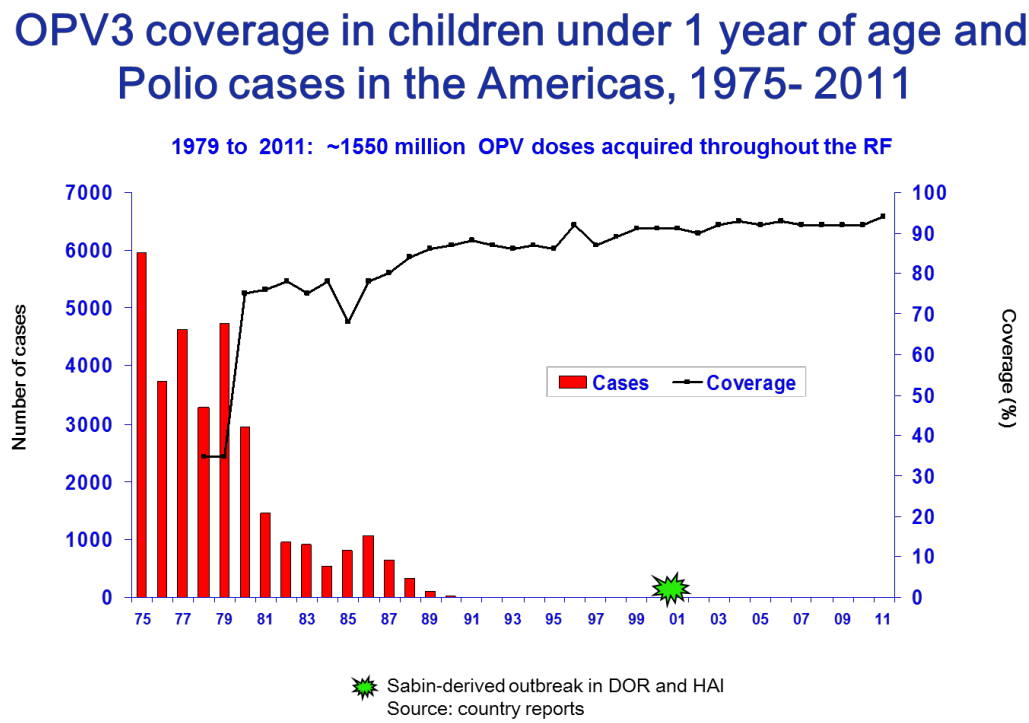
At its most recent meeting held in Geneva on 10-12 April, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended that, the World Health Organization (WHO) should promote switching from the trivalent oral polio vaccine (tOPV) to the bivalent oral polio vaccine (bOPV) for routine vaccination. This change should take place in a synchronized manner in order to minimize the risk of cVDPV2 circulation and outbreaks, as well as to accelerate the elimination of type 1 and type 3 wild viruses, since the bivalent vaccine provides better protection against those virus types than the trivalent vaccine.

The SAGE recommendation is based on the fact that "poliovirus type 2 was eliminated in 1999 and that the continued use of tOPV, in areas where coverage is not adequate, contributes to ongoing type 2 vaccine-associated paralytic poliomyelitis and vaccine-derived polio virus outbreaks (cVDPV2)." 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; and there should be an absence of outbreaks caused by cVDPV2 for at least one year, adequate epidemiological surveillance that makes it possible to detect and control any outbreak of cVDPV2, adequate quantities of bOPV available, an inactivated polio vaccine (IPV) at an affordable price, as well as a global reserve of type 2 monovalent vaccine (mOPV) and an international agreement to discontinue the global use of tOPV.

During its 65th meeting in May 2012, the World Health Assembly (WHA) adopted Resolution WHA65.5, which states that "Substantial planning is required for a globally synchronized switch from trivalent to bivalent oral poliovirus vaccine for routine immunization and, potentially, the introduction beforehand of one or more doses of inactivated poliovirus vaccine. In 2012, the SAGE will provide recommendations on the actual implementation of this strategy based on broad-based consultations across a number of work streams." In the Resolution, the WHA asks WHO's Director General to undertake the development, scientific vetting, and rapid finalization of a comprehensive polio eradication "endgame**"** strategy, and inform Member States of the potential timing of a switch from trivalent to bivalent oral poliovirus vaccine for all routine immunization programs.

Currently, there are still knowledge gaps to support this recommendation, and to address this issue several research projects are under way, promoted by WHO and the Bill and Melinda Gates Foundation. The research promoted by the BMGF will be conducted in 5 countries of Latin America and will evaluate the use of bOPV and IPV in sequential schedules.

The last indigenous case of wild poliovirus in the Region of the Americas was detected in 1991, and the Region was certified as polio-free in 1994. Since its elimination in 1991, the only cVDPVo outbreak occurred in 2000-2001 in the Dominican Republic and Haiti, and it was caused by a type 1 polio-derived virus (Figure). In 2010, the Region completed phase 1 of the laboratory containment of polioviruses. Since the elimination of polio in the Americas, countries continued to vaccinate and conduct surveillance of acute flaccid paralysis, with surveillance indicators similar to the pre-elimination era.



During this meeting, PAHO's Technical Advisory Group (TAG) on Vaccine-preventable Diseases discussed the implications of a potential change in vaccination recommendations, noting that the Region of the Americas managed to eliminate wild poliovirus in 1991; and since then has remained free of polio without outbreaks due to importation, using the tOPV vaccine.

Recommendations:

1. TAG awaits WHO's comprehensive polio eradication and endgame strategy as well as results from ongoing and planned research to revisit its recommendations for the Region of the Americas. At the present time, the trivalent oral poliomyelitis vaccine (tOPV) remains the vaccine of choice for the Americas. To this end, PAHO, in collaboration with WHO, should negotiate with providers to ensure sufficient supply of tOPV for countries of the Americas.
2. Countries considering the introduction of the inactivated polio vaccine (IPV) should first fulfill the sanitation and vaccination coverage conditions recommended during our last meeting (TAG XIX, Argentina 2011). If a country does not meet these basic conditions, it should conduct at least two annual vaccination campaigns, administering the tOPV vaccine to every child aged <5 years, without taking into account their previous vaccination status. Countries making plans to introduce the IPV should be able to guarantee its long-term supply, in addition to considering the price of the vaccine.
3. Countries should reinforce surveillance of acute flaccid paralysis (AFP), attain adequate levels in all basic surveillance indicators, and continue working to achieve >=95% polio coverage in every municipality.

4. As IPV will be considered for use in the polio *endgame* requested by the WHA, it will be important for WHO to maintain a fluid dialog with vaccine manufacturers to ensure an

adequate IPV supply at an affordable price for countries of all income levels, as this will be a factor in the rapid adoption of the vaccine.

5. PAHO is in an advantageous position to work with the GPEI, in the development of the endgame strategy and for the synchronized cessation of vaccines containing poliovirus type 2, and supporting cost-effectiveness studies for different scenarios. Additionally, the World Immunization Week could be used as an effective platform for global coordinated actions.

Use of Thiomersal in Vaccines

Mercury exists in different forms and compounds that can be found in the environment. Major sources of exposure include an accumulation of methylmercury within the food chain and through fish consumption. Methylmercury is a neurotoxic of major public health concern, with a half-life of approximately 50 days.

Thiomersal, which is also known as thimerosal, mercuriothiolate and sodium 2-ethylmercuriothio-benzoate, is a compound that contains ethylmercury and is used to prevent the proliferation of bacteria and fungus during storage and, above all, during the use of open multi-dose vials of certain vaccines, has a very short life of less than week, quickly excreting, therefore not accumulating in the human body.

Some vaccines contain traces of thiomersal (<0.5 µg per dose) if a preservative has been used during their manufacture, but has not been added to the end product. Other vaccines contain thiomersal in varying concentrations (from 10 to 50 µg per dose) added as a preservative in order to avoid contamination by microorganisms when multi-dose vials are produced. The diphtheria, pertussis, tetanus (DPT) vaccine, the diphtheria tetanus vaccine (DT), the tetanus toxoid vaccine (TT), and the hepatitis B, *Haemophilus influenzae* type b (Hib) and influenza vaccines are part of this group. These vaccines are used in over 120 industrialized and developing countries to immunize at least 64% of the annual world cohort of births, averting at least 80 million deaths per year, as well as illness and hospitalizations.

For over 10 years, through its Global Advisory Committee on Vaccine Safety (GACVS), WHO has closely followed scientific evidence pertaining to the use of thimerosal as a vaccine preservative for over 10 years. Following examination of available epidemiological information and the pharmacokinetic profile of this compound, it concluded that there was no evidence of mercury toxicity in infants, children or adults exposed to thiomersal from vaccines. Therefore, there is no safety-related reason to change current vaccination practices involving vaccines containing this preservative.

Based on the above discussions, at its most recent meeting held in April 2012, the SAGE acknowledged that vaccines containing thiomersal are safe and that replacing this compound with an alternative preservative could affect the quality, safety and effectiveness of the vaccine. In addition, it established that available information justifies the recommendation not to change the WHO immunization policy on vaccines containing thiomersal. Other groups of experts (the Institute of Medicine of the United States, the American Academy of Pediatrics, the United

Kingdom's Committee on Safety of Medicines, and the European Agency for the Evaluation of Medicinal Products) have reached similar conclusions.

In response to the United Nations Environment Program's (UNEP) proposal to approve a world treaty to prohibit the use of mercury in every product or process, which would entail replacing thiomersal in vaccines, the SAGE reaffirmed its conclusion that thiomersal-containing vaccines are essential and irreplaceable components of immunization programs, especially in developing countries. It also encouraged continuous dialogue between countries' health and environmental sectors, in order to facilitate a common understanding of the important role of thiomersal-containing vaccines in their population's health.

Finally, the fourth session of the Intergovernmental Negotiating Committee was held in Uruguay from 27 June to 2 July 2012 to prepare a global legally binding instrument on Mercury (INC4). The terms of prohibition – with exemptions and the provisional allowable use with or without deadlines for use – for the list of products containing mercury (list that includes thiomersal) were discussed during this meeting.

Recommendations:

1. Continue using ethyl-mercury (thiomersal) -containing vaccines, following current vaccination schedules for children.
2. PAHO should mount an aggressive strategy and plan to effectively communicate and educate health care workers as well as ministries of health and environment, parliamentarians, and other decision-makers, and the media on the safety of the thiomersal-containing vaccines.

Rotavirus vaccination schedule

Rotavirus infection is the leading cause of diarrhea in children aged less than five years worldwide. In 2008, it was estimated that 453,000 deaths (95% CI: 420,000-494,000) in children under 5 were attributable to rotavirus diarrhea. Five countries account for half of the deaths attributable to rotavirus: the Democratic Republic of the Congo, Ethiopia, India, Nigeria and Pakistan. Based on the data available, it has been estimated that rotavirus caused approximately 75,000 hospitalizations and close to 15,000 deaths annually in the Region of the Americas prior to the introduction of the vaccine in several countries in the Region.

There are two rotavirus vaccines available that have been pre-qualified by WHO and recommended for use by the SAGE since 2009, which are the monovalent and pentavalent vaccines. Since 2006, in Latin America and the Caribbean, 15 countries and one territory have introduced this vaccine into their national vaccination schedules: in 2006, Brazil, El Salvador, Mexico, Nicaragua, Panama, the United States and Venezuela; in 2007, Ecuador; in 2008, Bolivia; in 2009, the British territory of the Cayman Islands, Colombia, Honduras and Peru; in 2010, Guatemala, Guyana and Paraguay; and in 2012, the Dominican Republic. Several Canadian provinces/ territories also include rotavirus vaccine in their recommended vaccination schedules.

Currently, the vaccination schedules used in Latin America and the Caribbean follow the most recent WHO position paper, which recommends administering the first dose of the vaccine between 6 and 15 weeks of age and the last dose at 32 weeks of age (2nd dose for the monovalent rotavirus vaccine and 3rd dose of the pentavalent rotavirus vaccine).

Based on rotavirus vaccination coverage found in Latin America in the first years following introduction, there is a significant difference between DPT3 and rotavirus (2 or 3) coverage. This is probably due to two factors: adjustments related to the introduction of a new vaccine into the national vaccination schedules and the fact that the rotavirus vaccine has age restrictions for administration of the first and last dose. Beginning the third year following introduction, DPT3 coverage and rotavirus (2 or 3) coverage have been increasingly similar. This means that countries are vaccinating children at younger ages, since coverage of the rotavirus vaccine, with its age restrictions, is increasingly similar to that of DPT3.

A systematic review of mean ages for the occurrence of rotavirus infection shows that 10% of infections occur before 17 weeks of age and 32% before 32 weeks of age. In addition, mathematical models have been developed to estimate the risk/benefit of administrating the rotavirus vaccine without age restrictions. The results indicate that globally, 47,200 (18,700 – 63,700) deaths would be averted and 294 (161-471) additional deaths would occur due to intussusception associated with the vaccine.

During the SAGE meeting in April 2012, considering all of the above mentioned aspects, risk/benefit analysis continues to favor early immunization, but current age-related restrictions on administration of the first dose (<15 weeks) and the last dose (<32 weeks) prevent vaccinating many vulnerable children. If these restrictions were eliminated, children who are currently excluded from the benefits of rotavirus vaccines could be immunized, and it is likely that these include some of the children most vulnerable to this serious disease. Many thousands of deaths could be averted, with just a minimal increase in cases of intestinal intussusception. SAGE also stated that based on the age distribution of rotavirus disease, vaccinating children over 24 months of age would have few beneficial effects.

Recommendations:

1. In the Region of the Americas, countries should continue making efforts to administer rotavirus vaccines on their routine immunization schedules, at the recommended ages, usually at 2, 4, and 6 months. This schedule favors the early immunization of children at greater risk of morbidity and mortality due to rotavirus diarrhea. However, in areas of difficult access and /or high diarrheal mortality, vaccine can be administered later, at any time of immunization contact and before 1 year of age.

TAG encourages countries that have not introduced rotavirus vaccine to reassess the burden of disease in order to consider the introduction of rotavirus immunization, in light of the current evidence demonstrating the huge impact of rotavirus vaccine administered in the current schedule in reducing the morbidity and mortality from rotavirus diarrhea in the Region of the Americas.

Decade of Vaccines (DoV): From Planning to Action

The Global Vaccine Action Plan (GVAP) is the result of global consultation efforts, which gathered input from more than 1,100 people from 142 countries and 297 organizations in Asia, Africa, the Americas, Europe, the Middle East and the Western Pacific. The GVAP builds on the success of the WHO/UNICEF 2006-2015 Global Immunization Vision and Strategy (GIVS), which was launched in 2005 as the first 10 year strategic framework for immunization. The plan reiterates existing goals

and sets new goals for the Decade of Vaccines (2010-2020), proposes six strategic objectives and provides an initial estimate of resource requirements and return on investments.

On May 25, 2012, the 65th World Health Assembly endorsed the GVAP and passed resolution 65.17 supporting GVAP. Beyond the action plan, country, regional and global stakeholders need to take responsibility for specific actions, translate the action plan into detailed operational plans, complete the development of the monitoring and accountability framework for the Decade of Vaccines and mobilize resources to ensure the vision for the Decade of Vaccines becomes a reality.

In the Americas, the GVAP will complement the existing Regional Immunization Vision and Strategy (RIVS), which was developed to translate the GIVS into regional priorities in the late 2000s. The RIVS has three categories of strategies to guide the implementation of successful immunization programs in Latin America and the Caribbean, including strategies to maintain the achievements of control, elimination and eradication goals, to complete the unfinished agenda with the control of vaccine-preventable diseases, and to face new challenges with the introduction of new vaccines. Likewise, the GVAP encompasses these same strategies but with a more horizontal approach highlighted in its six strategic objectives (SOs):

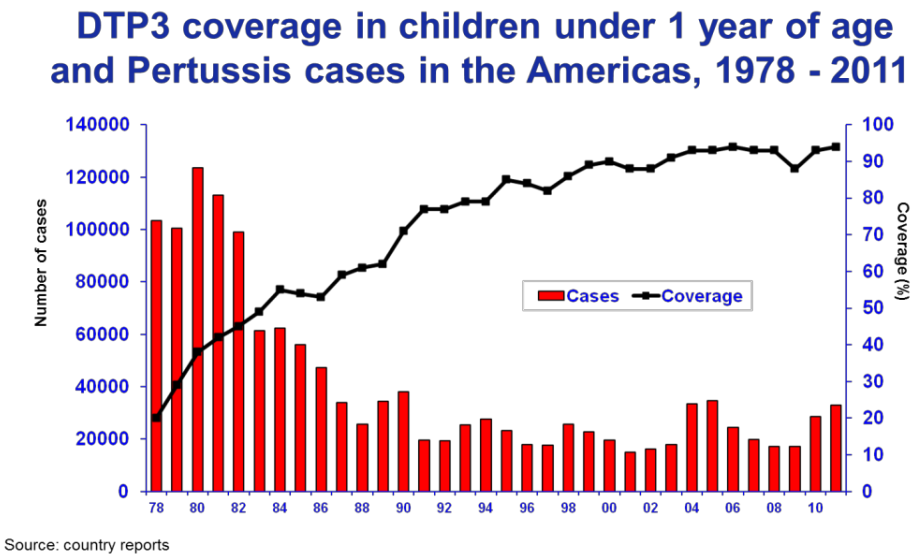
(SO1): All countries commit to immunization as a priority
(SO2): Individuals and communities understand the value of vaccines and demand
(SO3): The benefits of immunization are equitably extended to all people
(SO4): Strong immunization systems are an integral part of a well-functioning health system
(SO5): Immunization programs have sustainable access to predictable funding, quality supply and innovative technologies
(SO6): Country, regional and global research and development innovations maximize the benefits of immunization

The six strategic objectives set forth in the GVAP will help bring new focus to the existing RIVS. PAHO's regional immunization program will work to incorporate the six strategic objectives described in the GVAP into its existing RIVS framework by developing a regional vaccination action plan to 2020 and beyond. For this regional action plan, PAHO will lead discussions with Member States to develop and define indicators to track progress towards achieving regional goals and targets.

Evidence on Pertussis

Pertussis continues to be a significant cause of child mortality worldwide and a disease that causes serious public health concern, even in countries with high levels of vaccination coverage. The WHO estimates that in 2008, there were nearly 16 million cases worldwide, 195,000 of which resulted in death.

In the Region of the Americas, coverage with DPT3 among children aged less than 1 year is over 90%, and the annual number of cases has ranged from 15,000 to 34,000 over the last 10 years, with significant increases in the number of cases in Argentina, Brazil, Chile, Colombia and the United States in the last year.



Source: country reports

During its last two meetings, the TAG discussed matters related to this disease and issued recommendations. It also clearly stated that in order to issue new or different recommendations, it requires new epidemiological information to support them. In response to this call for action, a project titled "Improving Epidemiological Surveillance of Pertussis in Latin America" is now being carried out in Argentina, Mexico and Panama, with support from the Sabin Vaccine Institute, the US Centers for Disease Control and Prevention (CDC) in Atlanta, the and PAHO. Its objectives include: improving diagnostic capacity, developing a reliable and valid method of improving surveillance of pertussis in Latin America, and making the project findings and results available by the end of 2012.

In October 2007, PAHO convened a meeting of experts on pertussis, whose recommendations were presented at the XVIII TAG meeting held in 2009. At this meeting, the TAG issued the following recommendations: to consider controlling pertussis a priority and to improve epidemiological surveillance; to include a 4th dose of DPT as a component of the routine vaccination schedule; to begin DPT vaccination at 6 weeks of age during outbreaks, especially if this age group is affected; and to carefully consider the impact of introducing the acellular vaccine in place of the whole-cell vaccine currently used in vaccination programs. As of September 2012, fifteen countries in Latin American and the Latin Caribbean, and 9 countries in the British Caribbean reported vaccination coverage with the 4th dose of DPT. Sixteen Latin American countries, as well as 8 Caribbean states, Canada and the United States include a 5th dose of a pertussis-containing vaccine in their schedules. Three Latin American countries (Argentina, Costa Rica and Panama) are using an acellular pertussis containing vaccine (Tdap).

In March 2012, 32 professionals from 12 countries in the Region participated in a meeting called by PAHO to define what information is needed or could be presented to request that the TAG issue new recommendations or to implement the current recommendations. The countries were invited to present new epidemiological evidence. The conclusion drawn from the meeting was that the disease continues to appear among children under five without completed vaccination schedules for their age. No additional new evidence was presented to support new recommendations. The goal continues to be adequate implementation of the current recommendations.

During this meeting, the TAG received an update on the global pertussis situation, new trends in vaccination policies such as the "cocoon" strategy and vaccination of pregnant women, and a report on the current status of the "Improving Epidemiological Surveillance of pertussis in Latin America" project. Argentina, Chile, Mexico, and the United States presented information on recent pertussis outbreaks and the measures taken for their control. It was highlighted that most deaths occur and a significant proportion of cases occur among infants, often in the first months of life.

There is growing evidence of an increase in the incidence of the disease in adolescents in some settings, which suggests that the immunity conferred by the acellular vaccine is short-lived. In September 2012, WHO convened an informal expert meeting on pertussis to discuss the current situation of pertussis in Australia, Canada, the United Kingdom, and the United States. The experts concluded that there are limitations to aP, but that the problem remains poorly defined. At that meeting, it also was highlighted that countries are utilizing a range of strategies, including maternal vaccination and cocooning; and that use of aP or the TdaP booster is being contemplated. However, the data available to support these strategies is weak. Similarly, at this time there is insufficient evidence to support the use of a 5th DTP dose. It is expected that SAGE will review pertussis vaccination strategies in use at upcoming meetings.

Recommendations:

1. Countries should ensure vaccination coverage >=95% with 3 doses of pertussis-containing vaccines in children aged <1 year; **and encourage timely vaccination and completion of the schedule.** The 4th dose of the DPT vaccine should be incorporated into the regular vaccination program in every country, and the coverage attained with this dose should be the object of careful recording, monitoring, reporting and evaluation.
2. Every pertussis outbreak should be thoroughly investigated to improve the understanding of the current epidemiology of the disease in the Region of the Americas. PAHO should provide countries with specific guidance for outbreak investigation.
3. Countries should improve surveillance and the use of adequate diagnostic tools. The present surveillance pilot project being implemented in Argentina, Mexico and Panama by the Sabin Vaccine Institute, CDC and PAHO should be expanded to other countries of the Region.
4. Considering new evidence suggesting that the immunity conferred by the acellular vaccine may be shorter-lived than the immunity conferred by wP vaccines countries that are using whole-cell vaccine (wP) should not switch to an acellular vaccine (aP),. Similarly, countries currently using aP should not switch back to the use of wP until more evidence is available to support changes in vaccination strategies for pertussis.

Proposal for Standardizing Procedures of PAHO's Technical Advisory Group on Vaccine-preventable Diseases

Originally established in 1985 to recommend evidence-based strategies for polio eradication, the PAHO Regional Technical Advisory Group (TAG) on Vaccine-preventable diseases has held 19 meetings to date. Progressively expanding its mandate to the current aim of strengthening the immunization policy dialogue among key stakeholders in the Americas involved in efforts to control vaccine-preventable diseases, TAG functions as the leading regional forum to review and promote regional goals and strategies for immunization. Specifically, the TAG reviews national immunization

program progress and results, monitors the advancements in the implementation of the Regional Immunization Vision and Strategy (RIVS), assists in the identification of research needs, and oversees the progress of research efforts underway.

The TAG is currently composed of nine experts in areas related to vaccinology and immunization; additional experts can be identified as needed to address special areas related to vaccine-preventable diseases. TAG members are recruited and selected as recognized experts from the Americas in the fields of epidemiology, public health, vaccinology, pediatrics, infectious diseases, immunology, program management, health economics and health care administration. TAG members are appointed by the PAHO Director. The PAHO Comprehensive Family Immunization Project serves as the Secretariat for the TAG.

TAG members are appointed for a period of 4 years, with the option of one-term renewal. It is preferable for at least one TAG member to be also a member of WHO Strategic Advisory Group of Experts (SAGE) on Immunization.

TAG meetings are convened annually, with the following format:

<table>
<tr><th></th><th>Odd-numbered years (ex. 2011)</th><th>Even-numbered years (ex. 2012)</th></tr>
<tr><td>Participants attending in person</td><td>TAG members, PAHO Secretariat, Regional and International immunization experts, all EPI managers and all NITAG chairs.</td><td>TAG members, PAHO Secretariat, selected Regional and International immunization experts and selected EPI managers.</td></tr>
<tr><td>Virtual participants</td><td>None.</td><td>All other EPI managers, all other regional and international experts, all NITAGs.</td></tr>
<tr><td>Location</td><td>LAC country</td><td>PAHO HQ, Washington DC</td></tr>
<tr><td rowspan="3">Scope of the meeting</td><td>Discuss the progress of national immunization programs</td><td>Discuss the progress of national immunization programs and focus on specific rising issues</td></tr>
<tr><td colspan="2">Monitor the implementation of GVAP for the Region of the Americas and make recommendations.</td></tr>
<tr><td colspan="2">Discuss progress and barriers to implement TAG recommendations</td></tr>
</table>

The dates of TAG meetings should be set strategically to precede the meeting of PAHO's Governing Bodies, preferably the meeting of the Executive Committee.

TAG members shall be required to complete a Declaration of Interest similar to that requested of WHO SAGE members.

Functions of the TAG are the following:

1. Advise the PAHO Director with respect to program priorities;
2. Advise and guide the PAHO Secretariat concerning the optimal strategies to reach the overall goals of the immunization program, including rubella and measles elimination,

maintenance of a polio-free status, and introduction of new and underutilized vaccines in the Americas;
3. Monitor the implementation of the Regional Plan of Action to accomplish the above stated goals and those outlined by the Decade of Vaccines Global Vaccine Action Plan (GVAP);
4. Promote understanding and support for program goals among technical institutions, bilateral, multilateral and private agencies, as well as among political leaders;
5. Convene and chair working groups when necessary to inform TAG recommendations with the necessary evidence-based information; and
6. Promote activities geared towards National Immunization Technical Advisory Groups (NITAGs) strengthening, including encouraging the participation of NITAG members in TAG meetings and other PAHO Immunization Regional and Sub-Regional meetings.

Ad-hoc working groups could be formed as deemed necessary by the TAG and the Secretariat. These working groups will work on specific topics by reviewing and providing evidence and options for recommendations to be discussed by TAG members. The working groups will function for a limited period of time and should always be led by a TAG member.

The PAHO Revolving Fund and the Current Global Vaccine Market

For over three decades, as part of the Regional Expanded Program on Immunization (EPI) established in 1977, PAHO has managed the EPI Revolving Fund (RF) for the procurement of vaccines and vaccination supplies on behalf of Member States..

The EPI/RF began its operations in 1979 with the participation of 8 countries and territories, procuring 6 biologicals. In 2011, 28 biologicals were purchased along with syringes, cold chain equipment and vaccination supplies. A total of 178 million vaccine doses costing nearly US$400 million were purchased in the same year. For 2012, the forecasted purchase expenditures will be US$469 million. Through joint, active participation of 39 countries and territories, the EPI/RF is an important mechanism of technical cooperation, which brings economy of scale for procuring vaccines, syringes and related supplies of high quality at affordable prices. This mechanism was also a major facilitator for the rapid, equitable and sustained introduction of new and underused vaccines.

As a strategic mechanism, with these achievements the EPI/RF has contributed to the continuous strengthening of its management and planning tools, to the consolidation of procurement and overseeing a timely supply of products, and to supporting the development of a more structured and reliable market for vaccine producers.

In addition to its contributions, one of the strengths of the mechanism is its capital fund, which enables countries to reimburse PAHO 60 days after an order arrives, thereby obtaining a timely supply without being affected by delays in the release of national funds. Today, 32 countries make their procurements using the EPI/RF, with no need to obtain funds in advance. As of 2011, the capital fund reached US$85 million and is expected to reach US$100 million in 2012, as a result of the capitalization fee of 3% of the value of the purchases countries make.

In 2012, the EPI Revolving Fund has identified opportunities to create and maintain strategic regional stockpiles, such as a measles-rubella vaccine to be used in response to outbreaks. Other regional stockpiles are being explored.

Although the EPI/RF has gained relevant strengths and made significant contributions, it also faces considerable challenges including an insufficient supply of vaccines such as yellow fever vaccine, a reduction of the global supply of trivalent oral polio vaccine, a limited supply base of one or two laboratories for new vaccines and the existence of other stakeholders whose plans have an impact on the world vaccine market regarding dose availability and prices of some vaccines for the Region.

The RF continuously seeks to address these challenges, while preserving its principles of Pan-Americanism, equity, universal access and quality.

Other important international actors related to vaccine procurement include UNICEF, GAVI Alliance, Bill and Melinda Gates Foundation (BMGF) and Medecins Sans Frontiers.

UNICEF procures immunization supplies on behalf of around 100 countries annually, amounting to approximately $1.03 billion. Annual vaccine procurement has increased since 2000, mainly due to OPV, DTP/Hep B-Hib and PCV. UNICEF's procurement strategies are focused on achieving vaccine security – sustainable, uninterrupted supply of affordable vaccines of assured quality, based in three pillars: accurate forecasting, available funding and appropriate contracting. Given the diversified market situations, news strategies are required to achieve healthy market objectives. UNICEF is also developing a strategy for middle income countries, working on a hybrid strategy of pooled procurement and price ceilings references.

GAVI' strategy and business plan for the period of 2011-2015 has four pillars: (i) the vaccine goal; (ii) the health system goal; (iii) the financing goal; and (iv) the market-shaping goal. GAVI is currently supporting vaccines for routine, campaigns and stockpiles. The cash outflow is estimated in $1.7 billion, per year, for the period of 2012-2015, and $1.6 billion, per year, for the period of 2016-2020. For the market shaping, key objectives re supply and procurement strategies are balance supply demand, vaccines prices and appropriate products. GAVI is currently supporting low income countries, facilitating access to lower vaccine prices, even after graduation, and also UNICEF's middle income countries tender.

BMGF theory of change, focusing on the poorest countries in the world, states that overcoming the key barriers to delivery will drive adoption and uptake of necessary products and interventions. This strategy focus on two main groups: routine immunization and new vaccines. BMGF market innovation has four strategies: (i) take every opportunity to close program funding gap; (ii) engage with all parties willing to work with global health goals; (iii0 invest in specific product development projects; and (iv) seek novel and potentially transformative opportunities. Those strategies have a multi-faced approach that spans from the demand side to product development, launch and scale-up production with the common goal of broadening access to vaccines in the poorest settings.

MSF activities in PAHO region refer more to support on some diseases such as Chagas, violence and mental health. In other regions, MSF also supports vaccination activities; in that aspect, MSF procures directly from manufacturers. MSF proposals for a healthy vaccine market relies on some aspects, such as: competition and multiple sources of supply, strengthening manufacturing capacity in developing countries; global and regional procurement strategies should strengthen

government's negotiation capacity; purchasing power of existing mechanisms and strategies (PAHO RF, UNICEF, GAVI) should be used to influence the market to promote both innovation and access.

Recommendations:

1. TAG congratulates PAHO's EPI Revolving Fund for vaccine procurement and reaffirms its support to the Fund as a key pillar of immunization programs in the Americas.
2. Member States should continue to participate in the Revolving Fund to continue obtaining the benefits of a strong economy of scale in the procurement of vaccines, syringes and supplies.
3. The Revolving Fund should continue improving vaccine forecasting, including for those new vaccines newly available.
4. PAHO should maintain its commitment to strengthen operating and financial management of the Fund in order to provide increasingly better service and greater credit capacity to participating countries and territories.
5. In light of current challenges, PAHO should continue building its knowledge of global markets and strive for continuous communication and coordination with its major partners in the global immunization field, in order to maintain updated information on the markets in which it participates, for the development of its procurement strategies.
6. Tag recommends that all those agencies that deal with vaccine forecasting, procurement and distribution meet periodically to exchange information on their activities and strategies in order to identify those areas in which closer collaboration could facilitate the availability of vaccines of high quality at affordable prices.

Improving Regional Vaccine Production Capacity to Meet the Needs of the Americas

As a result of the use of high-quality, safe, efficient vaccines in national immunization programs (NIPs), over 2.5 million deaths have been averted in Latin America and the Caribbean since 1974.

In addition, Latin American and Caribbean countries have successfully introduced new and/or improved vaccines in their NIPs that have contributed to controlling a significant number of communicable diseases.

The provision of traditional vaccines and the introduction of new vaccines have been effectively facilitated through the PAHO RF. However, currently supplying priority vaccines to the Region of the Americas in order to guarantee sustaining achievements made in the control and elimination/eradication of vaccine-preventable diseases continues to be a challenge.

The supply of traditional vaccines, such as the oral polio vaccine, the yellow fever vaccine and the DPT vaccine remains erratic and often insufficient to cover demand from countries in the Region that purchase them through the RF. Although these vaccines continue to be essential, they are of little commercial interest to pharmaceutical companies, which in many cases have discontinued their production or diverted their interests toward the manufacture of other vaccines, such as the pentavalent vaccine (DPT-HepB-Hib).

In the case of new vaccines, their massive use in NIPs is frequently delayed due to the high prices for these vaccines and the impact of their cost to the healthcare systems of low and middle-income countries.

Improvement in the supply of traditional vaccines and competition in the new vaccine market would provide a good opportunity to improve access to these products of public health interest.

The Region of the Americas has proven experience in vaccine development and production.
In the Americas, there are national regulatory authorities (NRAs) with improved capacity for monitoring vaccine quality, safety and effectiveness during the pre and post-marketing phases.

Vaccine production in the public, as well as the private field has served to meet a significant portion of the demand from NIPs. Despite this fact, installed capacity has not necessarily been sufficient to cover growing regional demand, since in many cases the production volume is only geared toward fulfilling domestic needs, with little possibility of exporting vaccines. The establishment of technology transfer agreements between the transnational pharmaceutical industry and regional producers has not yet led to improvements in local capacity to produce new vaccines; therefore, a more thorough analysis of the role regional producers can play in meeting the needs of countries in the Region for safe, effective vaccines of high quality is needed.

Recommendation:

1. PAHO should convene a task group with representatives from vaccine manufactures from Latin America and the Caribbean (LAC) to identify common areas of work and brainstorm a LAC regional strategy for vaccine research, development and production. PAHO should then report back to TAG on this topic.

Measles, Rubella and CRS Elimination in the Region of the Americas

The last measles case due to indigenous transmission was reported in the Americas in September 2002. From 2003 to 2010, a historically low number of measles cases were reported in the Americas. During this eight-year period, 34 out of 45 countries and territories (76%) did not report cases of measles, and another 5 countries (11%) reported 10 confirmed cases of measles altogether. The remaining 6 countries (13%) reported a total of 1,239 cases, which account for 99% of the 1,249 cases confirmed in the Region during this period. The appearance of measles was mainly limited to cases that were imported from other countries or related to importation. However, in 2011, 1,374 cases of measles were reported in the Americas. This figure is more than eight times the previous annual average of 156 cases from 2003 to 2010. This increase coincided with several extensive outbreaks in Europe and Africa. Of 45 countries and territories, 33 (73.3%) did not report cases of measles, and 9 (20%) reported 14 confirmed cases. Three countries — Canada, Ecuador and the United States (6.7%) — reported a total of 1,290 cases; that is, 93% of the 1,374 confirmed cases in the Region in 2011.

The outbreak in Ecuador spread to nine different provinces. In 2011, there were 260 confirmed

cases of measles in six provinces and 69 more cases in three provinces in 2012 (data through epidemiological week (EW) 39/2012). The most affected age group has been that of children aged <5 years. Cases with genotype B3, which are commonly found in Africa, have been detected along with a case of D4, which is usually found in Europe. In order to guarantee a rapid response to this measles outbreak, the start of a follow-up campaign targeting children aged up to 15 years was moved to an earlier date. The Ministry of Health reports vaccination coverage ≥ 95% in the majority of provinces. The last case of measles was reported in EW 28/2012 (data through September 2012).

During 1998–2006, confirmed rubella cases in the Americas decreased by 98%, from 135,947 to 3,005. In 2007, however, the Americas experienced a resurgence of rubella cases due to importations of rubella virus into countries that initially targeted only females during mass vaccination campaigns. The last confirmed endemic rubella case was reported in February 2009, in Argentina. During that same year, two countries reported 7 import-associated rubella cases; in 2010, the regional total was 15 import-associated rubella cases; and in 2011, it was again 7 import-associated rubella cases (provisional data as of April 2012). As an unfortunate consequence of the rubella outbreaks of 2008–2009, a total of 27 CRS cases were reported in two countries. The last confirmed CRS case was a child born on 26 August 2009 in Brazil. No indigenous CRS cases were reported in 2010 or 2011.

In October 2007, considering the elimination of measles in 2002 and the progress made toward the goal of eliminating rubella and congenital rubella syndrome (CRS), the 27th Pan American Sanitary Conference approved Resolution CSP27.R2 calling for the documentation and verification of the elimination of measles, rubella and CRS in the Region of the Americas. The TAG was informed of the progress made on the implementation of Resolution CSP27.R2 (2007) and the challenges and risks that still existed in keeping the Region free of these diseases.

In response to the Pan American Sanitary Conference Resolution CSP27.R2, an International Expert Committee (IEC) was formed and 23 national commissions were established, including the Commission for French Overseas Departments in the Americas. In addition, the Sub-regional Commission for English-speaking and Dutch-speaking countries and territories in the Caribbean, including Suriname, was established. As of September 30, 2012, 20 commissions, among them those for French Overseas Departments in the Americas and English-speaking and Dutch-speaking countries and territories in the Caribbean, had submitted their final reports on disease elimination to PAHO for the consideration of the IEC. The four remaining countries (Colombia, Ecuador, Haiti and Peru) will submit their reports in late November. Following a detailed analysis of the reports submitted by the national commissions and the Sub-regional Commission, it appears that the interruption of endemic transmission of measles and rubella has been achieved.

However, the Region of the Americas is still exposed to a high risk of importation of viruses, given the continued circulation of measles and rubella in other parts of the world. In addition, all countries, with the exception of Chile, have reported weaknesses and flaws in their national surveillance systems and routine vaccination programs, which make them particularly vulnerable to the risk of virus reintroduction that could cause outbreaks.

Maintenance of the elimination of rubella and CRS in the Region of the Americas will be achieved if the 45 Member States and territories continue conducting integrated surveillance of measles

and rubella, strengthen CRS surveillance and continue implementing effective immunization interventions, including strengthening routine vaccination services and conducting follow-up campaigns.

In 2012, an emergency plan of action to maintain the elimination of endemic transmission of measles, rubella and CRS in the Region was presented and approved by the Pan American Sanitary Conference (Document CSP 28/16).

TAG congratulates the members of the IEC, Member States and their national commissions for their efforts to document and verify the elimination of measles, rubella and CRS in their respective countries and to maintain regional elimination. The PAHO Region has demonstrated that measles can be eliminated and that this can be sustained over time. The experience of the PAHO Region should be shared as an example for other Regions struggling to reach elimination targets.

Recommendations:

1. The TAG endorses and urges countries to implement the Emergency Plan of Action to maintain the elimination of measles, rubella and CRS in the Americas, as stated in Resolution CPS28PR5 of the Pan American Sanitary Conference 2012.

Haiti's Immunization Program

The vaccine-preventable diseases currently targeted by Haiti's immunization program remain a source of concern for the country's health system.

Measles, rubella and polio have been eliminated from Haiti, as well as from the rest of the Americas. Nevertheless, the risk of importing the viruses responsible for these three diseases is a reality for Haiti as it is for all countries in the Americas. At the beginning of 2012, the number of children susceptible to measles and rubella likely accumulated in Haiti (273,860) was above the national average birth cohort size (252,664); a condition that makes implementing mass vaccination activities imperative.

Neonatal tetanus (NNT) ranks sixth among the leading causes of neonatal death, while diphtheria is endemic/epidemic in the country. Additionally, it has been established that among children aged <5 years, the main etiological agents causing deaths due to acute respiratory infections (ARIs) and meningitis are *Haemophilus influenzae* type b and *Streptococcus pneumonia*; and the main etiological agent causing deaths due to diarrhea is rotavirus. The importance of mortality resulting from ARIs, meningitis, and diarrhea in children under 5—and the role attributable to these agents in the etiology of these diseases—formed the basis for the introduction of Pentavalent (DTP-Hib-Hepatitis B) vaccine, as well as the pneumococcal conjugate and rotavirus vaccines, within the framework of the country immunization multi-year plan.

The following table shows the routine coverage in the last 4 years:

Table 1: Vaccination coverage %, Children aged <1 year, Haiti 2008-2011

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**

Source: Country reports to PAHO (JRF)

(a) Value 2007 for measles vaccine

A strong demand for vaccination exists among the population; however, major deficiencies have been recognized in immunization service delivery that limit vaccinating young children in health facilities and through mobile posts, as part of the outreach strategy. Missed opportunities happen all the time. In addition, supervision, in terms of frequency and quality, merits strengthening.

Based on these challenges, the following are Haiti's Immunization Program priorities for the period 2011–2015:

1. Strengthening program governance in all aspects falling under the competence/jurisdiction of the national health authority (NHA).
2. Developing routine capacities in order to achieve and maintain satisfactory immunization coverage throughout the country—including rural, peri urban, and difficult to reach marginal areas, especially in the Metropolitan Area.
3. Achieving financial viability by mobilizing and utilizing national resources, as well as external resources both efficiently and reliably. This to meet current and future vaccination objectives in terms of access, utilization, quality, safety, and equity.

The main strategic guidelines for Haiti's Immunization Program are the following:

1. Strengthening routine vaccination to significantly improve coverage.
2. Broadening the range of targeted vaccine-preventable diseases and target groups, first through the introduction of new vaccines, beginning in 2012 with the pentavalent vaccine; and second, through the transition from a program for children and mothers to one for the entire family.
3. Revitalizing the offer of immunization outreach, using the following mechanisms:
   - Ensuring that mobile vaccination teams hold immunization events with vaccination posts at least quarterly, utilizing the existing platforms of Child Health Week and Vaccination Week in the Americas.
   - Optimizing support from Non-governmental organizations (NGOs) for routine vaccination.
   - Defining and implementing a feasible policy of remuneration and training for community health workers, thus guaranteeing the recruitment and retention of a capable and motivated community workforce to secure the outreach strategy.
4. Increasing cold chain capacity at all levels to meet the increased cold storage needs resulting from the introduction of new vaccines.
5. Improving management practices for the cold chain, vaccines, and other supplies in order to reduce wastage and avoid stock-outs.
6. Strengthening communications and social mobilization activities to optimize demand and improve service delivery, especially in difficult to reach areas.

7. Strengthening epidemiological surveillance through improved collaboration between the national immunization program (DPEV) and the Epidemiology Department (DELR), as well as through support from the main technical partners, particularly PAHO/WHO, UNICEF, and CDC.
8. Revitalizing support and monitoring activities at the local level—especially micro-planning, supervision, and vaccination coverage monitoring.
9. Strengthening managerial capacities and advisory bodies: Immunization Technical Committee and Inter-Agency Coordination Committee.

To strengthen the national immunization program, PAHO is providing technical cooperation in three phases:

- First, implementing supplementary immunization activities (SIAs) and active case search at the community level to reduce the risk of outbreaks. Both activities were implemented during the first semester of 2012. Between April and June 2012, more than 3 million children aged <10 years were vaccinated against measles, rubella and polio, reaching an administrative coverage of 99%. Rapid coverage monitoring found 96% of interviewed people to be vaccinated and an independent survey estimated that 91% children aged <10 years had ever received a measles-rubella vaccine.
- Second, implementing a short-term plan of action from July to December 2012 to strengthen the routine program and epidemiological surveillance. The focus of this plan of action is to continue building national capacities and to support introducing pentavalent vaccine; ensuring the cold-chain capacity and operation; and finalizing the documentation and verification process of measles, rubella and CRS elimination.
- Third, improving and sustaining the performance of the routine immunization program.

TAG congratulates Haitian national health authorities and health workers for their leadership and dedication and for all these accomplishments, including the results of the vaccination campaign, and urges them to maintain their efforts for the success of the activities that are currently being implemented.

Similarly, TAG thanks Haiti's strategic partners for their firm commitment, technical and financial cooperation to maintain a coordinated effort towards a common goal: strengthening Haiti's immunization program. TAG also requests continued support to mobilize additional resources to guarantee the successful implementation of the planned activities.

Cholera vaccination in the Americas

Background

Since October 2010, when cholera emerged in the Island of Hispaniola, 597,306 and 26,995 suspect and confirmed cases have been reported (as of September 29, 2012), in Haiti and the Dominican Republic, respectively. During the same period, 7,625 cholera-related deaths (case-fatality rate [CFR] = 1.28) were reported in Haiti and 407 (CFR = 1.51) in the Dominican Republic. Although incidence is lower in 2012 (January 1–September 29) compared to previous years, cholera still remains a significant public health problem in the Island: 79,302 suspect and confirmed cases and 607 cholera-related deaths (CFR = 0.77) were reported in Haiti and 5,433 cases and 37 deaths (CFR = 0.68) in the Dominican Republic. In 2010–2011, eight countries in the Americas reported 92 cases imported from the Island of Hispaniola (38 confirmed and 54

epidemiologically linked cases). In June–August 2012, 296 confirmed cases and 3 deaths were reported in Cuba.

A detailed epidemiologic analysis shows that cholera transmission is widespread and ongoing in the Island of Hispaniola. While transmission in the Dominican Republic is limited to some geographical areas, transmission in Haiti is more widespread. Compared to the 12-month period from October 2010 to September 2011, transmission has declined substantially in the 12-month period from October 2011 to September 2012. In Haiti, the majority (74%) of patients with diarrheal diseases that consulted since April 2012 at cholera treatment centers (CTC) and were captured through an enhanced surveillance system were diagnosed with a cholera infection. In contrast, only 25% of children aged <5 years in non-CTC facilities had cholera. A seroepidemiologic survey carried out in the Artibonite River delta during March–April 2011 (when cholera transmission had already subsided in the area) shows 2.5 unapparent cholera infections per each reported clinical cholera case. Access to CTCs is highly variable across the 140 Haitian communes, as does the level of care and travel time to facilities across departments. While 74% of internally displaced people who resided in camps in March 2011 received drinking water, only 12% did in August 2012. In contrast, provision of sanitation remained stable (toilet provision coverage of 82% and 78%, respectively). Recent and local data on access to drinking water and sanitation are not available.

In January 2012, the presidents of Haiti and the Dominican Republic, together with representatives of PAHO/WHO, UNICEF, and the CDC, issued a call to action to eliminate cholera transmission from both countries through new investments in water and sanitation infrastructure. This call led, in June 2012, to the creation of the Regional Coalition on Water and Sanitation for the Elimination of Cholera Transmission in the Island of Hispaniola, which will bring together the necessary technical expertise, raise new funds, and mobilize previously committed pledges. As of October 2012, the Coalition has expanded to include 17 signatory partners. This coalition presents a unique opportunity to reach out more extensively to the private sectors and non-government organizations. This work is a priority for PAHO and is grounded in the overarching strategy of safe water and sanitation for all the citizens of Haiti and the Dominican Republic.

Deployment of oral cholera vaccine (OCV) has been considered since October 2010. At that time, also considering the rapidly spreading epidemic and the limited vaccine supplies, PAHO recommended focusing emergency efforts on time-tested measures for cholera outbreak response, namely on treatment to prevent deaths and traditional preventative actions to halt transmission (i.e. delivery of safe potable water, provision of supplies for hand washing and other hygienic measures, sanitation, and proper waste disposal). An expert consultation convened by PAHO in December 2010 recommended that the limited vaccine supply be used for demonstration projects and that efforts be initiated to increase OCV availability.

Two oral cholera vaccines are marketed globally under the names of Dukoral and Shanchol and are now WHO-prequalified. When compared to Dukoral, Shanchol offers operational advantages such as: 1) it does not require administration with a buffer solution; 2) requires significantly less cold chain volume; 3) can be administered from 1 year of age (versus 2 years of age); and 4) costs one third per dose at current prices. As published in October 2011, results of Shanchol clinical trials show a 66% overall efficacy at three years of follow-up. Within a community, vaccination with OCV may also provide herd protection and thus reduce cholera burden among persons who remain unvaccinated. Contingent on firm orders, Shanchol's manufacturer has indicated the immediate availability of up to 600,000 doses and the capacity to scale up production to 2–4 million doses in 2013 and to 10–20 million doses in 2014 and thereafter. This availability is not exclusively reserved

for the Americas; WHO and partners are working toward the establishment of a 2-million-dose global stock and large vaccination initiatives are taking place in West Africa.

Following the above-mentioned recommendation of a PAHO-convened expert consultation, the two non-governmental organizations GHESKIO and Zanmi Lasante/Partners in Health conducted, between April and June 2012, separate but coordinated cholera vaccination in one urban and one rural area of Haiti. Overall, 97,725 persons received at least one vaccine dose and completion rate for the two-dose immunization series was 91%. Key lessons from these cholera vaccination demonstration projects in Haiti were community acceptance of cholera vaccination and feasibility of administering the vaccine on a large-scale in both rural and urban settings. At the same time, the demonstration underscored the need for substantial planning prior to vaccination, a reliable cold chain and other logistic resources, an ongoing monitoring of vaccination activities, and communication activities involving the community, opinion leaders and the media. Impact evaluation is now being planned.

Some knowledge gaps persist and activities of evaluation and research should be an integral part of deploying OCV. Research priorities include the development of a single-dose vaccine, efficacy proof of a single dose of current two-dose vaccines, safety studies of OCV use in pregnant women, occasional environmental bacteriology testing, serosurveys to determine which fraction of the population is already immune to cholera, and effectiveness studies of vaccine (including nested case-control studies).

National immunization programs throughout the Region remain committed to maintaining the elimination of polio, measles and rubella, reducing within-country inequalities in vaccination coverage, and advancing in the evidence-based and sustainable introduction of new vaccines. For instance, the local Ministry of Health, PAHO, and partners made significant progress in Haiti during the first semester of 2012 to improve routine vaccination and to carry out a nationwide intensification of measles/rubella/polio vaccination. In Haiti, vaccination with pentavalent vaccine (DTP-HepB-Hib vaccine) should begin in September 2012 and introduction of rotavirus and pneumococcal conjugate vaccines is planned for 2013.

At least four elements warrant a reconsideration of OCV deployment in the Island of Hispaniola: The ongoing occurrence of cholera now almost two years after the epidemic began; the WHO-prequalification in September 2011 of a second OCV (Shanchol) that eases some operational challenges; the immediate availability in principle of up to 800,000 OCV doses; and the demonstration that, with substantial planning and logistic resources, OCV deployment is feasible on the Island.

Most important, interventions to decrease cholera transmission through improvements in water and sanitation, the provision of clean water and sanitation to every household will take years to accomplish and will require the mobilization of billions of dollars, while immunization against cholera offers immediate short-term benefits to support the long-term vision.

Recommendations:

1. TAG commends the work of PAHO and partners for establishing and recently expanding the Regional Coalition on Water and Sanitation for the Elimination of Cholera in the Island of Hispaniola.
2. Advocated by this Coalition, the elimination of cholera transmission in the Island of Hispaniola, defined as cholera no longer being a public health burden, will only be

achieved in the long run through considerable investments towards significant and sustained improvements in access to potable water and sanitation. To achieve the overarching goal of cholera transmission elimination, TAG considers that several short-term actions should also be considered, including the expanded use of OCV. However, if water and sanitation are not improved in the long run, the Island will likely remain vulnerable to repeated epidemics, even though a large-scale cholera vaccination program is in place.

3. TAG recommends that OCV be used in Haiti, leveraging its delivery to strengthen the provision of other cholera prevention measures (such as, social mobilization and active case-finding) and national immunization services. To reach this objective, incremental advances are needed in the integration of OCV use with Water, Sanitation, and Hygiene (WASH) development plans, in assuring sufficient OCV availability and financial sustainability of its purchase and delivery, and in developing operational and monitoring immunization capacities. These advances need to build national and local capacity of immunization programs and the health system as a whole. The time frame during which vaccination will be needed depends on the advances in access to potable water and provision of sanitation and on the evolution of natural and vaccine immunities at population level. Up to 600,000 OCV doses are currently available; global production capacity could be scaled up to 2–4 million doses in 2013 and to 10–20 million doses in 2014 and thereafter. Therefore, a phased introduction based on global supply will need to be used in Haiti. OCV deployment could be prioritized in the following areas:
   a) OCV introduction as part of the routine national schedule for children aged one year linked to the delivery of the MR vaccine, b) in the metropolitan area, supplemental immunization activities (SIA) targeting internally displaced people residing in camps or the population of shanty towns, and c) in rural areas, SIA targeting the population who have difficult access to health care. This last phase will most likely require additional prioritization based on geospatial analyses of a defined set of criteria defined *a priori*. Regardless of the time and eventual scope of a cholera vaccination program, additional resources and funds will be needed for the program to be successful.

In the Name of God, the Compassionate, the Merciful

Address by
DR ALA ALWAN
REGIONAL DIRECTOR
WHO EASTERN MEDITERRANEAN REGION

to the

27TH INTERCOUNTRY MEETING OF NATIONAL MANAGERS OF THE EXPANDED PROGRAMME ON IMMUNIZATION

Sharm El-Sheikh, Egypt, 16–19 September 2012

Ladies and Gentlemen, Dear Colleagues,

It gives me great pleasure to welcome you to the 27th intercountry meeting of national managers of the Expanded Programme on Immunization, organized jointly by WHO and UNICEF. I wish to welcome and extend my sincere thanks to the representatives of various partner agencies for making the effort to come and for their continued interest, commitment and support to immunization activities in the Region. I wish also to welcome the chairpersons of the national immunization technical advisory groups, who shoulder a great responsibility for improving the capacity of national immunization programmes. My warm welcome goes also to our colleagues from WHO and UNICEF headquarters and regional offices as well as field officers participating in this meeting. My sincere thanks is due the managers of the Expanded Programme on Immunization for their tireless efforts to give EPI the attention it deserves.

Dear Colleagues,

Immunization programmes have adopted several important targets for control, elimination and eradication of vaccine-preventable diseases. At the top are polio eradication, measles elimination, maternal and neonatal tetanus elimination and hepatitis B control. In addition, as vaccine-preventable diseases accounts for more than 20% of child deaths, immunization is certainly a key tool for achieving the targets of Millennium Development

Goal 4. Reaching high routine immunization coverage in all districts, introducing new life-saving vaccines and technologies, and implementing the accelerated disease control strategies are the key pillars for achieving these targets. We have therefore been focusing in the past few years on supporting countries to strengthen routine immunization services to reach the un-reached, build national managerial and decision-making processes to support new vaccines introduction and partnership and mobilize additional resources for effective implementation of specific disease control, elimination and eradication strategies.

Dear Colleagues,

Since your previous meeting in July 2010, major political changes have taken place in several countries in the Region which have added to the challenges being faced. I acknowledge with satisfaction the major efforts spent and the innovative approaches followed in order to keep EPI functioning as a top priority and to overcome the major barriers faced in terms of security and accessibility, vaccine supply, cold chain and human resources. I am pleased to note that, based on reported data for 2011, Egypt and Tunisia were able to maintain the high vaccination coverage or avoid a significant drop in vaccination coverage. I have also to acknowledge the important role that high public awareness and demand for vaccines has played in maintaining the vaccination coverage in these countries.

I am pleased to note that reported DPT3 coverage reached more than 60% in South Sudan and more than 55% in Somalia in 2011. These significant achievements reflect enormous efforts and strong partner collaboration in these two countries. During the course of this meeting, we will learn more about the efforts of Somalia to re-establish EPI and the activities of Sudan and South Sudan to reach the hard-to-reach populations. You will as well be briefed on the constraints routine EPI is facing in Pakistan and the ongoing efforts to overcome them.

Dear Colleagues,

As you know, polio eradication was declared a programmatic emergency for global public health by the World Health Assembly this year. Following the declaration, emergency standard operating procedures were activated in the Region. There has been impressive progress in the programme maintaining the polio free status of the 21 countries. Nonetheless, significant challenges and risks remain in some of them while Pakistan and Afghanistan are still polio endemic.

Currently both endemic countries are intensifying their efforts to stop poliovirus circulation. Pakistan's Augmented National Emergency Action Plan indicates high commitment by the Government of Pakistan. However, places like the Federally Administered Tribal Areas, Quetta block and Gaddap town in Karachi, with ongoing wild poliovirus circulation, represent a continuing risk. Afghanistan has also developed a National Emergency Action Plan this year and, together with the recent independent review of the programme, has defined a roadmap to interrupt the transmission in the southern part of the country. Both countries have also made important recent changes, including an upsurge of human resources, oversight by the highest level and establishment of accountability mechanisms.

All other countries of the Region have maintained their polio-free status. However, recent developments in some countries have increased the risk of the circulation of poliovirus should it be introduced. The programme is closely watching the situation through the globally standardized criteria of risk assessment. You will be hearing more about this risk assessment model and I would like to encourage you to apply this model to your country at national and subnational level to identify the gaps in population immunity and surveillance, and to take this opportunity to close such gaps.

Dear Colleagues,

The Region has witnessed commendable progress in measles control and elimination since establishing the regional elimination target in 1997. The number of reported measles cases decreased by 88% between 1998 and 2010, measles mortality was significantly reduced and measles national case-based laboratory surveillance is being implemented in all countries. Eight countries continue to report very low incidence of measles and are close to validating measles elimination. In this regard, I would like to express our deep thanks to the Measles and Rubella Initiative for the significant financial support provided for implementation of measles supplementary immunization activities in the low-income countries of the Region.

Despite the progress, we have missed achieving measles elimination on time and the target date was postponed to 2015. Moreover, there has been resurgence of measles in several countries since 2009. I am sure you will agree with me that this resurgence is due only to failure to reach the level of measles vaccination coverage that is necessary to interrupt measles transmission or, at least, keep this transmission low. The worrying issue is that measles outbreaks have occurred in countries that have been reporting high routine or

supplementary vaccination coverage. A substantial proportion of the measles cases reported during these outbreaks have occurred among the vaccinated cohorts and a large percentage of these cases proved to be unvaccinated. This raises concern about the quality of the reported routine vaccination data and the quality of the supplementary immunization activities.

Dear Colleagues,

Achievement of MDG4, especially in the priority countries, will continue to be at risk unless we tackle the major causes of under-five mortality, at top of which are pneumonia and diarrhoea. As you all know, pneumonia caused by Hib and the pneumococcus and diarrhoea caused by rotavirus are the causes of up to 20% of under-five mortality in high burden countries of the Region. WHO and partners have been working with countries to promote new and underutilized vaccines introduction in the Region, an effort which has gained unprecedented momentum during the past few years. Hib vaccine in now part of the national immunization schedule in 19 countries and I am pleased to note that it will be introduced in Somalia early next year. Pneumococcal vaccine is now in use in 9 countries and its introduction in Djibouti and Pakistan will start in a few days. Rotavirus vaccine is in use in 6 countries and will be introduced in Djibouti, Libya and Saudi Arabia early next year. I am also pleased to note that the first phase of a vaccination campaign against one of the deadly diseases in Sudan, meningococcal meningitis, will start in a few days as well.

I would like to express my great appreciation to the governments of the GAVI-eligible countries for their increasing investment in immunization and their successful co-financing of new vaccines, and to the support provided by GAVI. However, introduction of these new vaccines still constitutes a real challenge in middle-income countries. While low-income countries are able to introduce these expensive vaccines with GAVI support and high-income countries are able to afford the vaccines, the cost of these vaccines continues to be unaffordably high for most middle-income countries.

Dear Colleagues,

In addition to the efforts at strengthening different aspects of immunization programmes, during the past few years our region has witnessed important initiatives aimed at improving national immunization programmes. Strengthening national immunization technical advisory groups (NITAGs), with the objective of strengthening country decision-making capacity, gained momentum, and 22 out of 23 countries have now established NITAGs. Important steps are being undertaken towards establishing pooled vaccine

procurement mechanism in the Region in order to support middle-income countries. The third Vaccination Week in the Eastern Mediterranean was celebrated with the same success as the first two years, and World Immunization Week was established. More countries are conducting comprehensive review of EPI and are using the results for developing and updating their multi-year plans.

Despite the commendable achievements in different areas of EPI, I am sure you agree with me that much remains to be done in order to achieve the targets set. Seven countries still have not reached the target DPT3 coverage of 90% at national level. Around 2 million infants missed their third dose of DTP vaccines in 2011 and more rigorous implementation of the effective strategies, such as the Reach Every District approach, Child Health Days and acceleration campaigns, is needed. Polio is still endemic in Pakistan and Afghanistan, the measles elimination target was not achieved and a lot still needs to be done for effective implementation of the measles elimination strategy if we are to achieve this target within the coming 3 years. New vaccines against the most killing childhood diseases are not yet offered to the vast majority of children in the Region, and innovative approaches are needed for effective use of available resources, along with stronger partnership for mobilizing additional resources, especially in middle-income countries.

Once again, I wish to express my sincere thanks to all of you for your efforts in promoting the immunization programmes in the Region and I urge you to make maximum benefit of this meeting through sound deliberations, open discussion and effective exchange of experience. I assure you of our continued support and collaboration and I wish you all a pleasant stay in Sharm El-Sheikh.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

منظمة الصحة العالمية

قـــرار

Resolution

REGIONAL COMMITTEE FOR THE EASTERN MEDITERRANEAN

EM/RC59/R.1
October 2012

Fifty-ninth Session
Agenda item 2

Annual report of the Regional Director for 2011 and progress reports

The Regional Committee,

Having reviewed the Annual report of the Regional Director on the work of WHO in the Eastern Mediterranean Region for 2011, the progress reports requested by the Regional Committee and recent developments in the Region[1];

Recalling resolutions EM/RC52/R.2 on emergency preparedness and response, EM/RC57/R.2 on emergency preparedness and response and regional solidarity fund, EM/RC58/R.1 on the annual report of the Regional Director for 2010 and progress reports, and EM/RC58/R.5 on scaling up the expanded programme on immunization to meet global and regional targets;

Concerned at the situation in the Syrian Arab Republic and the humanitarian conditions affecting refugees and internally displaced persons, and at the impact on neighbouring countries;

Concerned also at the potential threat to all Member States by the continuing presence of wild poliovirus in the Region;

Recognizing the concerted efforts made by Afghanistan and Pakistan to address the eradication of poliomyelitis as a national health emergency;

Recognizing also the increasingly successful efforts of Member States to implement the WHO Framework Convention on Tobacco Control, such as the banning of tobacco use in public places;

Welcoming the strategic directions proposed by the Regional Director in his opening address and in the document *Shaping the future of health in the Eastern Mediterranean Region: reinforcing the role of WHO*;[2]

1. **THANKS** the Regional Director for his comprehensive report on the work of WHO in the Region;

[1] Document nos. EM/RC59/2 and EM/RC59/INF.DOC 1,2,3,4,5

[2] Document no. WHO-EM/RDO/002

2. **ADOPTS** the annual report of the Regional Director 2011;

3. **REAFFIRMS** its solidarity with Afghanistan and Pakistan in their efforts to eradicate poliomyelitis;

4. **CALLS ON** Afghanistan and Pakistan to continue their concerted efforts to address the eradication of poliomyelitis as a national health emergency;

5. **URGES** Member States to:

   5.1 Provide support to alleviate the suffering of refugees and internally displaced persons in the Syrian Arab Republic and neighbouring countries, especially Jordan;

   5.2 Implement resolution EM/RC57/R.2 on emergency preparedness and response and regional solidarity fund;

   5.3 Express their solidarity for Afghanistan and Pakistan in their efforts to eradicate poliomyelitis, through political, financial and technical support;

   5.4 Ensure that a 100% smoke-free policy is implemented in all public places and accelerate the implementation of the other proven demand reduction measures of the WHO Framework Convention on Tobacco Control;

   5.5 Join the first stage of the regional pooled vaccine procurement mechanism (PVP) by utilizing UNICEF Supply Division vaccine procurement services, if they are middle-income countries that require procurement support for new vaccines (pneumococcal conjugate vaccine, rotavirus vaccine and human papilloma virus vaccine);

6. **REQUESTS** the Regional Director to:

   6.1 Take the necessary steps to ensure implementation of the strategic directions proposed for the next five years;

   6.2 Follow up on implementation of resolution EM/RC57/R.2 on emergency preparedness and response and regional solidarity fund;

   6.3 Implement, as soon as possible, the second stage of the regional pooled vaccine procurement mechanism.

12th meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE)

3-4 October 2012. Copenhagen, Denmark

DRAFT 11 October 2012

ABSTRACT

The European Technical Advisory Group of Experts on Immunization (ETAGE) met on 3-4 October 2011 to review and discuss immunization activities and developments in the WHO European Region and provide advice to the WHO Regional Office on appropriate activities. Five new members of the ETAGE were present for the meeting. Main topics for discussion included adult immunization strategies, National Immunization Technical Advisory Groups (NITAGs), tailoring immunization activities for underserved population groups, introduction of combined vaccines, introduction of rotavirus vaccine, Regional application of the Global Vaccine Action Plan (GVAP), rubella and congenital rubella syndrome.

Abbreviations

CRS	congenital rubella syndrome
DoV	Decade of Vaccines initiative
ETAGE	European Technical Advisory Group of Experts on Immunization
GVAP	Global Vaccine Action Plan
HCW	health care workers
IPV	inactivated poliovirus vaccine
IS	intussusception
NITAG	National Immunization Technical Advisory Group
RCC	Regional Commission for the Certification of poliomyelitis eradication
RVC	Measles and Rubella Regional Verification Commission
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	supplementary immunization activity
SIVAC	Supporting National Independent Immunization and Vaccine Advisory Committees initiative
TIP	Tailoring Immunization Programmes
UNICEF	United Nations Children's Fund
VENICE	Vaccine European New Integrated Collaboration Effort
VPD	Vaccine-preventable diseases
VPI	Vaccine-preventable Diseases, Immunization and Influenza Programme of WHO
WHO	World Health Organization
WHO EURO	World Health Organization European Regional Office, Copenhagen
WHO HQ	World Health Organization Headquarters, Geneva

Executive summary

The twelfth meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE) was held on 3 and 4 October 2012 in the WHO Regional Office for Europe, Copenhagen, Denmark. Five new members of the ETAGE were present for the meeting. Main topics for discussion included adult immunization strategies, National Immunization Technical Advisory Groups (NITAGs), tailoring immunization activities for underserved population groups, introduction of combined vaccines, introduction of rotavirus vaccine, Regional application of the Global Vaccine Action Plan (GVAP), rubella and congenital rubella syndrome. Updates were provided on conclusions and recommendations from appropriate recent Regional and Global technical, administrative and advisory meetings.

Although the intention is for ETAGE to meet formally at least once every year, the last meeting was held in March 2011. A primary reason for the delay was the staffing changes that have taken place in the WHO Regional Office associated with the organisational restructuring. In addition, the terms of reference for ETAGE membership have been revised to make the new terms are more closely aligned with those of SAGE members. Six new members of ETAGE have been appointed, and five were present for this meeting. As this was the first attendance at ETAGE for the five new members, a significant portion of the presentation material in each meeting session was devoted to providing background information on the history and strategies of the programme. Also present at the meeting were representatives from the newly formed NITAGs from Armenia, Belarus, Kazakhstan, Kyrgyzstan and Uzbekistan. Again, during each session time was taken to solicit the views, opinions and responses from the NITAG members to specific discussion points.

Development of the Tailoring Immunization Programmes (TIP) toolkit by the WHO secretariat was welcomed and further refinement leading to roll-out next year was encouraged. Establishment of an ETAGE working group to oversee and support the further development and roll-out would be of benefit and was recommended by the Group.

Outbreaks of measles among adults continue to be a problem with 27% of cases reported since 2009 being ≥20 years of age. Among reported adult cases, data suggests that 70% have no history of measles immunization. In addition, in a number of countries there appears to be an increasing incidence of measles cases among health care workers (HCWs). The problem is not restricted to measles as approximately 20% of reported rubella and 29% of reported mumps cases in the Region occur among adults. However, it is clear that targeting immunization services on adult populations faces considerable challenges. While there is extensive data to show that some adult groups, HCWs for example, are under-immunized, there is a continuing need to focus immunization resources on the highest priority groups. Questions remain as to whether adults, with the possible exception of HCWs, represent one of the highest priority groups.

While the Global Vaccines Action Plan (GVAP) and Decade of Vaccines (DoV) initiatives present an opportunity to establish a global approach to immunization, the nature and implications of GVAP reporting and monitoring requirements remain unclear, as does the expected role of ETAGE. It remains uncertain how much additional reporting burden this will place on Member States, and questions remain over the added value of this Plan to middle- and upper-income countries. It is also unclear where additional resources will come from. While ETAGE is supportive of the goals of the GVAP, there are reservations and concerns over how this Plan will be implemented in the Region.

There is an increasing use of combination vaccines in middle-income countries within the Region, driven largely by the adoption of inactivated poliovirus vaccine (IPV)-containing or

acellular pertusis combination vaccines. Introduction can bring advantages but can also create additional problems for immunization services, including complication of schedules, increased number of vaccine formulations, increased cost and a requirement for increased cold chain and storage facilities. ETAGE is concerned that Member States should be supported to resist pressures to switch to combined vaccines until more evidence on their comparative advantages and disadvantages becomes available.

NITAGS are now established in 35 countries, but the status, stage of development and extent of activity varies considerably. WHO has provided capacity-building training support to NITAGs and has assisted countries to secure funding support for their NITAGs. Further training, on evaluation of cost effectiveness of vaccine introduction, will be provided later this month. SIVAC has continued its role in supporting countries to establish and strengthen NITAGs, and in providing information exchange through the web-based NITAG Resource Centre.

Questions on the effectiveness of NITAG information sharing have been raised as it appears that for some NITAGs information sharing is vertical, between the NITAG and the national health authorities. Clearly more horizontal information sharing mechanisms would be beneficial to the process of strengthening NITAGs and increasing their effectiveness. Increasing transparency of NITAG activities may also be an issue. NITAGs should be independent of national health authority influence and should not be allowed to drift into the role of national regulators. Recommendations from NITAGs should be in the public domain, and should be used to engender public trust in national immunization services.

At its meeting in April 2012 SAGE recommended that the current age restrictions for the first dose of rotavirus vaccine (>15 weeks) and last dose (<32 weeks) are preventing vaccination of many vulnerable children. By removing the age restrictions, programmes should be able to immunize children who are currently excluded receiving vaccine. ETAGE recommends that relaxation of the age-limit restrictions for the receipt of rotavirus vaccines may be considered by Member States based on local rotavirus disease epidemiology and available immunization resources. However, for many countries in the Region it is not obvious if there is a cost-benefit to the introduction of rotavirus vaccine, since rotavirus-associate mortality is low. Surveillance for intussusception (IS) is inadequate in many countries and needs to be improved before a realistic risk-to-benefit ratio for rotavirus introduction can be calculated.

While there has been a decline in the reported incidence of rubella over the past decade, reported immunization coverage appears to have plateaued and outbreaks of rubella continue to occur. Romania and Poland have reported the highest incidence of disease in the past two years, with continuing year-round transmission in Poland and a large outbreak from the end of 2011 to mid-2012 in Romania. The Romania outbreak predominantly involved adolescents and young adults, the age cohorts most likely to have missed both natural infection and immunization when rubella was introduced to the national childhood immunization schedule in 2004. The lesson to be learned for other countries that have introduced childhood rubella immunization over the past decade or so is that they need to conduct catch-up campaigns to protect children in known at-risk age cohorts. Surveillance for CRS continues to be problematic with many Member States only reporting annual CRS incidence.

Introduction

The European Technical Advisory Group of Experts on Immunization (ETAGE) meets to review the progress of the Vaccine-preventable Diseases and Immunization programme (VPI) towards the European Regional disease prevention goals. The 11th meeting of the ETAGE was conducted from 17-18 March 2011; the 12th meeting was held at the WHO Regional Office for Europe, Copenhagen, from 3-4 October 2012.

Professor Pierre Van Damme chaired the meeting, Professor Christian Perronne was vice-chair, and Dr Ray Sanders was rapporteur.

Objectives of the meeting were to:

1. Request advice and guidance from ETAGE members on the following key topics and issues:
    - Adult immunization strategies
    - National Immunization Technical Advisory Groups
    - Tailoring activities for underserved population groups
    - Immunization schedules and inactivated polio vaccine
    - Regional recommendations on rotavirus vaccine
    - Regional interpretation and applicability of the Global Vaccine Action Plan (GVAP)
    - Rubella surveillance (and related issues) and congenital rubella syndrome
    - The challenges of silent reporting areas in the European Region
2. Provide updates on:
    - Activities to strengthen National Immunization Technical Advisory Groups in the Region; Polio (the European Regional Certification Commission) and progress towards maintaining the polio-free status of the European Region;
    - Measles (the European Regional Verification Commission for Measles and Rubella Elimination),
    - Strategic Advisory Group of Experts on Immunization (SAGE) recommendations
    - Outcomes of the WHO European Regional Committee (RC)
3. Provide insight and activity reports, as required by ETAGE, from the different sub-teams and technical officers of the Vaccine Preventable Diseases and Immunization Programme.
4. Discuss Terms of Reference for ETAGE, Membership and composition of the newly formed ETAGE, and the schedule for the ETAGE meetings in 2013 (closed session).

Opening remarks

Dr Guenael Rodier, Director, Division of Communicable Diseases, Health Security, and Environment (DCE), opened the meeting and welcomed ETAGE members, representatives of partner agencies and Regional immunization initiatives, representatives of selected NITAGs, and staff from WHO headquarters on behalf of the WHO Regional Director.

Professor Pierre Van Damme welcomed the five new ETAGE members present and explained that one other new member was unable to attend due to a conflicting commitment. He informed the meeting that the terms of reference for ETAGE membership were being revised and that new terms are more closely aligned with those of SAGE members.

Introduction and report on responses to recommendations of the 11th ETAGE

In accordance with the revised terms of reference for ETAGE membership, each member is required to complete a declaration on conflict of interests. All new members have done so, and the meeting was informed of their responses.

Although the intention is for ETAGE to meet formally at least once every year, no meeting was held in the past 16 months. This delay was due to the staffing changes that have taken place in the WHO Regional Office associated with the organisational restructuring. Organograms of the new administrative structure of the WHO Regional Office were provided to the meeting. Despite the lack of formal meetings, the Secretariat has maintained close working communications with ETAGE and meetings with the ETAGE Chair and Vice-chair have been conducted.

Of the recommendations made during the 11th meeting of ETAGE, most have been addressed or are in process. At its 11th session ETAGE requested VPI to collate all ETAGE recommendations made during that and previous meetings to provide a comprehensive list to serve as a reference for new ETAGE members. This has not yet been completed, and at the request of ETAGE, the checklist, indicating the implementation status of each recommendation, will be provided as soon as possible.

Reviewing the experience of ETAGE over the past 7 years, improvement in quality and quantity of data presentation and analysis was most obvious and the efforts of the WHO secretariat in achieving this were acknowledged. Although greatly improved, connections between ETAGE and the NITAGs and national immunization programmes remains less than optimal and the recent nomination of a focal point within the VPI should strengthen the exchange of information level of collaboration between the Regional and country levels. However, transferring the expertise and experience of ETAGE members to country level in support of immunization activities remains a challenge.

Session 1. Tailoring Immunization Programme (TIP) activities, vaccine advocacy and communications

In the European Region, reasons for not vaccinating an infant or child are complex and multiple. Lack of access, marginalisation, low risk perception, fear, distrust, hesitancy and complacency, as well as alternative philosophical health beliefs, are some of the myriad of reasons vaccination of an infant or child may not take place. With the guide to Tailoring Immunization Programmes (TIP), WHO/Europe offers an approach that proposes practical solutions to help Member States to shape innovative and targeted responses to immunization programming and communications that reach out to populations susceptible to VPD. The guide aims to place vaccination of infants and children as a positive care-giving practice, with important community and societal benefits.

The overall aim of TIP is to provide proven methods and tools to design targeted programmes that increase uptake of infant and child vaccination, thereby increasing immunization coverage rates and curbing the risks of VPD in the region.

To do this, the TIP guide offers:

- A step-by-step approach to segment groups of caregivers based on a child's vaccination status: up-to-date on vaccinations – missing vaccinations – not vaccinated.

- Formative research tools and conceptual maps to provide a detailed level of understanding of what drives caregivers' vaccination practices.
- Maps and tools to explore the role that vaccination providers play in influencing caregivers' vaccination choices and actions.
- Resources for designing, implementing, monitoring and evaluating TIP interventions based on the results of the segmentation and profiling process. This includes a menu of lessons learned and best practices in immunization programming.

TIP has been piloted in Bulgaria to target immunization resources on underserved populations there. It is expected that the toolkit will be finalized for publication by the end of 2012 and roll-out will take place starting in 2013. It is not yet determined who the institutional partners contributing to the roll-out process will be, or how ETAGE will be involved in the roll-out process.

Discussion:

It is essential to avoid stigmatization, or further stigmatization of target populations, when introducing new approaches to delivery of immunization services. For this reason the term ***hard to reach*** should be replaced by ***underserved***, and it is essential to work with existing minority-linked mediator groups such as NGOs and community associations. It should be emphasised that this toolkit is designed as a self-help measure. It is not designed to institute individual behaviour change but is concerned with identifying problems in accessing immunization services from an individual perspective. Use of the toolkit requires endorsement of the National health authorities, but implementation should be by non-governmental and community groups.

The toolkit has been developed as a generic instrument that will require tailoring to specific needs. Prioritization of the determinants used to tailor the instrument requires further work. It may be possible to conduct a literature review and determine the highest priority determinants through a meta-analysis.

It is difficult to formally evaluate the effectiveness of the toolkit at this stage. As the toolkit is rolled out and used in countries it should be possible to make an evaluation through observation of the impact on target populations. Recognising the need for evaluation, an appropriate tool is in development by John Snow International.

This clearly represents an important initiative from the EURO secretariat that requires further refinement and development. Establishment of an ETAGE working group to oversee and support the further development and roll-out would be of benefit.

Session 2: Adult immunization strategies (with focus on measles and rubella elimination)

Discussions for this session focussed on measles and rubella cases. Within the Region, since 2009, 27% of the total number of reported measles cases was over 19 years of age. Several countries in the Region strengthened measles immunization actives between 1991 and 2004, through specific targeted immunization activities, but children who were not targeted when these activities were implemented are now teenagers and young adults. Among reported adult cases, data suggests that 70% have no history of measles immunization. In addition, in a number of countries there appears to be an increasing incidence of measles cases among

health care workers (HCWs). Available data suggests that because of proximity and frequency of contact, risk of acquiring measles is 13-19 times higher for susceptible HCWs than for the general public. The problem is not restricted to measles as approximately 20% of reported rubella and 29% of reported mumps cases in the Region occur among adults.

WHO recommends immunization against measles for adults likely to be susceptible and at risk of being exposed to measles virus, particularly HCWs. For Member States focusing on interrupting transmission of rubella virus, WHO recommends that depending on the burden of disease and available resources, countries may choose to accelerate their progress towards elimination by conducting rubella immunization campaigns that target a wide age-range of both males and females. WHO also recommends that strategies to control mumps should be closely integrated with existing goals of measles and rubella control or elimination, particularly where MMR vaccine is used as a common tool.

In 2011, no country in the Region recommended measles vaccine for all adults. According to the VENICE II Report (2010) 12 out of 30 EU countries do have recommendations for vaccinating specific risk and age groups, including adults. However, there are problems with interpretation of specific national recommendations on immunization of HCWs and other at-risk adults. To reduce the uncertainty and provide clear and strong recommendations to Member States it is proposed that the recommendations from WHO should include involvement of occupational health authorities for HCWs, teachers, military personnel, airport and port staff, shopkeepers; widespread use of MMR as a pre-travel vaccine by liasing with travel health centres and travel agencies, and; establishment of mobile vaccination clinics visiting educational facilities, military barracks, police headquarters and airport and port facilities.

Discussion:

There is evidence that adults can play an important role in the transmission of VDPs from location to location, but may not play an important role in transmission during outbreaks. In the absence of disease elimination it may be more effective use of resources to target immunization on susceptible children to prevent transmission. However, more information is required on the relative contribution of transmission by adults under different conditions. It is clear that susceptible pools of adults exist, but potential interventions need to be prioritized according to resource availability. It may be possible to determine the size of susceptible populations by conducting serosurveys, but again, this is dependent on resource availability. Past experience of interventions targeted on adults suggests that a significant amount of background information on susceptibility thresholds and target population size is required.

In 2011 an outbreak of measles in Denmark prompted the government to establish a temporary programme for the administration of a single dose of measles vaccine to all adults born between 1974 and 1994 who were without a documented measles vaccine history. Of the estimated target population of 10,000 to 20,000 less than 1,000 registered to receive vaccine. As yet no decision has been made to continue the programme into 2013. There was no recommendation for this programme from the National Board of Health, and communications and advocacy for the programme appear to have been lacking.

It is clear that targeting immunization services on adult populations faces considerable challenges. The experience with measles is likely to be faced by other control programmes, pertussis for example. While there is extensive data to show that some adult groups, HCWs for example, are under-immunized, there is a need to focus immunization resources on the

highest priority groups. Questions remain as to whether adults, with the possible exception of HCWs, represent the highest priority group.

Session 3: Updates: RC, SAGE, RCC, RVC, AOB

Update information was provided to ETAGE from recent meetings of the WHO Regional Committee (RC), the Regional Certification Commission (RCC), the Regional Verification Commission for Measles and Rubella Elimination (RVC) and the Strategic Advisory Group of Experts on Immunization (SAGE).

Discussion:

Polio risk indicators for 2012 were reviewed during the RCC. Although the assessment of risk has changed over the years, the highest risk areas have remained fairly constant. For 2012 the number of high risk countries has reduced slightly, but the RCC concluded that significant risk of polio reintroduction remains because of low population immunity in several countries. Ukraine in particular, is considered at significant risk since disruption of immunization services in May 2008. There is a clear need to improve population immunity and surveillance quality in all at-risk countries, but there is no room for complacency in other Member States as many also have sub-populations with sub-optimal immunization coverage.

A draft framework for the Regional verification of measles and rubella elimination has been developed, based on the global guidelines. Member States are scheduled to make first reports to the RVC during the first quarter of 2013, but no country in the Region has a National Verification Committee (NVC) yet in place. Letters from the RD and RVC are being sent to Member States requesting them to nominate NVC members. Some Member States with limited numbers of available experts may need to combine the functions of existing polio National Certification Committees (NCC) with the new NVCs, but they need to be aware of potential conflict of interests and make appropriate arrangements. The potential to establish sub-Regional committees for Member States with limited resources is being investigated.

During its April meeting SAGE was presented with a review of the influenza disease burden, vaccine performance, and safety in populations of all ages and at-risk groups, incorporating available data from low and middle-income country settings. Based on the review, SAGE proposed specific recommendations with the objective of revising the 2005 WHO position paper on influenza vaccines.

SAGE recommended pregnant women as the most important risk group for inactivated seasonal influenza vaccination. Other risk groups to be considered include HCWs, children aged 6–59 months, the elderly and those with high-risk conditions. SAGE recommended that countries with existing influenza vaccination programmes targeting any of these groups should continue to do so and should incorporate immunization of pregnant women into such programmes. Countries should decide which other risk groups to prioritize for vaccination based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations. It must be recognised, however, that many countries lack appropriate evidence on disease burden, cost-effectiveness and feasibility and would need to collect additional data before decisions on target groups can be made, particularly immunization of pregnant women. This issue of lack of country data should be raised with SAGE.

Session 4: Global Vaccine Action Plan (GVAP)

The GVAP and Decade of Vaccines (DoV) initiatives present an opportunity to establish a global approach to immunization. Despite the advances made in recent years, VPDs remain a major cause of morbidity and mortality, and for many middle- and low-income countries immunization needs remain unmet.

Six principles have guided development of the Global Vaccine Action Plan:

- Country ownership: countries have primary ownership and responsibility for establishing good governance and for providing effective and quality immunization services for all.
- Shared responsibility and partnership: immunization against vaccine-preventable diseases is an individual, community and governmental responsibility that transcends borders and sectors.
- Equity: equitable access to immunization is a core component of the right to health.
- Integration: strong immunization systems, as part of broader health systems and closely coordinated with other primary health care delivery programmes, are essential for achieving immunization goals.
- Sustainability: informed decisions and implementation strategies, appropriate levels of financial investment, and improved financial management and oversight are critical to ensuring the sustainability of immunization programmes.
- Innovation: the full potential of immunization can only be realized through learning, continuous improvement and innovation in research and development, as well as innovation and quality improvement across all aspects of immunization.

The GVAP was endorsed by the 65th meeting of the World Health Assembly in May this year, so Member States, WHO Regional Offices and their advisory groups need to be aware of the Plan and of their expected roles and responsibilities. Although the plan has been endorsed, considerable work remains on defining the process and developing requirements for implementation.

Discussion:

The nature and implications of GVAP reporting and monitoring requirements remain unclear, as does the expected role of ETAGE. This may be an area for establishment of an ETAGE working group to determine the roles and responsibilities of ETAGE and NITAGs in complying with GVAP requirements and developing the Regional review process. It remains unclear how much additional reporting burden this will place on Member States, and questions remain over the added value of this Plan to middle- and upper-income countries. It is also unclear where additional resources will come from. While ETAGE is supportive of the goals of the GVAP, there are reservations and concerns over how this Plan will be implemented in the Region.

Session 5: Combined vaccines schedules (IPV)

There is an increasing use of combination vaccines in middle-income countries within the Region. This increase has been driven largely by countries adopting acellular pertusis or inactivated poliovirus vaccine (IPV)-containing combination vaccines, with only 10 Member States in the Region now use oral poliovirus vaccine (OPV) in their schedules. Reasons for adopting combined vaccines differ, however, among Member States, and for most the advantages are clear. However, introduction can create additional problems for immunization

services, including complication of schedules, increased number of vaccine formulations, increased cost and requirement for increased cold chain and storage facilities. WHO has provided recommendations on the introduction of new vaccines, including combined vaccines, and on modification of existing immunization schedules. Political, administrative and commercial pressures, however, can lead Member States to ignore these recommendations.

Discussion:

There is no revolving fund for procurement of vaccines in this Region, although the possibility of establishing one was investigated and few Member States expressed an interest. Countries can make use of the UNICEF procurement system if national legal requirements permit. There is an EU vaccine procurement system in development, but this is not yet available.

Immunization schedules are often based on historical precedent, leading to significant diversity but also to schedules tailored to national requirements. Rather than demanding standardization and uniformity of schedules, the heterogeneity of existing schedules should be used to investigate the strengths and weaknesses and develop best practices guidelines. Furthermore, the use of combination vaccines has raised questions regarding the duration of protection afforded by these vaccines. ETAGE is concerned that Member States should be supported to resist pressures to switch to combined vaccines until more evidence on their comparative advantages and disadvantages is available.

When countries decide to include combination vaccines they should be supported to adopt a flexible approach best suited to their circumstances. A flexible approach does not always permit following the recommended use and safety information provided by the vaccine manufacturers in their package insets. Unfortunately, due to legal restrictions associated with vaccine licensing, countries may not be able to deviate from the recommended use and safety information. This situation is further complicated by vaccine producers using different package inserts, containing different information, in different countries. This problem needs to be addressed at the global level.

Session 6: National Immunization Technical Advisory Groups (NITAGs)

An update on the development and status of NITAGs in the region and the continuing role of SIVAC in supporting countries to establish and strengthen NITAGs was provided. NITAGS are now established in 35 countries, but the status, stage of development and extent of activity varies considerably. There have been requests from some smaller Member States with a shortage of appropriate experts for advice on combining the responsibilities of different advisory groups, for example AEFI, within the NITAGs.

WHO has provided capacity-building training support to NITAGs and has assisted countries to secure funding support for their NITAGs. Further training, on evaluation of cost effectiveness of vaccine introduction, will be provided later this month. Future training will be provided data acquisition and analysis and making evidence-based recommendations for immunization programmes. Members of established NITAGs have attended meetings of newly-established NITAGs, and representatives of NITAGs have been invited to the ETAGE meeting. It is essential that information and recommendations from ETAGE are disseminated to all NITAGs. SIVAC continues to support countries to establish and strengthen NITAGs through provision of direct support and hosting of its web-based NITAG Resource Centre.

The potential role of NITAGs with respect to implementation of the GVAP was discussed. GVAP calls for countries to develop a national immunization monitoring framework, and NITAGs will be expected to support this development. NITAGs will also be expected to review national progress in developing the new framework and in advocacy with national authorities. It is possible that some NITAGs will be required to update their terms of reference in order to do this.

Discussion:

With regard to setting the agenda for NITAG meetings, responsibility is often taken by the national health authorities and the addenda is set to address current national priorities. For many new NITAGs the highest priorities have been introduction of new vaccines and changes to immunization schedules. Although polio eradication and measles/rubella elimination are important, they have not been considered highest priorities for many NITAGs.

Questions on the effectiveness of NITAG information sharing have been raised. It appears that for some NITAGs information sharing is vertical, between the NITAG in the national health authorities. Clearly more horizontal information sharing mechanisms would be beneficial to the process of strengthening NITAGs and increasing their effectiveness. Language barriers are a challenge to more horizontal information sharing, as is the different levels of development of NITAGs in different countries. It is sometimes not apparent to newly-formed NITAGs how they can learn from the experience of established NITAGs.

Transparency of NITAG activities may also be an issue. NITAGs should be independent of national health authority influence and should not be allowed to drift into the role of national regulators. Recommendations from NITAGs should be in the public domain, and should be used to engender public trust in national immunization services. In several countries the recommendations of the NITAG presently go only to the national health authority or the Interagency Coordinating Committee.

Potential roles for ETAGE in strengthening NITAGs were discussed. Representative members of NITAGs present welcomed the involvement of ETAGE in capacity building, training and sharing of expertise with the NITAGs. Details of how ETAGE members can be included in NITAG development and training activities remain to be formulated, but the opportunity to participate was welcomed, in principle, by the ETAGE members present.

Session 7: Rotavirus vaccines schedule

At its meeting in April 2012 SAGE recommended that the current age restrictions for the first dose of rotavirus vaccine (<15 weeks) and last dose (<32 weeks) are preventing vaccination of many vulnerable children. By removing the age restrictions, programmes should be able to immunize children who are currently excluded from the benefits of rotavirus vaccines and this is likely to include some of the children most vulnerable to severe rotavirus disease. Globally, many thousands more deaths would be averted, but with a small additional increase in intussusception (IS) cases. Countries using rotavirus vaccine, or planning introduction, should consider the SAGE recommendation in light of their own circumstances and local information on rotavirus epidemiology. There is a need for improved surveillance for IS and countries would benefit from support in improving their surveillance and integrating this into their national programmes.

For many countries in the Region it is not obvious if there is a cost-benefit to the introduction of rotavirus vaccine, since rotavirus-associate mortality is low. In these countries the

potential increased incidence of IS associated with the vaccine may be counter-indicative to vaccine introduction.

Rotavirus mortality in the Region is low, with most countries reporting rotavirus-associated mortality rates of <5/100,000. Only 2 countries report mortalities in the region of 51-100/100,000. Within the Region there are 6 countries that have introduced rotavirus vaccine. Moldova is the first MIC in the country to introduce the vaccine; Armenia and Georgia will introduce the vaccine; and Uzbekistan is considering introduction. For most countries in the Region the risk-to-benefit-ratio for rotavirus introduction is low, and to increase the benefit they need to increase the vaccine coverage level. One way to do this would be to relax the time-restrictions on rotavirus immunization and Member States are requesting advice on changing the age restrictions for receipt of vaccine.

Discussion:

There is a need to improve the timeliness of delivery of all childhood vaccines, particularly DTP if rotavirus vaccine is to be introduced. It is also essential to understand the risk of IS before rotavirus is introduced, recognising that much of the evidence on IS is based on estimates rather than hard data. [redacted] The epidemiology of IS is a rapidly moving field and it is possible that with additional vaccines coming onto the market in the near future guidelines for rotavirus vaccine administration will require further revision. It appears that surveillance for IS is inadequate in many countries and this needs to be improved before a realistic risk-to-benefit ratio can be calculated.

Session 8: Rubella and CRS surveillance in the context of elimination efforts

An overview of the history and current status of the rubella and congenital rubella syndrome (CRS) elimination initiative in the Region was presented. While there has been a decline in the reported incidence of rubella over the past decade, reported immunization coverage appears to have plateaued and outbreaks of rubella continue to occur. Decreasing commitment to rubella elimination, the effects of health sector reforms and increasing momentum of the vaccine refusal movement are all slowing further progress towards the Regional elimination goal. There are also unimmunized or under-immunized communities in both the marginalized/underserved populations and in the general population in several countries.

Romania and Poland have reported the highest incidence of disease in the past two years, with continuing year-round transmission in Poland and a large outbreak from the end of 2011 to mid-2012 in Romania. The Romania outbreak predominantly involved adolescents and young adults, the age cohorts most likely to have missed both natural infection and immunization when rubella was introduced to the national childhood immunization schedule in 2004.

Challenges to rubella surveillance in the Region include the absence of specific rubella surveillance systems in Belgium, Denmark and France, with Germany only starting surveillance this year; aggregate reporting in more than 20 countries; lack of comparability between the number of laboratory reported results and clinically reported cases; and a lack of genotyping data for molecular epidemiological analysis. All countries have been requested to provide case-based reporting by 2012, but even for countries with case-based reporting the data is frequently incomplete and of low quality. Surveillance for CRS is even more problematic with many Member States only reporting annual CRS incidence.

Discussion:

From the available evidence Romania should have conducted a mass rubella immunization campaign when it became evident that an outbreak was starting. It appears that institutional barriers to procuring and allocating vaccine prevented this from taking place. Given the size of the outbreak, with more than 17,000 reported cases, Romania should be preparing for an anticipated epidemic of CRS over the next few months. The lesson to be learned for other countries that have introduced childhood rubella immunization over the past decade or so is that they need to conduct catch-up campaigns to protect children in the at-risk age cohorts. There is a clear responsibility here for WHO to alert susceptible Member States to the risk of rubella outbreaks.

Conclusions and recommendations

Conclusions:

- ETAGE welcomes the development of revised ETAGE terms of reference and appreciates this opportunity to introduce new ETAGE members to the programme. The group also appreciates the opportunity for representatives from newly established National Immunization Technical Advisory Groups (NITAGs) to participate in the meeting.
- ETAGE appreciates the designation of a nominated ETAGE focal point within the VPI Unit to facilitate communications and coordination between ETAGE and the WHO Regional Office and recognises the significant contributions to the programme the focal point has already made.
- ETAGE recognises that restructuring of the WHO Regional Office and associated staff changes have caused delays in fully implementing all recommendations made at the 11th session of ETAGE and urges the VPI Unit to collate all ETAGE recommendations made during this and previous meetings of ETAGE to provide a comprehensive list to prevent repeating key recommendations and to be a helpful reference for new ETAGE members.
- ETAGE appreciates the update and summary of SAGE activities and strongly endorses the requirement to maintain strong working relationships between SAGE, ETAGE and the NITAGs.
- ETAGE is encouraged by progress made in the development of NITAGs within the Region, and acknowledges the high level of commitment shown by Member States, WHO and its partners, particularly SIVAC, in establishing and strengthening these groups.
- ETAGE recognises that NITAGs have specific requirements for information and support and encourages sharing of data and expertise both between NITAGs and with ETAGE and WHO. ETAGE encourages Member States to make good use of the NITAG Resource Centre developed by the SIVAC initiative.
- While supporting the aims of the Global Vaccine Action Plan (GVAP), ETAGE recognises that some specific requirements of the plan have yet to be fully defined and that the Region will need to address Region-specific challenges related to monitoring and reporting.

- ETAGE is greatly concerned at the continuing lack of understanding of immunization requirements and benefits among health care workers (HCWs) in many Member States. Urgent action is needed to improve the quality and accuracy of understanding among HCWs on the need to immunize and protect themselves and the communities they serve from vaccine-preventable diseases.
- ETAGE recognises [redacted] Member States to adopt combined vaccines, particularly IPV-containing vaccines. It must be recognised that whilst these vaccines offer [redacted] advantages, they also offer the potential to disrupt existing immunization programmes by requiring changes to schedules, supply of multiple formulations of vaccines and additional cold-chain and vaccine storage capacity. Member States are advised to learn from the example of other countries in adopting combination vaccines and pursue a flexible approach to introduction that results in the greatest benefit and the least disruption to existing services.
- ETAGE is concerned that for some Member States the global eradication of polio and regional elimination of measles and rubella are no longer high priorities. There is a continued low level, or lack, of rubella and CRS surveillance in many Member States and ETAGE urges all countries to establish and maintain systems meeting the standards described in the WHO surveillance guidelines. High level surveillance and immunization for polio must be maintained and immunization coverage and surveillance quality for measles and rubella must be improved throughout the Region if Global and Regional goals are to be achieved.
- ETAGE is alarmed by the recent outbreaks of rubella in older age groups as a consequence of the introduction of rubella vaccine into childhood immunization programmes, without catch up campaigns, leaving several age-cohorts susceptible to rubella infection. This risk needs to be appreciated by Member States. The apparent inability of national authorities to respond to these outbreaks by holding SIAs is also of great concern and institutional barriers to mounting emergency immunization responses must be overcome.

Recommendations:

1. ETAGE recommends that development and evaluation of the Tailoring Immunization Programmes (TIP) toolkit be continued and that a strategy for implementation and evaluation of impact be developed. ETAGE urges institutional partners to support roll-out of the toolkit and promotion of its use by Member States and recommends establishment of an ETAGE working group to support and oversee implementation.
2. Recognising that recent outbreaks of measles and rubella have been associated with unimmunized adult populations, ETAGE urges WHO to continue with the development of strategies, including use of serosurveys, to identify needs and approaches to identifying and immunizing these susceptible groups.
3. ETAGE urges all NITAGs to ensure that polio eradication and measles/rubella elimination remain priority goals for all national immunization programmes and recommends WHO to take every opportunity to remind Member States of the Global polio eradication and Regional measles and rubella elimination goals.
4. ETAGE recommends that WHO encourage, and where appropriate facilitate, opportunities to share information and expertise between NITAGs and ensure that

NITAG members have full access to information on ETAGE concerns and recommendations.

5. To ensure early protection and high impact of vaccination, ETAGE recommends that Member States introducing, or considering the introduction, of rotavirus vaccine to their infant immunization schedules, should take effective measures to improve timeliness of infant immunization. ETAGE further recommends that relaxation of the age-limit restrictions for the receipt of rotavirus vaccines, as recommended by SAGE, may be considered by Member States based on local rotavirus disease epidemiology and available immunization resources.
6. ETAGE urges WHO to continue the support of Member States in strengthening their AEFI monitoring and to include the addition of surveillance for intussusception for countries introducing or considering introduction of rotavirus vaccine.
7. ETAGE recommends that Member States review their rubella immunization programmes to assess requirements for catch-up campaigns in at-risk age cohorts. With the support of WHO, Member States must develop activities to detect and document rubella-susceptible populations. They must also develop mechanisms to overcome existing institutional barriers to providing timely and effective responses should an outbreak threaten or occur.

21st Meeting of the Technical Advisory Meeting
on Immunization and Vaccine Preventable Diseases in the Western Pacific Region
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MEASLES ELIMINATION AND RUBELLA CONTROL

Conclusions

The Regional Committee in its 2005 meeting endorsed the year of 2012 as the target year of measles elimination in the Western Pacific Region. All countries and areas in the Region have made tremendous efforts to achieve and sustain measles elimination. As a result, the Region is making rapid and remarkable progress and now is on the verge of eliminating measles. Thirty-two countries and areas may have already interrupted endemic measles transmission. The number of measles cases declined by 86% from 145,935 in 2008 down to 21,054 in 2011, and the annual measles incidence reduced from 81.6 per million in 2008 to 11.6 per million population in 2011. In 2012, the number of measles cases has continued to decrease in the Region, with a reduction of 69% from 5,150 measles cases in January-June 2012 compared to 16 431 cases in the same period in 2011; and the number of measles cases is at historic low in most countries.

However, some critical challenges remain to interrupt endemic transmission eventually in all countries and areas, requiring greater political commitment and resources and intensified efforts. In the remaining months of 2012 and in 2013, commitment from and further progress made by the countries with sustained measles virus transmission will largely determine the status of measles elimination in the Region; thus urgent actions will be required to interrupt measles virus transmission as soon as possible. Experiences in Australia, Japan and other countries, sounds the alert that importation of measles virus poses an ongoing threat to all countries and areas.

Sustaining the achievement of measles elimination is also challenging while it provides a great opportunity for countries to reach every community with adequate vaccination services and promote equity in immunization. It is imperative for every country and area to implement proper strategies and activities to close immunity and surveillance gaps using practical means, and rapidly identify risks (areas and population groups), adequately prevent, prepare for and respond to outbreaks caused by either endemic or imported measles virus. The Region and countries should continue prioritizing measles elimination and use measles elimination as a means to advocate for synergy with rubella control activities and equity of immunization and other health care services.

The TAG acknowledges the good progress made in the Region towards establishing the regional verification mechanisms for measles elimination, including criteria, indicators, structure and processes.

Recommendations

1. The TAG reaffirms the critical importance, based on the 2009 WHO measles vaccine position paper, that all children receive at least two doses of measles vaccine, either through the routine programme or supplementary immunization activities (SIAs). Ideally MCV2 should be provided in the second year of life, to minimize the accumulation of susceptible.

2. The TAG urges that countries with sustained measles virus transmission identify and implement the intensified and focused efforts to interrupt measles virus as a matter of urgency. This includes China, Malaysia, New Zealand, Philippines and Singapore.

3. The TAG recommends countries to systematically and precisely identify high risk communities with underserved populations, and make effective and sustained efforts to reach these communities with measles-containing vaccines and other EPI vaccines, and regularly monitor progress.

4. The TAG urges all countries and areas to assess their measles surveillance performance by province and district, to plan activities to address existing surveillance gaps and to improve sensitivity and specificity of surveillance, emphasizing case detection and notification, in-depth case investigation, sample collection for serology and virus identification (blood and swab), and proper case classification.

    - The TAG advises that every country and area should comprehensively describe every measles case and the affected community, including social-economic and service delivery details, to help guide a decision on rational outbreak control interventions.

    - The TAG recommends all countries to implement the 2010 TAG recommendation calling for the establishment of Expert Review Committees (ERC) whenever possible, while clear instruction should be developed to ensure that ERC function properly.

5. The TAG emphasizes that regular risk assessment, adequate preparedness and response to measles outbreaks (caused by either endemic or imported measles virus) are critical for all countries and areas to achieve and sustain measles elimination. Preparedness plans should address the risk of cross border and remote importations. Where appropriate, countries should convene cross border coordination activities. Given the growing concern about importation from extra-regional locations, the TAG recommends that the Regional Director, the WHO Western Pacific Regional Office and Member States advocate with other regions for achieving their regional elimination or control goals, which will reduce the risk of importation into the Western Pacific Region.

6. The TAG suggests countries and areas synergize measles elimination and rubella control activities, through using measles and rubella combination vaccines and integrating measles and rubella surveillance whenever possible.

7. The TAG encourages WHO and UNICEF, as a priority, to provide technical assistance to the GAVI eligible countries in the Western Pacific Region to prepare their applications to GAVI for conducting catch-up supplementary immunization activities (<15 years old) with measles-rubella containing vaccine (MR),and the introduction of rubella containing vaccine and routine measles second dose into their routine immunization programmes.

8. TAG encourages the Region and countries and areas to adopt good communication strategies/messages to advocate for measles elimination including promotion of equity in immunization and immunization days/weeks.

9. The TAG acknowledges the efforts of the WHO measles and rubella laboratory network to support the regional goal. It encourages network laboratories with pending accreditation status to be accredited as soon as possible and the high performance level of all network laboratories to be maintained.

Country-specific recommendations:

a. The TAG acknowledges the strong political commitment from the Chinese government and tremendous efforts made at each level, and congratulates China on the remarkable progress made to dramatically reduce the number of cases in recent years. Given the diversity in epidemiology, demography, geography and health systems by province, the TAG recommends that the country implements tailored strategies for each province based on in-depth review. Joint national and international consultation may be helpful.

b. The TAG finds the increased and ongoing measles transmission in Malaysia worrying and recommends that the country implement intensified vaccination strategies to: rapidly interrupt the current transmission, take further actions to reach 95% routine coverage at community level, strengthen cross border coordination of measles control activities, and more effectively reach migrant and transient populations.

c. In support of efforts to improve routine immunization, the TAG recommends that Papua New Guinea considers a second dose of measles vaccine in the second year of life and reconsiders the need and relevance of a 6-month dose of measles in the present context. Papua New Guinea should make use of GAVI assistance and consider introducing MR vaccine in the routine immunization schedule following a wide age range catch-up MR SIA.

d. The TAG acknowledges the great efforts made by the Philippines to control large measles outbreaks during 2010-2011 by conducting a national MR SIA in 2011. Measles transmission is now concentrated in only a few provinces. Further focused efforts will be needed to interrupt residual transmission in these provinces as well as to prevent re-emergence of measles in other provinces. Given the challenges in reaching 95% coverage universally throughout the country, TAG urges the country to develop or intensify the current strategies to regularly conduct risk assessment, identify high risk areas, take effective actions and monitor the progress.

e. The TAG recommends that Singapore closely measures immunity gaps and ensure that proactive strategies are in place to close the immunity gaps that are identified.

HEPATITIS B CONTROL

Conclusions

This year China and Mongolia were verified to reach the <1% goal marking a tremendous public health achievement. While the final status of the 2012 milestone of reducing hepatitis B prevalence in children to <2% is not yet confirmed it is estimated to be met by the Region as a whole and by least 30 countries and areas (>95% of Region's population). This is based on seroprevalence estimates of hepatitis B surface antigen and immunization coverage available to date. The six remaining countries (Papua New Guinea, the Philippines, Kiribati, Samoa, Solomon Islands,Vanuatu) have not conducted recent prevalence surveys or reached target coverage levels. These countries have substantial challenges of reaching home births and/or not fully integrating hepatitis B vaccination in facility settings. In addition, although seroprevalence surveys indicate that Lao People's Democratic Republic, Cambodia and Vietnam may have met the <2% milestone, they are also priority countries for strengthening birth dose vaccination.

The TAG is pleased with the <2% milestone progress. Hepatitis B birth dose assessments have provided valuable data to guide programmes, have raised awareness, and have been an efficient and worthwhile use of public health resources. The hepatitis B birth dose consultation provided

an opportunity for collaboration and joint planning between immunization and mother and child health programmes; especially regarding activities to facilitate administration of birth dose vaccination during home deliveries or during the first post-natal care visit. Serosurveys conducted in priority countries have been valuable for gauging the progress and next steps for strengthening immunization programmes. The value and efficiency of the verification process is noted and the TAG is encouraged by the number of countries that have embarked on or completed the process since their last meeting.

In 2011, the TAG recommended to set a target year for the <1% goal: in January 2012, the Region's ERP recommended 2017 as the target year for the <1% goal. Member States accepted the 2017 proposal.

Recommendations

1. Endorse 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%. The TAG encourages Member States to communicate their position on the target year in preparation for the 2013 Regional Committee Meeting meeting.

2. Increased birth dose coverage will be needed in some countries to reach the <1% goal. The TAG agrees with the conclusions of the 2012 birth dose consultation and encourages priority countries to implement actions identified especially in the areas of:

    a. Ensuring at least 90% birth dose coverage among facility-delivered births;
    b. Coordinating EPI and MCH activities to train and equip staff to give birth dose vaccination during home deliveries and during first post-natal care visits, especially when EPI and MCH are different organizational units;
    c. Exploring special efforts to reach home births including outreach vaccination and using vaccine in a controlled temperature chain.

3. Encourage specific activities to take place in the next 12 months including seroprevalence surveys to document impact of vaccination programmes and verification of achievement of prevalence targets:

    a. The following 10 Pacific Islands to conduct seroprevalence surveys to document impact of their vaccination programmes: Federated States of Micronesia, French Polynesia, Guam, Marshall Islands, Nauru, New Caledonia, Niue, Tokelau, Tuvalu, Wallis and Futuna;
    b. The following four countries to proceed with verification: American Samoa, Brunei Darussalam, Cook Islands and Fiji;
    c. ERP to confirm if the following four countries should proceed with verification: Palau, Commonwealth of Northern Mariana Islands, Japan, and Singapore.

4. All countries should ensure vaccination of health care workers with occupational exposure to hepatitis B virus; the WHO Regional Office should monitor and support implementation as per the 2009 TAG recommendation and report status back to the 2013 TAG.

5. Request that ERP in collaboration with SAGE review issues related to implementation of hepatitis B control in the Western Pacific Region such as using hepatitis B immune globulin (HBIG) for infants born of mothers with known chronic HBV infection, using vaccine in a controlled temperature chain, spacing the birth dose and the first dose of hepatitis B-containing combination vaccine, developing methods for estimating coverage needed to achieve the <1% goal, providing guidance on improving the understanding of

contraindications to birth dose vaccination in line with the 2009 WHO position paper on hepatitis B vaccine, and providing guidance on the types of rapid tests are that acceptable.

MAINTAINING POLIO-FREE STATUS

Conclusions

The TAG and Regional Commission for the Certification of Poliomyelitis Eradication (RCC) have continuously highlighted the risk of polio to return to the Region as long as global eradication has not been achieved, no matter how long a country has been polio-free. While the morbidity and mortality caused by the polio outbreak in China following wild poliovirus importation is unfortunate, the TAG is highly impressed by the rigorous response the Government of China has mounted and considers it a model for other countries facing an importation. With all key milestones met in a timely fashion, the TAG is optimistic that the RCC will be able to re-affirm China's and the Region's polio-free certified status later in the year.

The WHO polio regional reference laboratory in China CDC provided timely and reliable laboratory confirmation including sequencing results during the WPV outbreak in 2011. Excellent collaboration among provincial laboratories in China, WHO, United States Centers for Disease Control and Prevention and National Institute of Health Pakistan allowed the immediate detection of wild polio cases and the identification of the source of importation.

The TAG notes that sharing of China's experience in achieving and sustaining polio eradication is of benefit to the rest of the world and applauds the government's efforts to participate in the 'Stop Transmission of Polio' (STOP) programme including the current assignment of 10 staff to Pakistan.

Considering global eradication as the ultimate protection for the Region to stay polio-free, the TAG welcomes the World Health Assembly (WHA) resolution declaring the completion of polio eradication a programmatic emergency for global public health. Every Member State has to fully recognize the responsibilities that come with it and act accordingly. Failure to eradicate polio would present a major failure for global public health.

The TAG acknowledges the polio risk assessment work conducted at various levels and in coordination with neighbouring Regions. While the results help to guide targeted risk mitigation activities, still too many gaps in immunization coverage and surveillance in several countries remain and need to be addressed as a matter of priority, so that certification quality standards will be achieved and maintained.

The TAG commends the identification of vaccine derived polioviruses (VDPVs) indicating good levels of AFP surveillance and laboratory performance but is concerned about the gaps in immunization coverage that their emergence signals. These community situations could also easily support spread of imported wild poliovirus and major polio outbreaks.

Recommendations

1. The TAG strongly encourages the China Ministry of Health to summarize for publication the epidemiology of the 2011 polio outbreak and disseminate in detail the implementation response activities in line with the national preparedness plan; with particular focus on lessons to be learnt on political commitment, accountability, intersectoral coordination, support mechanisms and social mobilization.

2. The TAG urges all countries and polio partners in the Western Pacific Region to strongly support full implementation of the 2012 WHA resolution. Future control of polio outbreaks following importation will get increasingly complex due to the epidemiology changing over time; adolescents and adults are also likely to be affected and there will be increased disease severity in adults with higher fatality rates. Outbreaks due to gaps in population immunity affecting a wider range of age groups will be more difficult to control and have higher resource requirements. In this context the polio surveillance system should have heightened awareness of the potential for polio to occur in persons >15 years of age.

3. The TAG strongly encourages Member States to conduct regular subnational risk assessments and take additional measures to reduce the risk of new outbreaks caused by the international spread of wild polioviruses or the emergence of cVDPV; as required. These measures include supplementary and routine immunization activities to close gaps in population immunity, very high quality surveillance and considering vaccination of travellers to and from polio-affected areas.

4. The TAG highlights the need for the following elements to be included in their regular risk assessment, including at subnational levels where appropriate.

    a. Plan for supplementary immunization that integrates OPV in other SIAs (e.g. measles) and health interventions in countries concerned;

    b. Catch-up immunization for populations for which insufficient polio vaccine coverage has been identified;

    c. Successful approaches for reliable identification of high risk communities and failures and achievements should be widely shared;

    d. Plans to address surveillance challenges are urgently required; this may include performance desk reviews and in-country field reviews as appropriate; and

    e. Ensure that updated importation preparedness plans remain in place.

5. The WHO Western Pacific Regional Office should closely monitor the introduction of the new algorithm among provincial laboratories in China and the implementation of real time PCR for intratypic differentiation (ITD) and VDPV screening for China and countries that participated in the second hands-on training for the real time PCR and VDPV screening planned in December 2012, to ensure sensitivity and timeliness of poliovirus identification in 2013.

    a. China CDC should closely follow up with the implementation of the new virus isolation algorithm and real time PCR for intratypic differentiation of polioviruses and VDPV screening among provincial laboratories in China.

6. The TAG welcomes the continued cross-regional collaboration WHO WPRO is coordinating and encourages WHO and relevant polio partners to prioritize plans for conducting cross-border meetings for countries concerned, including organizing an event to follow-up on the 2011 international polio workshop among polio-free countries and regions that occurred in Urumqi, and providing support for synchronized SIAs among bordering countries, where appropriate).

MATERNAL AND NEONATAL TETANUS (MNT) ELIMINATION

Conclusions

The TAG commends the continued progress towards and commitment for MNT elimination in the countries concerned (Cambodia, China, Lao PDR, Papua New Guinea and Philippines) but also notes the remaining challenges of incomplete surveillance, improving routine immunization in hard to reach communities and counteracting controversies about tetanus toxoid.

As an indication for its continued importance and priority, the TAG notes that the Global Vaccine Action Plan (GVAP) has established global MNT elimination by 2015, as one of its overarching goals. Being very advanced in reaching MNT elimination, the Western Pacific Region and its countries are leading these efforts.

Recommendations

The TAG reminds national programmes and partners that MNT elimination strategies are a means of reaching women that are usually unreached and thus offers opportunities for comprehensive health service delivery (EPI, MCH, basic newborn care); to contribute to reducing maternal and neonatal mortality. Special efforts should be made to promote the benefits of immunization to counteract the TT controversy which is a strong example of the potential damage anti-vaccination groups can cause.

STRENGTHENING NATIONAL IMMUNIZATION PROGRAMMES (NIP)

Conclusions

WHO-WPRO and Member States in the Western Pacific Region have been actively implementing key elements of the Global Immunization Vision Strategy (GIVS) since 2006 for strengthening National Immunization Programmes (NIPs) and many of these elements are consistent with the vision and the strategies of the new Global Vaccine Action Plan (GVAP).

The impact of GIVS, however, still varies in the Region, between and within countries, leaving disparities between different geographic areas and population groups. Several priority countries in the Western Pacific Region are still facing substantial challenges in achieving GIVS coverage targets, which in turn have been adapted as GVAP coverage targets, i.e. >90% at national level and >80% in every district.

Recommendations

To further strengthen NIPs as a critical foundation for VPD control in the Western Pacific Region, achieving the regional disease control goals, and contributing to reaching the MDGs, Member States, WHO and immunization partners in the Region, including Civil Society Organizations, should continue to closely collaborate in implementing strategies and activities as outlined in the GIVS and now in the GVAP and adding new strategies and activities as needed. This should also include logistics, cold chain and vaccine management.

Member States should:

1. Review the national immunization programme from the perspective of the GVAP's vision and strategies on the following points: its organizational position within MOH, coordination between central and the local governments, including current relevant national policies and future plans related to strategies and activities.
2. Ensure that a national action plan for further strengthening of the national immunization programme is in place according to the country's specific situation, drawing from GVAP principles.

WPRO should:

1. Develop a draft Western Pacific Regional Vaccine Action Plan 2013–2015 to support Member States and ensure that national action plans are in place for implementation of the GVAP at country level. WPRO should also ensure that key GIVS strategies and activities being carried out by WHO and Member States in the Western Pacific Region are incorporated into these regional and national plans, as well as any additional relevant strategies and activities as outlined in the GVAP.
2. Submit the draft plan to the next TAG meeting for its review and endorsement.

NATIONAL REGULATORY AUTHORITIES (NRA), VACCINE SAFETY, MANAGEMENT AND SECURITY

Conclusions

The TAG noted the Region's National Regulatory Authority systems and functions in many countries and areas can be strengthened. The TAG appreciates Regional Office and Member States for the new initiative to formulate a Regional Alliance to coordinate and support countries with non-functional NRAs.

Due to lack of required expertise needed for adverse events following immunization (AEFI) causality assessments in most Pacific island countries and areas, there is a need to establish a sub-regional AEFI expert committee to support decisions and conclusions of reported AEFI cases.

The TAG notes the frequent vaccine shortages that have taken place in the Region and takes seriously this missed opportunity to protect children from vaccine-preventable diseases. The contributing factors are many but most importantly countries need to improve their ability to do vaccine forecasting, better stock management and to prevent shortages of vaccine that disrupt the routine immunization programme.

The TAG considers thiomersal to be a safe and necessary component of vaccines.

Recommendation

1. The TAG supports the proposal for formulating a Regional Alliance for NRAs in the Western Pacific Region as a platform to strengthen NRA systems and functions (including NCL functions) in countries that lack functioning NRAs. The TAG asks the secretariat to support and conduct necessary activities to implement this Alliance in coordination with countries and other partners. The secretariat should consider this proposal as an agenda item in the 2013 Regional Committee Meeting (RCM).

2. The TAG endorses the proposal for establishing a sub-regional AEFI causality assessment committee for Pacific island countries and areas. The WHO secretariat should support and

conduct necessary activities to facilitate this establishment. The secretariat should consider this proposal as an agenda item at the 2013 RCM and at the Pacific Islands Health Minister's meeting in 2013.

3. Countries experiencing problems with their vaccine stock management and monitoring systems should devote attention to strengthening their capacities; in order to prevent disruptions in their vaccine supply.

4. The TAG urges countries to develop their positions in preparation for the upcoming Intergovernmental Negotiating Committee meeting (January 2013) in recognition of the ongoing need for thiomersal use in vaccines to continue to saving lives and ensuring viability of immunization programmes and cost effectiveness of vaccines.

NEW VACCINES

Conclusions

As the mortality due to traditional vaccine-preventable diseases has been substantially reduced, the TAG notes that over 90% of vaccine-preventable deaths among children under five years old in the Western Pacific Region are now due to pneumococcus, Hib and rotavirus. Japanese encephalitis continues to cause substantial morbidity and mortality among children and many countries in the Region have a high burden of cervical cancer. Despite significant progress, most low- and middle-income countries in the Western Pacific Region have not yet been able to introduce new or underutilized vaccines other than Hib. Key challenges include obtaining the disease burden evidence needed to determine the public health priority of the vaccine, conducting the economic analyses required to assess the cost-effectiveness and long-term sustainability of vaccine introduction, and developing systems to reach age groups beyond the traditional EPI target groups (e.g., adolescents for HPV vaccine). Several Member States are gaining experience successfully addressing these challenges, and these experiences can be useful for other Member States in working towards introduction of priority new vaccines.

Surveillance provides important inputs to disease burden evidence and is critical to measuring the impact of vaccine introduction. The WHO-coordinated rotavirus surveillance network is now relatively stable and producing useful data on disease burden and strain variation. The WHO-coordinated IB-VPD surveillance network continues to face challenges and substantial improvements in enrolment and testing are needed to ensure that data are useful to programme decision-making. TAG notes the significant progress made in transitioning rotavirus and IB-VPD surveillance to MOH ownership during the past year.

Recommendations

1. The TAG recommends countries to continue obtaining the evidence necessary for policy decisions on key new vaccines, and to raise the priority of introducing new vaccines as cost-effective strategies to decrease morbidity and mortality caused by vaccine-preventable diseases.

2. The TAG requests the WHO to provide technical support to selected countries as needed to develop burden of disease evidence including high-quality surveillance data; to conduct economic analyses, post-introduction evaluations and impact assessments; and to collect and use other data to support policy decisions on new vaccine introduction and scale-up.

3. The TAG reaffirms the importance of MOH ownership in enhancing the value and relevance of rotavirus and IB-VPD surveillance data to programme decision-making, and urges countries to take steps to improve the quality of IB-VPD surveillance and to continue to strengthen MOH leadership in this area.

GAVI Alliance Board Meeting

12-13 June 2012
Washington, DC, USA

FINAL MINUTES

1. Chair's report and consent agenda

Chair's report

1.1 Finding a quorum of members present, the meeting commenced at 9.02 Washington time on 12 June 2011. Dagfinn Høybråten, Board Chair, chaired the meeting.

1.2 The Chair opened the meeting by referencing the Norwegian concept of a "dugnad," which he explained was a group of people who come together to solve problems for the common good. He observed that this Board was a dugnad, and encouraged Board members to engage with each other in that spirit.

1.3 The Chair referenced the Child Survival Call to Action organised by USAID, UNICEF, and the governments of India and Ethiopia to be held at Georgetown University on 14-15 June 2012. He also announced the publication of the GAVI 2011 progress report, noting that a special online edition was available. He reminded the Board that 2011 had been a successful year: routine immunisation rates reached 80%, the Board hired a new CEO, and GAVI met its funding challenge. Now the Chair declared GAVI must "deliver, deliver, deliver" on the promises made at the pledging conference in June 2011.

1.4 Standing declarations of interest were tabled to the Board (Doc 1a in the Board pack). Alan Hinman noted that the Novartis research grant reported in Doc 1a was for rabies rather than measles. However, he declared an interest in the measles decision since he leads a project that works with the Measles-Rubella Initiative (MR Initiative). He would recuse himself from that item. Anne Schuchat reported that the US Centers for Disease Control is involved with some of the special studies to be discussed at this meeting and in the MR Initiative; she would recuse herself from those matters. Nicholas Alipui and Simon Bland declared they had no financial/personal interests in any of the matters to be discussed at this meeting; so their only interests were in matters involving UNICEF and DFID, respectively. Maria C. Freire declared interests in any matters involving the Lasker Foundation (where she serves as president) or Johns Hopkins University (where a family member is employed),

and would recuse herself accordingly. Amie Batson declared interests in any matters involving Johns Hopkins University as well (where a family member is employed), and would recuse herself accordingly.

1.5 The Board noted the minutes of its meetings on 16-17 November 2011 (Doc 1b) and 12 April 2012 (Doc 1c), which were approved by no-objection on 3 February 2012 and 1 June 2012, respectively.

1.6 In addition, the Board noted the action sheet (Doc 01d). Going forward the Secretariat should ensure items on the action sheet described as "in progress" and not addressed elsewhere in the Board pack include a short statement on activity. The Board also noted its forward workplan (Doc 01e). The Board determined that holding executive sessions the evening prior to the first opening session was a useful practice and so, going forward, the Board workplan should include executive sessions.

Consent agenda

1.7 The Chair reminded the Board that during its retreat in April 2012, the Board decided to include a consent agenda at its meetings. It will allow the Board to approve items without discussion that had been thoroughly vetted by the appropriate committees. However, any Board member could request to move a consent agenda item onto the general agenda should he or she believe discussion was warranted.

1.8 The consent agenda included committee member appointments recommended by the Governance Committee (Doc 1f), the Ethics Policy and revised Conflict of Interest Policy recommended by the Governance Committee (Doc 1g), and the revised Evaluation Policy recommended by the Evaluation Advisory Committee (EAC) (Doc 1h).

Discussion

- The Board noted Cristian Baeza's comment that, on legal advice, there could be situations when as an employee he would have to disclose confidential commercially sensitive information to the members of the World Bank despite the inclusion of the confidentiality clause in the Ethics Policy.

- Nicholas Alipui, alternate Board member representing UNICEF requested clarification on the outcome of the discussion in Oslo with regard to GAVI's role in market shaping pertaining to lower and middle income countries (LMIC). He informed the Board that UNICEF has a programme of work to help middle income countries obtain access to new vaccines and welcomed GAVI's involvement. It was clarified that although the Board had not made any decisions, at the retreat the Board suggested in relation to GAVI support to LMICs that GAVI might play a role in facilitating access to lower vaccine prices. It was also noted that GAVI's activity in this area would be conducted in close collaboration with UNICEF and other interested partners such as the Bill & Melinda Gates Foundation and the Clinton Health Access Initiative.

Decision One

The GAVI Alliance Board:

- **Appointed** the following member to the Audit and Finance Committee effective immediately and until the committees are refreshed for the 2013 year:
  - **Yifei Li**

- **Appointed** the following members to the Programme and Policy Committee effective immediately and until the committees are refreshed for the 2013 year:
  - **Clarisse Loe Loumou** in the seat currently occupied by Joan Awunyo-Akaba;
  - **Magid Al-Gunaid**; and
  - **Jos Vandelaer** in the seat currently occupied by Mickey Chopra.

- **Appointed** the following member to the Governance Committee effective immediately and until the committees are refreshed for the 2013 year:
  - **Maria C. Freire**

- **(Re)appointed** the following members to the Evaluation Advisory Committee effective immediately:
  - **Angela Santoni** until the earlier of the end of her Board term or 31 July 2015; and
  - **Bernhard Schwartlander** until 31 July 2015.

Board members who were candidates for these positions, or who had submitted their alternate or a committee delegate for appointment, recused themselves from voting on those appointments.

Decision Two

The GAVI Alliance Board:

- **Approved** the GAVI Alliance Ethics Policy attached to Doc 01g; and

- **Approved** the Revised GAVI Alliance Conflict of Interest Policy attached to Doc 01g.

Decision Three

The GAVI Alliance Board:

- **Approved** the Revised GAVI Alliance Evaluation Policy attached as Annex 1 to Doc 01h.

1.9 The Chair concluded by showing a short film on Ghana's unprecedented introduction of pneumococcal and rotavirus vaccines simultaneously. GAVI will be carefully evaluating these introductions to see what the Alliance can learn, including whether simultaneous introductions should be more widely encouraged.

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2. CEO report

2.1 Seth Berkley delivered his report to the Board on the activities, achievements, and challenges of the Alliance (Doc 2). His presentation covered new results, accelerated activities, expenditures and resources, opportunities and challenges, and key decisions and themes for discussion by the Board.

2.2 The CEO reported that GAVI is generally on track to meet its ambitious goals, though because of unprecedented demand and the normal difficulties of industrial scale up, the Alliance has to work hard to overcome some of the vaccine supply capacity issues. He also reiterated that GAVI's obligation to deliver on its promises remains the top priority, and that ensuring comprehensive management of the supply chain and improving the quality of information flows remain key components to fulfilling these promises.

2.3 He updated the Board on the process of reviewing the country delivery business model. It is being driven by a time-limited cross cutting country team, involving people from departments and skill sets across the Secretariat and partners, and supported by experts in change management and organisational development.

2.4 The CEO updated the Board on the uptake of pneumococcal and rotavirus vaccines, and the groundwork for introducing HPV vaccine. Per the Board's request, GAVI had received strong indication of an acceptable price reduction from at least one supplier for HPV vaccines. In addition, only countries that have demonstrated capacity to roll out the vaccine to adolescent girls can apply for national introduction of HPV; applications will come to the IRC later in the year.

2.5 He also remarked that designing a health system strengthening programme will require an iterative process involving countries and partners, an assessment of health system frameworks, constraints to immunisation programmes, and judgments about the comparative advantage of partners, whilst making sure that governments remain in charge of and responsible for the programme. He announced that he had created an expert technical advisory group led by Anders Nordström (in his technical personal capacity and not as a Board member) to advise him on optimal health system approaches and tailoring to GAVI's business.

2.6 He concluded by referring the Board to a short report card issued on the occasion of the first anniversary of the pledging conference, which provided a concise narrative of new results and challenges ahead.

Discussion

- Underpinning the Board's discussion was the need to ensure delivery on the 2011-2015 strategic plan, which served as the foundation for pledges received during the 2011 pledging conference. Though it is appropriate to think about and plan for strategies past 2015, this work will not matter if GAVI does not deliver on its current promises. Also, to the extent that GAVI eventually finds it may not be able to live up to certain targets du for example to supply constraints, it will need to craft a narrative to explain why these shortcomings occurred, and be able to credibly say that the Alliance did everything possible to try to live up to those promises and there should be no surprises.

- Several Board members highlighted the need to link costs to outcomes, not only as a way of demonstrating oversight of activity, but also to plan for the future. (This conversation continued later in the meeting as part of the discussion on the business planning process; see section 7.)

- The Board considered how to take forward the discussion at its April retreat on the landscape of strategic options facing the Alliance. In the short term, it was noted that the priority was on delivering on the 2011-2015 strategic plan, and that the discussion on options could serve to incrementally optimise that plan. In the longer term, the options discussed could shape the post-2015 strategic plan. To help inform future discussions, the Secretariat should follow-up on the retreat options paper to provide analysis on opportunities, trade-offs, and costs between options.

- One of the options present in the retreat paper was funding a stockpile of the powerful new cholera vaccine for routine and campaign use in endemic areas, and to support the creation of a viable cholera vaccine production base. The Secretariat should add a discussion on cholera to the Board workplan for one of the next meetings but needs to do so in the context of overall investments and trade-offs.

- It was noted that the presence of endemic polio can reflect the underlying weakness of a country's EPI programme. Developing country Board members stressed that polio eradication should be developed as part of routine immunisation. In the final stages of eradication, extraordinary measures are often required, but if done well, these measures can benefit the entire immunisation system.

- The Board noted the movement towards a national roll-out of pentavalent vaccine in India, and greater interest in new vaccine introductions. For example, following the successful introduction of pentavalent vaccine in two states, India formally decided to introduce the vaccine in six additional states. There was discussion on whether GAVI needed a more state-centric approach to countries that have federal structures such as India and Pakistan, but it was noted that an extensive state-centric approach would require staff on the ground, which was not part of GAVI's current business model.

- It was noted that a number of countries still have less than 50% DTP coverage. Many of these countries will not be eligible to receive support for pneumococcal or rotavirus vaccine prior to 2015, but it is hoped they will be ready shortly thereafter.

- The Board also discussed recent developments with the supply of pentavalent vaccine and disruptions due to delisting of some suppliers and production related issues. The global debate around the environmental treaty on mercury and mercury containing Thimersol preservative use in vaccines was also raised and Board members were encouraged to advocate for their continued use.

- The Board noted the discussion from the previous evening's executive session on restructuring within the Secretariat led by the CEO. The Secretariat should provide the Board with an organogram when the current restructure and recruitments have taken place.

- There was some discussion on the GAVI brand and how to better highlight GAVI's work. It was acknowledged that there are opportunities for increased exposure, particularly in working with implementing partners to co-brand.

- The Board welcomed Anders Nordström's leadership of the technical advisory group to the CEO, noting that while he was leading the group as a health systems expert and not as a Board member, it sent a strong signal that the Board is supporting the CEO on this effort.

- There was some discussion as to how "fragile states" are defined and the special challenges involved in those countries. It was noted that there is no direct correlation between immunisation coverage rates and standard definitions of fragile states, though it is still a useful data point.

- The Board noted civil society's role in being able to reach the hardest-to-reach children in rural areas and underserved communities.

- Risk oversight continues to be an important component of the Board's agenda. GAVI is rapidly improving its risk management capabilities, and the Secretariat is working with partners to create better systems and explore synergies. This also includes implementation of the Transparency and Accountability Policy (TAP), where pooling resources between GAVI, the Global Fund, and the World Bank may be useful and cost-effective.

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3. Committee chair reports

3.1 The Chair invited each of the committee chairs to deliver reports on committee activity since the Dhaka Board meeting on 16-17 November 2011, noting that the Evaluation Advisory Committee report would be delivered the following day due to the EAC Chair's availability.

Executive Committee

3.2 The Chair delivered the report of the Executive Committee, noting that it had met twice since the Dhaka Board meeting to look at time-critical issues requiring decisions or guidance on behalf of the Board.

3.3 He reported that at its meeting on 9 March 2012, he shared his ideas on the workplan for the year and held a discussion on the role of the Committee in advance of the April Board retreat. In addition, the Executive Committee received a performance update and in this context endorsed the business planning process for 2013-2014 (see section 7). There was also an update from the Secretariat on risk management as well as information and discussion on the Decade of Vaccines and GAVI's earmarked funding pilots.

3.4 Next, he reported that the Executive Committee held a short meeting on 16 April 2012 to be briefed by the Chair and CEO on a commercially-sensitive matter. He concluded by noting that the Governance Committee had recommended an amendment to the Executive Committee Charter that would allow it to approve market and/or commercially sensitive decisions as part of the implementation of the supply and procurement strategy.

Governance Committee

3.5 Geeta Rao Gupta, Board Vice Chair and Chair of the Governance Committee delivered the report of the Governance Committee, noting that it had met twice since the Dhaka Board meeting.

3.6 She reported that at its meeting on 10 April 2012, the Governance Committee recommended new Board and Programme and Policy Committee (PPC) members. At its meeting on 14 May 2012, the Governance Committee recommended additional committee members. The Board subsequently appointed all of these nominees. The Governance Committee also recommended approval of the Ethics and revised Conflict of Interest Policies (see section 1).

3.7 In addition, she reported that at its May meeting, the Governance Committee continued governance-related discussions started at the Board retreat. The Governance Committee recommended amendments to the Statutes, By-Laws, and Executive Committee Charter to implement the industrialised and developing country vaccine industries' offer to step down from the Executive Committee and to allow the Executive Committee to consider commercially-sensitive matters (see section 8). It also discussed the role of alternate Board members; committee composition, size, and charters; the role of developing country Board members; reopening decisions; dedicated seats on the Executive Committee; and the Board's working language.

3.8 She concluded by noting that the minutes of the May meeting would be available shortly and that the committee chairs were to meet during the Board's lunch break to discuss identified overlaps in their committee charters.

Programme and Policy Committee

3.9 Gustavo Gonzalez-Canali delivered the report of the Programme and Policy Committee. He noted that the Committee had met once since the Dhaka Board meeting.

3.10 He reported that at its meeting on 23-24 April 2012, the PPC made three recommendations for decisions at this Board meeting: vaccine introduction grants and operational support for campaigns (see section 13), continued funding for special studies (see section 14), and support to civil society organisations (CSOs) (see section 17). The PPC also discussed the business planning process, country programmes, the Advanced Vaccine Introduction (AVI) programme, co-financing, and market shaping activities.

3.11 In addition, he previewed the indicative agenda for the PPC's October 2012 meeting, commenting it was currently scheduled to include discussions on GAVI's approach to under-performing countries, potential investments in cholera, options for engagement with non-GAVI eligible lower middle income countries, GAVI's approach to self-procuring countries, and a "use it or lose it" policy.

Audit and Finance Committee

3.12 Wayne Berson delivered the report of the Audit and Finance Committee, noting that it had met once since the Dhaka Board meeting.

3.13 He reported that at its meeting on 11 April 2012, the Committee made recommendations on a Currency Hedging Policy and a revised Programme Funding Policy (see section 6). He noted that the Annual Financial Audit for 2011 was on track with no issues arising that would require a management letter comment. He also noted that the audits for the IFFIm Company, GAVI Fund Affiliate (GFA), and GAVI Campaign were on track.

3.14 Further, he noted that the Audit and Finance Committee reviewed updates to various accounting policies, and discussed principles for forming a policy on the selection of the external auditor. He also reported that the Audit and Finance Committee continues to have confidence in the quality and robustness of GAVI's financial forecasting processes. Also, the Committee discussed GAVI's insurance coverage, and the IFFIm/GFA restructuring (see section 20). Finally, he noted that the Committee had discussed risk management and the implications of the departure of the Director of Internal Audit.

Investment Committee

3.15 George W. Wellde, Jr delivered the report of the Investment Committee, noting that it had met twice since the Dhaka Board meeting; on 28 March 2012 and 24 May 2012.

3.16 He began by providing his observations on the market environment generally, including investment safe havens, central bank rates, GDP forecasts, and risks to global recovery from the recent financial crisis.

3.17 He then reviewed the investment portfolio, including efforts to diversify assets to better balance economic risks. He also provided an overview of the portfolio's credit quality and asset class distributions, net performance returns, and contribution to mission. He reported on progress to conform to the new investment policy passed by the Board in Dhaka, stating that progress was steady and deliberate. Finally, he commented on the constraints on GAVI's ability to optimise the management, including fiduciary oversight, of its investment portfolio due to the agreements it enters into with UNICEF for vaccine volume guarantees that require the granting of a lien to UNICEF on components of the portfolio.

Discussion

- Nicholas Alipui acknowledged the challenge faced regarding securing volume guarantees and the need within UNICEF's rules to either receive cash or place a lien on GAVI's investment portfolio for the full amount of long-term procurement contracts in order to secure the most favourable pricing possible. He noted UNICEF's on-going dialogue with the Secretariat to seek solutions that will appropriately mitigate risk while recognising the need for GAVI to have flexibility in investing its assets. The Board also support the Secretariat's explorations to use the GAVI balance sheet to guarantee such orders directly to the manufacturers.

- The Board found it useful to have the committee reports at the beginning of the meeting to receive advice, understand deliberations that have already taken place, and to inform decision-making. The Board also thought it was a good idea for the committee chairs to meet together from time to time, particularly given the interconnectedness of the various work streams and committee discussions.

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4. Updated financial forecast

4.1 Barry Greene, Managing Director of Finance and Operations and Treasurer, informed the Board of the updated financial forecast for 2011-2020 (Doc 4), which incorporated the latest demand estimates and funding decisions. He reviewed projected demand, changes to the forecast, available and needed resources through 2015 and through 2020, and the impact of funding decisions.

4.2 He reminded the Board that at the Dhaka meeting, he had reported that expected demand during 2011-2015 would require US$ 7.7 billion in resources and that GAVI could rely on $7.7 billion in qualifying resources to meet that anticipated demand. The current forecast estimates expected

demand to increase to $7.97 billion, due mainly to the change proposed to GAVI's policy on vaccine introduction grants. Qualifying resources available are now forecast at $7.84 billion, including an allowance of $0.11 billion for pledge extensions. That latest demand estimate would require additional funding estimated at $0.13 billion to fully meet demand that may be sought through future applications for GAVI support through 2015. Further resources of approximately $0.14 billion would be required if the Board were to approve additional support for measles under an option for consideration at this Board meeting. Contributions yet to be pledged for 2014 and 2015 from existing and new donors would be a source of resources for these needs. In the event that insufficient additional resources became available to fully meet anticipated demand, then the Board could constrain support for programmes expected to seek support in the future, without impacting existing programmes.

4.3 Looking forward to 2016-2020, he presented a tentative indication of the demand that GAVI could expect based on its existing range of support, estimated to total US$ 7.9 billion for those five years. He explained that after taking account of resources already pledged (mainly through IFFIm and AMC), if other contributions were maintained at their current level of US$ 1.1 billion per year, the needs of all existing programmes could be fully met. However, that current level would need to increase to approximately US$ 1.5 billion per year in 2016-2020 in order to fully meet the demand that may be sought in the future for new programmes.

Discussion

- It was asked whether the financial forecast incorporated potential investments in measles and polio. It was noted that any programmes that had been considered and recommended by the committees through the normal processes were incorporated into the forecast. The potential measles investment was not incorporated as it had been a direct request from the Board during its April retreat, had not been through the normal committee process, and was being presented for expedited review without the opportunity for the PPC to review. Accordingly, the financial implications were separately identified in the presentation of the financial forecast.

- In this context the Board returned to the question of trade-offs regarding future support, given that the additional resources available following the London Pledging Meeting in June 2011 had been absorbed by the higher than expected demand in 2011. It was noted that the Board needed to be confident that the opportunity cost in funding measles was worth it and that scenario planning would be helpful. The Secretariat noted that the Board was also able to manage the trade-off risk through its cash reserve or future choices not to fund certain new applications. In addition, the Board's approval of the Currency Hedging Policy in April 2012 will help to mitigate foreign exchange risk on pledges that will be contributed in future years.

- It was also noted that the Secretariat prudently uses conservative estimates in the financial forecast. The forecast expenditure could be expected to decrease because proposed implementation schedules are often delayed,

and this would be the case in the event that potential supply availability constraints materialise. Furthermore, the resource estimates do not include revenue from likely additional contributions to the GAVI Matching Fund programme.

- The Secretariat clarified how demand was calculated: partners provide estimates of the birth cohort and this is multiplied by the number of doses needed to immunise that population in specific years, which in turn is multiplied by the forecasted price of the vaccine. Estimates of time to reach full implementation tend to overestimate demand in the initial years, and this is adjusted in later years following review by the Monitoring IRC.

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5. Report of the internal auditor

5.1 The Chair reminded the Board that Cees Klumper, Director of Internal Audit, had recently accepted the position of Chief Risk Officer for the Global Fund, but that he had agreed to continue with GAVI on a part time basis, of approximately the equivalent of one day per week, until the new internal auditor was retained in order to provide continuity. The Chair thanked Cees Klumper for his work to build the internal audit function and for his communication with the Board and partners on important matters.

5.2 Cees Klumper then delivered his report on activities over the past year and provided a look ahead for what the Board could expect from the internal audit function (Doc 5). During the past year, internal audit had reported to senior management of the Secretariat and to the Audit and Finance Committee on risk mitigation of cash support programmes, including an analysis of the Global Fund's review of how it mitigates risk in its grant portfolio; his audit of the country programmes team; a new protocol for publication of internal audit and investigation reports; investigations into potential and actual misuse in cash-support programmes; vaccine programme risk management; removing bottlenecks in funds flows to countries for cash-support programmes; and succession planning for the internal audit function.

5.3 He reported that the risk management process was now "relatively good" considering the newness of the process and the maturity of risk management in comparable organisations. He suggested further improvements including involving implementing partners in GAVI's risk mitigation process concerning programmatic risk; more clearly articulating the Alliance's risk appetite; completing the analysis of risks and mitigation actions concerning vaccine programmatic risks; expanding risk mitigation processes to team and individual levels within the Secretariat; and increasing scrutiny of reported risk mitigation activities.

Discussion

- Simon Bland, who also serves as Chair of the Global Fund Board, remarked that collaboration between GAVI and the Global Fund on risk mitigation activities, including sharing resources, could yield benefits to both organisations. Armin Fidler also noted the increasing collaboration between GAVI and the World Bank on risk mitigation. Cees Klumper acknowledged these collaborations and their usefulness, but also commented on the challenges faced in coordinating risk mitigation programmes.

- It was noted that during the formative period for the Transparency and Accountability function, which currently resides under Internal Audit, some cash-support programmes were delayed as Financial Management Assessments were performed in countries. This was due to the newness of the Transparency and Accountability Policy and that certain information thought to be in place was not. However, as the function has matured, these delays have been minimised.

- Cees Klumper confirmed that a protocol was now in place, and internal audit was publishing audit and investigation reports. The reports concerning Cameroon and Niger were available on the website and reports of investigations in progress would likewise be disclosed in due course.

- One Board member commented that more information in the annual report to the Board would be helpful. Cees Klumper acknowledged trying to find a balance in the volume of reporting, but would relay to his successor the Board member's request to receive a more substantial report.

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6. Amendment to the Programme Funding Policy

6.1 Wayne Berson reported that the Audit and Finance Committee recommended to the Board that it approve the revised Programme Funding Policy (Doc 6). He commented that the revised policy provided a sensible delegation to the Secretariat to allot amounts to individual programmes in the course of the year for new cash-based proposals and extensions, renewals, and adjustments of existing vaccine and cash-based programmes within a Board or Executive Committee-approved funding envelope. He noted this arrangement would be more efficient than the current governance-intensive process, while retaining sufficient Board and committee oversight of Secretariat decision-making.

6.2 Barry Greene then reviewed the current approach to approving cash programmes and extending vaccine programmes, the proposed new approach, the pros and cons of each approach, and the safeguards in place for Board and committee oversight of Secretariat decision-making.

Discussion

- The Chair commented that this was the right type of decision-making to delegate and that it would result in fewer ad-hoc committee meetings by reserving the large funding envelope decision to the Board or Executive Committee but delegating decision-making within that envelope to the Secretariat. It is based on proper routines of reporting back to the Board.

- It was asked what would happen if after the funding envelope amount was fully allotted there were further needs to be addressed. It was confirmed that in that event, the Secretariat would have to approach the Board or EC to adjust the envelope. While Secretariat authority was limited to amounts approved for the envelope the Board or EC could approve additions to the envelope at any time. Accordingly, the envelope did not limit the Board's ability to approve additional funding.

- Some Board members expressed concern that the Secretariat's authority to approve new cash programmes would decrease the Board's fiscal ownership over health systems programming and the Health Systems Funding Platform. To ensure this ownership is maintained, it was agreed that health systems strengthening should be a standing item on the Board agenda, and as part of the Secretariat's reporting, the Board should be updated on revisions to programme funding commitments. The conclusions of the Health Systems Funding Platform IRC (HSFP IRC) should be included in this report. In addition, the Chair of the HSFP IRC, or his/her delegate, should report to the Board upon request.

- The Board discussed the frequency of reporting and to what entity such reports should be made. It was agreed that the Secretariat shall report back to the Board at each meeting on utilisation of the funding envelope.

- Armin Fidler, alternate Board member representing the World Bank voiced reservations with regard to the Secretariat's proposal and offered a compromise solution in terms of a no-objection alternative. However, this proposal was not endorsed by the full Board

Decision Four

The GAVI Alliance Board:

- **Approved** the revised GAVI Programme Funding Policy attached as Appendix A to the report on the Amendment to the Programme Funding Policy, Doc 06, with the following amendment to the first sentence of Annex 2, 4(d):
    - The Secretariat shall report back to the Board at each meeting on utilisation of the funding envelope.

7. Business planning process and risk management update

7.1 Helen Evans, Deputy CEO, reported on the outcomes of consultations on the development of priorities that will drive the definition of deliverables, associated activities, and budget for the period 2013-2014 (Doc 7). She reminded the Board that it had approved a five year strategy and business plan (2011-2015) with a two year budget (2011-2012). As the first two year period began to draw to a close, it was necessary to refine the business plan building on lessons learned over the first two years. Given the Board's guidance in Dhaka, the proposed principles were constructed based on consultations including one-on-one interviews with Board members, workshops with technical staff from GAVI's constituencies, and discussions within the Secretariat.

7.2 She reviewed the process for constructing the 2013-2014 business plan, noting that the Executive Committee had reviewed the process during its 9 March 2012 meeting. She described the proposed priorities for the next two years: improving implementation of vaccine introductions and roll out; accelerating progress on improving vaccine coverage and equity; ensuring sustainability of programmes after graduation from GAVI support; improving access to and use of quality, timely data; and supporting health systems. She also provided examples of activities where GAVI could scale back, refinements of the operating model, and current key risks.

Discussion

- There was considerable consensus that the business plan should link costs to results. The business plan must be outcome-oriented and once constructed, the Board needs to keep a sharp eye on accountability. To help inform this discussion, as part of their requests for funding from the 2013-2014 business plan, WHO and UNICEF should provide information on their contributions to GAVI-related activities.

- Many Board members commented on the need for timely, quality data, stating that GAVI would not be able to raise funds for the next strategic period unless it could credibly demonstrate results from the present period. It was noted that creating a "GAVI system for data" was not intended, but that even with WHO and UNICEF data as the starting place for facts and statistics, it was necessary to supplement this data with other sources which may be more timely in order to allow real time decision-making.

- Board members representing industry added that data which provides additional certainty regarding country need and uptake can allow it to make consistent and sustain investments in quality and innovation. However, it was also acknowledged that countries themselves apply for support and that GAVI's role, and specifically AVI's role, in that decision-making is to assist countries that have reduced capacity to make decisions.

- There was some discussion as to the role of the Secretariat's Country Responsible Officers (CROs), and whether part of their mandate is to help coordinate and facilitate at country level. It was confirmed that they would play a convening role in leveraging a wide set of partners at country level, even though they will not be based in countries themselves, because it is critical that GAVI has a better understanding of what is happening in-country and to tailor approaches.

- In addition, to assist the Board in its decision-making and oversight, it was agreed that going forward, business plan updates should include more detail on assessment of risk and ranking of risk, including attaching the risk register in the Board pack. The risk register is reviewed and updated every quarter and is available on myGAVI to Board members.

- The Chair reported that the committee chairs had met to discuss the business planning process and had recommended a procedure of consultation that would include the Executive Committee, which had oversight responsibility, PPC, and Audit and Finance Committee prior to Board approval. They considered that an external technical advisory group was unnecessary so long as the endorsed planning process for the business plan is followed. The Board agreed with the committee chairs' approach.

Decision Five

The GAVI Alliance Board:

- **Endorsed** the strategic priorities for the 2013-2014 business plan;

- **Requested** the Secretariat and partners to take these priorities into account when preparing the business plan deliverables and budgets for 2013-2014; and

- **Endorsed** the following planning process:
  - Secretariat to prepare a draft business plan in consultation with Alliance partners involved in implementation
  - PPC to review programmatic aspects of the business plan
  - Secretariat to incorporate PPC suggestions on programmatic aspects
  - Joint PPC and AFC to enable programmatic and financial aspects of business plan to be reviewed
  - Joint recommendations from this meeting to EC for review
  - EC to make final recommendation to the Board

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8. Amendments to the Statutes and By-Laws

8.1 Debbie Adams, Managing Director of Law and Governance and Secretary to the Board, presented several amendments to the Statutes, By-Laws, and Executive Committee Charter that had been recommended by the

Governance Committee during its meeting on 14 May 2012 (Doc 8). As the Governance Committee Chair had mentioned earlier in the meeting, these amendments would implement the industrialised and developing country vaccine industries' offer to step down from the Executive Committee and to allow the Executive Committee to consider commercially-sensitive matters.

8.2 In addition, the Governance Committee Chair reviewed a principle agreed by the Governance Committee that after the conclusion of 2012, Board Committees shall be composed of Board members or alternate Board members. However, Board members may submit for nomination and appointment someone to serve as the Board member's delegate on any Board Committee, except the Executive Committee, Governance Committee, Investment Committee, and Audit and Finance Committee. It was not suggested that the principle be enshrined in the By-Laws so that the Committee would retain flexibility and discretion as circumstances warranted. However, the Committee wanted representative Board members to participate in the committees. It also sought to address the fact that committee delegates often advocated different positions than their Board members, or did not communicate the conclusions of their committees to their Board members.

Discussion

- Some Board members were concerned that restricting Committee membership to the Board members and their alternates risked losing technical expertise available within constituencies but not necessarily possessed by the Board member or alternate. They were also concerned that representative Board members who were senior members of the constituencies would be more hesitant to join the Board if it included this additional responsibility. It was also thought to be particularly burdensome on developing country Board members. Instead, Board members thought better communication between a Board member and his/her alternate and committee delegates would be an effective solution.

- Other Board members felt that personal membership on committees was an essential responsibility. They felt that the committees should be more strategically focused and, to the extent they required technical expertise, a technical expert could be invited to a meeting to advise the committee (and may also be a way to find future Board members). The unaffiliated Board members noted that many of them were senior professionals in the private sector who were also busy, did not have support staff to help them on GAVI matters but deemed committee membership as an essential part of their responsibility. Some also felt that they were disproportionately leaned upon at times.

- The Chair noted this discussion and asked the Governance Committee to continue discussion on this principle and refine it accordingly.

Decision Six

The GAVI Alliance Board:

- **Amended** By-Laws Article 3.1.1, clause 3 as follows:

  Up to eight additional Board Members (or Alternate Board Members), who shall each be a voting member of the Executive Committee

- **Amended** By-Laws Article 3.1.2 in its entirety as follows:

  The composition of the eight additional Board Members shall be as follows:
  - *WHO, UNICEF, and the World Bank: Two seats*
  - *Bill & Melinda Gates Foundation: One seat*
  - *Developing country governments: One seat*
  - *Donor country governments: One seat*
  - *Unaffiliated Board Members: Three seats*

- **Amended** Article 3 of the Executive Committee Charter to include the following bullet point:

  Approve market and/or commercially-sensitive decisions as part of the implementation of the supply and procurement strategy.

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9. Chair's reflections on day one

9.1 The Chair and Vice Chair provided some reflections on the Board's deliberations thus far. The Vice Chair concluded the day's discussion by reminding the Board that it had been one year since the replenishment conference. She pointed out that it was important to remember that many of the challenges that GAVI now faces, which were discussed during the first day of the meeting, are because of that success.

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10. Chair's overview of day two

10.1 The Chair referred briefly to the discussions held on the previous day and the number of items for decision to be addressed on day two of the meeting.

10.2 The Board viewed a short film on the introduction of the pentavalent vaccine in Haiti in April 2012 and the Chair extended his thanks to PAHO and all GAVI partners for their contribution to making the launch successful.

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11. Report of the Evaluation Advisory Committee

11.1 Sania Nishtar delivered the report of the Evaluation Advisory Committee of which she has been Chair for a year. During that time the Committee had looked at the revised Evaluation Policy which had been recommended for approval by the Board on the previous day. The Committee had endorsed and validated the methodology of the evaluation of GAVI support to CSOs and agreed that it is a useful report and a fair evaluation of a complex programme. The Committee had reviewed and approved the Request for Proposals for the Advance Market Commitment for Pneumococcal Vaccine Process and Design Evaluation, as well as the Request for Proposals for Full Country Evaluations. At its meeting in July 2012 the Committee would be selecting a bidder for the latter.

11.2 The Committee has asked the Secretariat to conduct a desk-top review of how GAVI evaluations result in programme and policy changes. This review would be submitted to the next Board meeting for consideration. Finally, Sania Nishtar emphasised the importance of Board participation on the EAC and in this context welcomed Angela Santoni as a new Board representative on the Committee.

Discussion

- Anne Schuchat expressed concerns about the high number of evaluations being carried out and suggested that GAVI should be looking forward and focussing on performance and results as opposed to conducting a retrospective review of how evaluations have been used.

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12. Options for enhancing GAVI's investment in measles prevention

12.1 The Chair reminded the Board that at their retreat in Oslo in April 2012 they had asked the Secretariat to develop options and a recommendation to the June Board meeting to provide additional financial support for measles vaccination in GAVI-eligible countries prior to the full roll out of the MR vaccine.

12.2 Nina Schwalbe, Managing Director of Policy and Performance, presented the options to the Board, providing background information on GAVI's engagement to date and its commitment to measles control (Doc 12). The proposal contained two elements: support for measles vaccines and operational costs for six large countries at high risk of measles outbreaks, and support for outbreaks and other emerging needs requiring rapid responses.

12.3 Wayne Berson informed the Board that relevant figures had not been reviewed by the Committee due to time constraints and the request at the retreat for expedited review. However, in view of the somewhat conservative financial forecast for 2011-2020 he considered that GAVI does have the

financial capacity to invest in measles prevention as recommended to the Board.

Discussion

- Alan Hinman informed the Board that he had a personal conflict of interest in relation to this item and requested permission to make a statement before handing over his seat to the Alternate Board member from his constituency. He stated that the two real issues in relation to GAVI's investing in measles prevention are whether and how. In his view it is critical that GAVI supports this initiative in particular as measles is resurging in many countries in Africa. GAVI support for MR and routine second dose will provide great assistance but will unfortunately not become available immediately. He indicated his own personal support, but also the support of his constituency, for the option recommended in the paper, namely funding both through the MR Initiative and also using GAVI mechanisms.

- Anne Schuchat, who also had a conflict of interest in relation to this item, left the table.

- Board members welcomed the initiative and partners appreciated the extensive consultation with them on the issue despite the short time line. Whilst acknowledging that it had been a request from them to the Secretariat to develop options in a short timeframe, the Board agreed that it would be preferable to follow the normal committee process as a general matter.

- It was also agreed that the approval of such support, including disbursement through another organisation, should be exceptional. Several donors commented that they did not fund GAVI to be simply a pass-through mechanism but to add value. It was suggested that the Board might wish to discuss the issue of providing support through other organisations in the future.

- Board members welcomed the proposal to develop an indicator as a strong signal to the immunisation community and highlighted the importance of developing country ownership.

- Board members from the developing countries welcomed the proposal to provide this support through existing GAVI Alliance mechanisms.

Decision Seven

The GAVI Alliance Board:

- **Approved**, on an exceptional basis, the Secretariat to put in place the necessary arrangements in accordance with Annex 2, Option 2 of Doc 12, for six large countries at high risk of measles outbreaks (Afghanistan, Chad, DR Congo, Ethiopia, Nigeria, and Pakistan) to be able to receive GAVI support for measles vaccines and operational costs until these countries are forecasted

to have implemented a measles-rubella (MR) campaign, or by no later than 2017. This support would be provided in collaboration with the Measles & Rubella Initiative (MR Initiative, formerly the Measles Initiative).

- **Approved** US$ 55 million to be made available to the MR Initiative through the UN Foundation for use through 2017 for outbreaks and other emerging needs requiring rapid responses, using the mechanism described in Annex 2, Option 1 of Doc 12.

- **Requested** the Secretariat - given the importance of measles as an indication of country support for routine immunisation – to develop an indicator for measles first dose routine vaccine coverage as part of the achievement of GAVI's 2011-2015 Strategy for review by the Evaluation Advisory Committee.

Alan Hinman (Civil Society Organisations) and Anne Schuchat (Research and Technical Institutes) recused themselves and did not vote on this item.

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13. Vaccine introduction grants and operational support for campaigns

13.1 Gustavo Gonzalez-Canali informed the Board that the PPC had unanimously supported the proposal for vaccine introduction grants and operational support for campaigns (Doc 13).

13.2 Aurélia Nguyen, Director, Policy and Market Shaping, provided information to the Board on the objective, scope and guidelines for vaccine introduction grants and operational support for campaigns, highlighting the recommended changes and funding levels, as well as information on implementation and on the financial implications for GAVI.

Discussion

- Board members agreed on the importance of ensuring justification for such an increase in support and in this context acknowledged that there is a need to improve the conditions of vaccine introductions, in particular around social mobilisation and training.

- Board members noted that the Secretariat and implementing partners have been fully engaged in analysing introduction costs and that this proposal reflects the full costs in countries. Previous levels of support had not had the advantage of such an analysis.

- Board members noted that one of the weaknesses highlighted in the past related to the timeliness of disbursement. The Secretariat is working on this to ensure disbursement six months before introduction, in line with the preference indicated by countries.

- Board members were informed that countries very much appreciate the simplification of the policy, that there will be a framework in place to measure impact and that there will be an improved feedback mechanism for countries through GAVI's CROs.

Decision Eight

The GAVI Alliance Board:

- **Approved** the GAVI vaccine introduction grant and operational support for campaigns policy (the "Policy"), as described in Annex 1 of Doc 13;

- **Requested** the Secretariat to make the necessary arrangements to ensure that vaccine introductions and campaigns occurring on or after 1 September 2012 benefit from the Policy regardless of when the country proposal was approved.

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14. Continued funding for special studies

14.1 Gustavo Gonzalez-Canali informed the Board that the PPC had discussed the role GAVI plays in implementing research and agreed that whilst research is critical for GAVI in the context of studies on key policies relevant to the role of new vaccines, there should not be a separate window for research (Doc 14). The studies being proposed are critical in that they fund the continuation of on-going cohort studies urgent to ensure that there is adequate data from developing countries doing GAVI's work.

14.2 Nina Schwalbe provided background information on special studies funded by GAVI to date, as well as on the goal and objectives of AVI special studies. She highlighted the four urgent studies recommended by the PPC and an additional study requested by the Committee. She specified that the PPC had advised that studies should be part of the business plan.

Discussion

- Before the discussion started Board members noted that Anne Schuchat and Maria Freire would not take part in the discussion or vote and that Amie Batson, who had earlier declared a conflict of interest on this item, was not present.

- Whilst there was general support for the recommendation to fund the special studies presented, some Board members expressed concern with regard to GAVI's funding research. It was suggested that further proposals should be put forward in the context of the business plan.

- The importance of linking the studies to work being carried out by the vaccine manufacturers was highlighted, as was the importance of ensuring that the

special studies funded by GAVI are mission critical and do not overlap with studies being carried out by other partners.

- Board members were informed that an independent group of experts had put together a list of topics for special studies on the critical path for GAVI, confirming that the studies proposed were all identified as priorities. Further, all proposals were independently peer reviewed before being put forward for approval.

Decision Nine

The GAVI Alliance Board:

- **Approved** an amount of up to US$ 9.3 million for AVI-TAC to continue two urgent pneumococcal studies and conduct two urgent rotavirus studies over a three year period, through 2015; and

- **Approved**, subject to the Secretariat receiving satisfactory peer review reports, an amount of US$ 1.8 million for AVI-TAC to conduct a study to monitor the impact of the SAGE recommendation on widening age restrictions related to rotavirus vaccine delivery.

Anne Schuchat (Research and Technical Institutes)and Maria Freire recused themselves and did not vote on this item. It was not necessary for Amie Batson to recuse herself as she was not present during discussion or the vote.

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15. Programme update: Accelerated Vaccine Introduction

15.1 Jon Pearman, Senior Technical Adviser, Vaccines, presented the Board with an update on the status of roll out and supply of rotavirus and pneumococcal vaccines including information on the factors influencing the difference in supply and demand (Doc 15).

15.2 Shanelle Hall, Director, Supply Division, UNICEF, reported that there are a number of variables that have to be managed in a situation which is complex and dynamic both on the demand and supply side. All measures are being taken to maximise supply and minimise risks to the manufacturers and to make vaccines available to the countries.

Discussion

- Board members agreed on the importance of sharing information and close cooperation between all relevant stakeholders. It was highlighted that communication at the country level is important in particular as this may be a reputational issue for them.

- Board members expressed a wish to be kept updated on the situation, acknowledging that this is a rapidly changing issue and that it will be

necessary to ensure that communication to the Board is done as and when appropriate.

- Board members were reassured that should there be supply constraints during 2011-2015 that delayed countries graduating in 2015 from commencing roll out of vaccines for which they had been approved, they would be supplied for the full period for which they had been approved.

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16. Country presentation: India

16.1 Ms Anuradha Gupta, Additional Secretary and Mission Director National Rural Health Mission from the Indian Ministry of Health and Family Welfare gave a presentation on India's universal immunisation programme. She highlighted the success of polio eradication, provided information on the measles mortality reduction initiative and on the introduction of the pentavalent vaccine. She informed the Board that 2012 has been declared the year of 'Intensification of Routine Immunisation' in India and in this context presented the country's strategic actions to improve immunisation.

16.2 Ms Gupta expressed her thanks to GAVI for supporting introduction of the pentavalent vaccine stating that India is now in a position to generate its own funding for this vaccine. She also thanked the Board for having considered special requirements for India, highlighting the catalytic effect GAVI support has had on the country.

Discussion

- The Chair commended Ms Gupta for the impressive work on immunisation in India and extended his congratulations on the success of polio eradication. The CEO highlighted Ms Gupta's leadership role which has contributed to India's success in immunisation.

- Board members noted that the immunisation programme is overseen and financed by the central government.

- Board members noted with interest the innovative tracking system which is used in India, which has huge potential, and which India would be willing to share with other countries.

- The Chair concluded by commending the CEO for the way in which he has prioritised developing GAVI's relationship with India.

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17. GAVI support to Civil Society Organisations

17.1 Paul Kelly, Director, Country Support, presented the recommendations of the PPC to the Board on GAVI support to Civil Society Organisations. He highlighted the important role of the Interagency Coordinating Committees (ICC) in ensuring CSO inclusion in country HSFP applications.

Discussion

- Alan Hinman informed the Board that his constituency would recuse itself from the discussion and from voting on this item, requesting permission to make a statement beforehand. He indicated that while his constituency would have preferred the option for CSOs to request support through a country focal point it did support the recommendation. He pointed out that the country-by-country approach being developed would help identify the exceptional circumstances in which GAVI should maintain the flexibility to engage CSOs directly.

- Board members noted that proposals for directly funding CSOs will be considered on a country-by-country basis in particular taking into consideration countries where CSOs play an important role in vaccine delivery and where the relationship between governments and CSOs are not well developed.

- Board members also noted that some countries have ongoing GAVI HSS multi-year commitments. CSOs in these countries may not be able to engage until the country prepares a new HSFP application. Some countries may not apply at all. GAVI will work closely with countries to promote the involvement of CSOs in HSS/HSFP discussions and where appropriate, facilitate reprogramming of current grants to integrate CSO participation. A majority of GAVI-eligible countries are expected to have applied for new HSFP support involving CSOs by the end of 2013.

Decision Ten

The GAVI Alliance Board:

- **Decided** that Government remains the default approach but direct funding for CSO activities can be requested as part of a country Health Systems Funding Platform (HSFP) application (Option 3).

  While provision of funds to CSOs through the HSFP is the recommended option, it should not limit GAVI's flexibility to engage CSOs directly where rare and exceptional circumstances require different approaches. Approaches should be developed in response to country-specific analysis.

- **Requested** the Secretariat to prepare an implementation framework recognising an increased risk in procurement and financial management and potential resource implications for the Secretariat and which draws on the

findings of the evaluation of GAVI support to CSOs and presents why and how GAVI works with and supports CSOs.

Alan Hinman (Civil Society Organisations) and Joan Awunyo-Akaba (his alternate), recused themselves and did not vote on this item.

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18. Long-term funding strategy

18.1 Marie-Ange Saraka-Yao, Director, Programme Funding, presented this item to the Board introducing some of the lessons learnt from the first GAVI replenishment (Doc 18). She highlighted the challenge of mobilising long-term and flexible funding, the importance of building a diverse capital structure, and of moving towards sustainable burden-sharing.

Discussion

- Board members agreed that one of the key functions of the Board is to look at resources. It will be necessary to continue to make the case for vaccines in the context of child survival. It will also be important to continue to make the case for vaccines in the developing countries so that immunisation remains a priority for them.

- A member noted that in the future a new seat on the Board may need to be created to meet the expectations of potential new donors.

- Board members agreed that there will be a need for GAVI to secure long-term funding, including through innovative finance, to power market-shaping and support programmatic commitments.

- It was agreed that there should be a focus on evidence, results, and achievements to date and suggested that results should be looked at in terms of forecasting.

- Board members discussed the issue of diversification and emphasised the importance of broadening the partnership with new sovereign donors and the private sector. In this context, and although donor governments are expected to continue to provide the majority of GAVI funding, the private sector could play an increasingly important role. The early success of the GAVI Matching Fund in this regard was noted approvingly. Some Board members felt that further possibilities should be explored in this context. It was stated that the private sector will want results and accountability. It was also stated that many companies will expect tax incentives, which the current structure with charities in the US and the UK may not be sufficient to address. Some Board members suggested re-establishing the Development Committee of the Board to assist GAVI with its private sector funding initiatives.

- The issue of earmarked funding was raised. Although the GAVI Alliance needs to recognise that this subject will increasingly become relevant and topical because of donor preferences and developments in our target donor groups, it was agreed that GAVI needs to be prudent in relation to this. The matter is under review with an evaluation of the early pilots, and the final strategy to be presented to the Board in December will include specific recommendations with regards to earmarking.

- The issue of sustainability was raised, both in terms of sustainability of resources and the sustainability of countries in introducing vaccines. In relation to the latter it was suggested that GAVI could help countries, and in particular graduating countries, to develop their sustainability plans.

- Board members noted that an implementation strategy will be included as part of the paper submitted to them at their next meeting in December 2012.

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19. IFFIm report

19.1 René Karsenti, Chair of the IFFIm Company, and David Ferreira, Managing Director for Innovative Finance, delivered the report of the International Finance Facility for Immunisation (IFFIm), highlighting how IFFIm continues to work for GAVI. René Karsenti provided the Board with an update on IFFIm credit ratings, IFFIm's continued attractiveness in the debt markets, and the IFFIm donors workshop which had been held in April 2012. He informed the Board about recent changes to the IFFIm Board and that the search process is currently underway to fill three IFFIm Board seats. René Karsenti emphasised that in the view of the IFFIm Board, IFFIm should continue to form part of GAVI's funding strategy in future.

Discussion

- The Board thanked Alan Gillespie for his role in chairing IFFIm since its inception and wished him well. The Board welcomed René Karsenti as IFFIm Chair.

- The Chair acknowledged the importance of IFFIm as a part of GAVI's long-term funding strategy and commended the IFFIm Board and staff on their work in the context of the current economic environment.

- The Board briefly discussed the possibility of new donors joining IFFIm and noted that it was not impossible for private companies to join IFFIm as donors, but that it would be challenging given the current structure.

- The Board noted that IFFIm provides different attractions to different donors and that it would probably need to be able to be marketed as such.

- A Board member asked if IFFIm could be applied to a specific immunisation challenge, such as the eradication of polio.

- A Board member remarked that within the objective of adding assets to IFFIm, one would need to make clear what else IFFIm adds above a long-term direct pledge to GAVI.

- The World Bank reiterated its commitment to support GAVI through IFFIm.

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20. IFFIm/GFA restructuring

20.1 Debbie Adams provided the Board with background information on the proposed removal of the GAVI Fund Affiliate (GFA) from the IFFIm structure and what this restructuring would mean to GAVI.

Decision Eleven

The GAVI Alliance Board:

- **Approved** GAVI entering into any new grant agreements with the IFFIm donors once the Finance Framework Agreement is amended to remove the GFA from the IFFIm structure; and

- **Approved** the immediate assignment to the IFFIm Company of any new grant agreements entered into between GAVI and the IFFIm donors.

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21. Review of decisions

21.1 Debbie Adams went through the decision language and actions with the Board which subsequently approved both.

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22. Closing remarks and any other business

22.1 The Chair concluded the meeting by thanking all present for their contribution to the work of the Alliance.

22.2 After determining there was no further business, the meeting was brought to a close.

Mr Dagfinn Høybråten Chair of the Board	Ms Debbie Adams Secretary to the Board

Participants

Board Members

- Dagfinn Høybråten, Chair
- Geeta Rao Gupta, Vice Chair
- HRH the Infanta Cristina of Spain
- Cristian Baeza
- Amie Batson
- Wayne Berson
- Simon Bland
- Dwight Bush
- Flavia Bustreo
- Suraya Dalil
- Mahima Datla
- Maria C. Freire
- Fatchou Gakaîtangou (Alternate)
- Ashutosh Garg
- Gustavo Gonzalez-Canali
- A.F.M. Ruhal Haque
- Johan Van Hoof
- Alan Hinman
- Steve Landry (Alternate)
- Yifei Li
- Anders Nordström
- Christine J.D. Ondoa
- Angela Santoni
- Anne Schuchat
- George W. Wellde Jr.
- Seth Berkley (non-voting)

Regrets

- Christopher J. Elias
- Guillermo González González

Alternates Observing

- Joan Awunyo-Akaba
- Nicholas Alipui*
- Jenny Da Rin
- Armin Fidler
- Suresh Jadhav
- Siv Cathrine Moe
- Jean-Marie Okwo-Bele
- Olga Popova
- Annie Vestjens

* Served as the eligible organisation's voting member per Section 2.6.5 of the By-Laws

Presenters not otherwise referenced

- Debbie Adams
- Helen Evans
- Barry Greene
- Paul Kelly
- Cees Klumper
- Aurélia Nguyen
- Jon Pearman
- Marie-Ange Saraka-Yao
- Nina Schwalbe

Additional Attendees

WORLD HEALTH ORGANIZATION

- Claudia P. Castillo, Alliances Specialist, Family and Community Health, PAHO
- Lidija Namisa Kamara, Programme Manager
- Gina Tambini, Manager, Area of Family and Community Health, PAHO / WHO, USA

UNICEF

- Jonathan Cauldwell, Senior Advisor, Public-sector Alliances & Resource Mobilization Office (PARMO)
- Shanelle Hall, Director, Supply Division
- Susan Mathiesen, Accounting Manager, Supply Division
- Jos Vandelaer, Chief, Immunization

THE WORLD BANK

- Natalia Antsilevich, Financial Officer, Multilateral Trusteeship and Innovative Financing
- Claudia Cadwallader
- Susan McAdams, Director, CFPMI
- Robert Oelrichs, Senior Health Specialist
- Shirmila Ramasamy, Counsel, Corporate Finance
- Ludovica Soderini, Senior Adviser
- Derek Strocher, Senior Financial Officer

BILL & MELINDA GATES FOUNDATION

- Nicole Bates, Deputy Director, Global Policy & Advocacy
- Violaine Mitchell, Interim Deputy Director
- Greg Widmyer, Senior Programme Officer

AFGHANISTAN

- Ghulam Sakhi Kargar Norughli, Spokesman, Ministry of Public Health, Afghanistan
- Ahmad Jawd Osmani, Acting Director, International Relations Department, Ministry of Public Health

From the United States Government in Afghanistan

- Sharifa Abbasi, Legal Assistant, Embassy of Afghanistan, U.S.A.
- Carol Horning, Social Development Director of USAID in Afghanistan

AUSTRALIA

- Tim Poletti, Health Advisor, AusAID (Australian Permanent Mission, Geneva)
- Sally Truong, Director, Sectoral Funds Section, AUSAid

BANGLADESH *(represented by its Board member)*

CANADA

- Micheline Gilbert, Senior Analyst, CIDA
- Jennifer Goosen, Director, MCHN Division, Canadian International Development Agency

CHAD *(represented by its Alternate Board member)*

EUROPEAN COMMISSION

- Eric Sattin, Health Officer, European Commission
- Walter Seidel, Head of Sector, DEVCO

FRANCE

- Agnès Surry, Deputy Head of Official Development Assistance and Multilateral Development Institutions, Ministry of the Economy, Finance and Industry

GERMANY

- Dirk Gehl, Advisor, Federal Ministry for Economic Cooperation and Development (BMZ)
- Rafael Teck, Policy Officer, Federal Ministry for Economic Cooperation and Development

IRELAND

- Diarmuid McClean, Development Specialist Global Health, Irish Aid

JAPAN

- Minori Ishii, Chief for Health Aid Policy, Ministry of Foreign Affairs
- Naoyuki Kobayashi, Deputy Director General, Human Development Department, Japan International Cooperation Agency (JICA)
- Keiko Osaki, Senior Advisor on Health, Human Development Department, JICA
- Hiroko Sakai, Associate Expert, JICA

NORWAY

- Lene Lothe, Senior Advisor, Norad

SPAIN

- Javier Aparicio, Adviser, Spanish Embassy, Washington, D.C.
- Estibaliz Garcia, Technical Adviser, Spanish Agency for International Cooperation
- Jorge Romeu, Adviser, Spanish Embassy, Washington, D.C.

SWEDEN

- Katarina Martholm Fried, Counsellor, Permanent Mission of Sweden to the United Nation Organisations in Geneva
- Mia Rimby, Deputy Director, Ministry for Foreign Affairs

UNITED KINGDOM

- Abigail Robinson, Programmes & Policy Manager for GAVI, DFID
- Samrita Sidhu, Programme Manager/Economic Adviser, DFID

UNITED STATES OF AMERICA

- Susan McKinney, Senior Technical Advisor for Immunization, USAID
- Angela Shen, Technical Advisor for Immunization and Vaccine Policy, USAID

UGANDA *(represented by its Board member)*

CIVIL SOCIETY ORGANISATIONS

- Amy Dietterich, GAVI CSO Constituency Communications Focal Point, Health Department, International Federation of Red Cross and Red Crescent Societies, Switzerland
- Kate Elder, Vaccines Policy Advisor, Médecins Sans Frontières, Access Campaign
- Clarisse Loe Loumou, Alternative Santé, Cameroon
- Elena McEwan, Catholic Relief Services
- Rozina Mistry, Aga Khan Health Service, Pakistan

VACCINE INDUSTRY – DEVELOPING COUNTRY

- Rajiv Modi, Chief Executive Officer, Cadila Pharmaceuticals, India
- Sonia Pagliusi Uhe, Executive Secretary, DCVMN

VACCINE INDUSTRY - INDUSTRIALISED COUNTRY

- Joan Benson, Executive Director, International Organizations, Merck Vaccines, U.S.A.
- Lynn Bodarky, Senior Director, Pfizer, U.S.A.
- Isabelle Deschamps, Director, Vaccination Policy and Advocacy, Sanofi Pasteur, France
- Lindsey Dietschi, Director, Pfizer, U.S.A.
- Stefano Malvolti, Director, Global Policy, Novartis Vaccines & Diagnostics, Switzerland
- Kathleen Vandendael, Director, Government Affairs & Public Policy, International Relations, GlaxoSmithKline Biologicals, Belgium (tbc)

RESEARCH AND TECHNICAL HEALTH INSTITUTES

- Orin Levine, Executive Director, PneumoADIP, Johns Hopkins Center for Global Health
- Rebecca Martin, Director, Global Immunization Division, U.S. Centers for Disease Control
- Benjamin Schreiber, COO, Agence de Médecine Préventive à l'Institut Pasteur, France
- Alfred Da Silva, Executive Director, Agence de Médecine Préventive à l'Institut Pasteur, France

SPECIAL ADVISERS

- Gian Gandhi, Senior Adviser to the GAVI Alliance Board Vice Chair
- Nazmul Huda, Special Adviser to the Board Member from Bangladesh
- Aksel Jakobsen, Senior Adviser to the GAVI Alliance Board Chair
- Silvia Noguer Figuerol, Special Adviser to HRH the Infanta Cristina of Spain
- Laura Quintana, Special Adviser to the Board Member from Nicaragua
- Fred Musoke Sebisubi, Special Adviser to the Board Member from Uganda

EVALUATION ADVISORY COMMITTEE

- Sania Nishtar, Chair, Evaluation Advisory Committee; Founder and CEO, Heartfile, Pakistan

GAVI CAMPAIGN

- Paul O'Connell, Board Chair
- Daniel Schwartz, Board member and Treasurer

GAVI FUND AFFILIATE

- André Prost, Board member

INTERNATIONAL FINANCE FACILITY FOR IMMUNISATION

- René Karsenti, Board Chair
- Sean Carney, Audit Committee Chair
- Didier Cherpitel, Board member

ADDITIONAL OBSERVERS

- Joshua Young Chu, Director, Vaccine Markets, Clinton Health Access Initiative
- Marta Espelta, Programme Officer, "La Caixa" Foundation
- Alan R. Gillespie, Founding Chair, International Finance Facility for Immunisation
- Anuradha Gupta, Additional Secretary & Mission Director National Rural Health Mission (NRHM), Ministry of Health and Family Welfare, India
- Alice Kang'ethe, Executive Vice President MCH and Director Vaccines, Clinton Health Access Initiative
- Ajay Khera, Deputy Commissioner Maternal and Child Health (MCH), Ministry of Health and Family Welfare, India
- David Lorenzo, Program Officer, Vaccine Access and Delivery, PATH
- Kathleen Neuzil, Director, Vaccine Access and Delivery, PATH
- John F. Olson, Distinguished Visitor from Practice, Georgetown University Law Center
- Vesta Richardson López-Collada, Director, National Center for Childhood and Adolescence, Ministry of Health, Mexico
- Fred Riley, Manager, Special Projects, LDS Humanitarian Services

Global Advisory Committee on Vaccine Safety, June 2012

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO to provide independent, scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 26th meeting in Geneva, Switzerland, on 6–7 June 2012.[2] The committee reviewed the following specific topics:

- the safety of thiomersal;
- the safety of aluminium adjuvants;
- the safety profile of influenza vaccines during pregnancy.

It also reviewed 3 general issues for vaccine pharmacovigilance:

- safety of immunization during pregnancy and lactation;
- causality assessment for serious individual cases of adverse events following immunization (AEFI);
- core variables for AEFI monitoring.

Thiomersal in vaccines

In 1999, concerns were raised in the United States of America (USA) regarding exposure to mercury following immunization with thiomersal-containing vaccines. This was based on the calculation that the cumulative amount of mercury in primary infant immunization schedules in the USA potentially exceeded the recommended threshold set by its Environmental Protection Agency for methyl mercury. Hence, the policy decision in the USA to use only vaccines without thiomersal was based on a precautionary principle founded on the presumption of equal pharmacokinetics of ethyl mercury and methyl mercury, despite the fact that thiomersal contains only ethyl mercury.

Between 2002 and 2008, GAVCS reviewed several pharmacokinetic and epidemiological studies concerning thiomersal. Pharmacokinetic data in human infants, including premature and low birth-weight infants, established that the half-life of ethyl mercury is 3–7 days, and that ethyl mercury is efficiently excreted in the stools and does not accumulate over the long-term in blood, since levels returned to baseline within 30 days of vaccination.

Comité consultatif mondial de la Sécurité vaccinale, juin 2012

Le Comité consultatif mondial de la Sécurité vaccinale (GACVS), un organe consultatif, composé de spécialistes des questions scientifiques et cliniques, a été créé par l'OMS pour traiter en toute indépendance et avec la rigueur scientifique voulue des problèmes de sécurité vaccinale pouvant avoir une importance mondiale.[1] Le GACVS a tenu sa 26e réunion à Genève (Suisse) les 6 et 7 juin 2012.[2] Il s'est penché sur les questions spécifiques suivantes:

- l'innocuité du thiomersal;
- l'innocuité des adjuvants à base d'aluminium;
- le profil d'innocuité des vaccins antigrippaux pendant la grossesse.

Il a aussi étudié 3 autres questions, d'ordre général, relatives à la pharmacovigilance des vaccins:

- l'innocuité de la vaccination pendant la grossesse et l'allaitement;
- l'évaluation du lien de causalité dans les cas de manifestations postvaccinales indésirables (MAPI) graves;
- les variables fondamentales pour le suivi des MAPI.

Présence de thiomersal dans les vaccins

En 1999, on s'est inquiété, aux États-Unis, d'une exposition au mercure après l'administration de vaccins contenant du thiomersal, car on a calculé que la quantité cumulée de mercure que supposaient les calendriers de vaccination initiale des nourrissons pouvait dépasser le seuil recommandé, fixé par l'Agence de Protection de l'Environnement concernant le méthylmercure. Il a donc été décidé, par précaution, que les États-Unis n'utiliseraient que des vaccins ne contenant pas de thiomersal, en partant de l'hypothèse que la pharmacocinétique de l'éthylmercure et celle du méthylmercure étaient identiques, bien que le thiomersal ne soit composé que d'éthylmercure.

Entre 2002 et 2008, le GACVS a examiné plusieurs études pharmacocinétiques et épidémiologiques portant sur le thiomersal. Les données sur la pharmacocinétique chez le nourrisson, y compris prématuré et de petit poids à la naissance, montraient que la demi-vie de l'éthylmercure était de 3 à 7 jours, qu'il était efficacement excrété dans les selles et qu'il ne s'accumulait pas durablement dans le sang puisque les concentrations revenaient aux niveaux de référence moins de 30 jours après la vaccination.

[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: Bambino Gesù Hospital, Rome, Italy; Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD, USA; John Hopkins Bloomberg School of Public Health, Baltimore MD, USA; Program for Applied Technologies in Health, Seattle, USA; Rochester General Hospital Research Institute, Rochester NY, USA; Shantha Biotechnics Limited, Hyderabad, India; University of California, Los Angeles CA, USA; University of Washington, Seattle WA, USA; Uppsala Monitoring Centre, Uppsala, Sweden.

[1] Voir No 41, 1999, pp. 337-338.

[2] Le GACVS a invité d'autres experts à présenter et à analyser des données relatives à des sujets particuliers. Parmi eux figuraient des personnes affiliées à: l'Hôpital Bambino Gesù de Rome (Italie); le Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD (États-Unis); la John Hopkins Bloomberg School of Public Health, Baltimore MD (États-Unis); le Program for Applied Technologies in Health, Seattle (États-Unis); le Rochester General Hospital Research Institute, Rochester NY (États-Unis); Shantha Biotechnics Limited, Hyderabad (Inde); l'University of California, Los Angeles CA (États-Unis); l'University of Washington, Seattle WA (États-Unis); l'Uppsala Monitoring Centre, Uppsala (Suède).

At the June 2012 meeting, GACVS reviewed the most recently available information concerning the safety of thiomersal since it last reviewed this topic in 2008. A comprehensive review identified 28 publications that addressed mercury blood levels in the short and long term following vaccine administration, and epidemiological studies that examined the relation between thiomersal receipt and several health outcomes. Three ecological studies suggesting an association between thiomersal and neurodevelopmental disorders were found to be fraught with methodological flaws. In addition, the continuous increase in the number of cases of autism diagnosed in the USA despite removal of thiomersal from most vaccines strongly argues against a causal association (fulfilling the exposure and removal criteria). All other studies reviewed, which were conducted with more robust epidemiological designs and in different countries, failed to identify any association with neurodevelopmental disorders.

Recently published studies confirm that in all populations studied, including pre-term and low birth-weight babies, the half-life of ethyl mercury in blood is between 3 and 7 days. A quantitative risk assessment model for cumulative toxicity of thiomersal in humans by US Federal Drug Administration (FDA) was also reviewed. This methodology is based on a pharmacokinetic model of ethyl mercury and provides a framework for interpreting studies in animals and humans that evaluate linkages among dose, blood and brain levels, and toxicity. Using this framework the GACVS concluded that animal or human toxicity studies suggest that the levels of ethyl mercury attained in the blood and brain from cumulative doses of vaccines do not reach toxic levels, making biologically implausible any relation between thiomersal in vaccines and neurological toxicity.

Based on the current evidence, GACVS considers that no additional studies of the safety of thiomersal in vaccines are warranted and that available evidence strongly supports the safety of the use of thiomersal as a preservative for inactivated vaccines. GACVS believes that consideration of additional evidence suggestive of the contrary should be based on studies using the same high standards of epidemiological and causal inference needed for scientific research. Thiomersal allows millions of people worldwide to have access to life-saving vaccines and to date, no other safer and equally efficacious alternative has been identified for many vaccines.

Aluminium adjuvants

The GACVS reviewed 2 published papers alleging that aluminium in vaccines is associated with autism spec-

Lors sa réunion de juin 2012, le GACVS a examiné les informations disponibles les plus récentes sur l'innocuité du thiomersal depuis qu'il avait étudié cette question pour la dernière fois, en 2008. Une revue de littérature complète a permis de recenser 28 publications sur les concentrations de mercure dans le sang à court terme et à long terme après l'administration d'un vaccin et des études épidémiologiques portant sur le lien entre l'exposition au thiomersal et plusieurs conséquences sur la santé. Trois études écologiques qui semblaient indiquer l'existence d'un lien entre le thiomersal et des troubles du développement neurologique se sont avérées comporter des failles méthodologiques. En outre, l'augmentation constante du nombre des cas d'autisme diagnostiqués aux États-Unis malgré le retrait du thiomersal de la plupart des vaccins tend à démontrer de manière convaincante l'absence de lien de cause à effet (lorsque les critères d'exposition et de retrait sont remplis). Toutes les autres études examinées, qui ont été menées avec des structures épidémiologiques plus solides et dans différents pays, n'ont mis en évidence aucun lien avec des troubles du développement neurologique.

Des études publiées récemment confirment que, dans l'ensemble des populations étudiées, y compris les nourrissons prématurés et de petit poids à la naissance, la demi-vie de l'éthylmercure dans le sang est de 3 à 7 jours. Un modèle d'évaluation quantitative des risques concernant la toxicité cumulative du thiomersal chez l'homme, réalisée par la Federal Drug Administration (FDA) des États-Unis, a également été examiné. Cette méthodologie, basée sur un modèle pharmacocinétique de l'éthylmercure, fournit un cadre pour interpréter les études qui évaluent, chez l'animal et chez l'homme, les liens entre la dose, les concentrations dans le sang et dans le cerveau, et la toxicité. Sur la base de ce cadre, le GACVS a conclu que les études de la toxicité chez l'animal et chez l'homme tendaient à montrer que les concentrations d'éthylmercure dans le sang et dans le cerveau dues aux doses cumulatives de thiomersal présent dans les vaccins n'atteignaient pas un niveau toxique, ce qui rendait peu plausible du point de vue biologique un lien entre le thiomersal présent dans les vaccins et sa toxicité neurologique.

Sur la base des données actuelles, le GACVS considère qu'il n'est pas nécessaire d'effectuer des études supplémentaires sur l'innocuité du thiomersal dans les vaccins et que les données disponibles montrent de manière convaincante que son utilisation comme conservateur dans les vaccins inactivés est sans danger. Le GACVS estime que d'autres données suggérant le contraire ne devraient être prises en compte que sur la base d'études suivant les mêmes normes de haut niveau concernant l'inférence épidémiologique et causale, exigées pour la recherche scientifique. Le thiomersal permet à des millions de gens dans le monde de bénéficier de vaccins salvateurs et, à ce jour, aucune autre alternative plus sûre et aussi efficace n'a été trouvée pour de nombreux vaccins.

Adjuvants à base d'aluminium

Le GACVS a examiné 2 articles publiés avançant que l'aluminium contenu dans les vaccins est associé à des troubles du

trum disorders[3,4] and the evidence generated from quantitative risk assessment by a US FDA pharmacokinetic model of aluminium-containing vaccines.

GACVS considers that these 2 studies[3, 4] are seriously flawed. The core argument made in these studies is based on ecological comparisons of aluminium content in vaccines and rates of autism spectrum disorders in several countries. In general, ecological studies cannot be used to assert a causal association because they do not link exposure to outcome in individuals, and only make correlations of exposure and outcomes on population averages. Therefore their value is primarily for hypothesis generation. However, there are additional concerns with those studies that limit any potential value for hypothesis generation. These include: incorrect assumptions about known associations of aluminium with neurological disease, uncertainty of the accuracy of the autism spectrum disorder prevalence rates in different countries, and accuracy of vaccination schedules and resulting calculations of aluminium doses in different countries.

The GACVS also reviewed the US FDA risk assessment model of aluminium in vaccines. The FDA calculations incorporate the most recently published aluminium risk assessments by adjusting for gastrointestinal absorption and uptake from the site of injection. The FDA analysis indicates that the body burden of aluminium following injections of aluminium-containing vaccines never exceeds safe US regulatory thresholds based on orally ingested aluminium even for low birth-weight infants. GACVS concludes that this comprehensive risk assessment further supports the clinical trial and epidemiological evidence of the safety of aluminium in vaccines. Current research on pharmacokinetics of aluminium in vaccines is ongoing and should be encouraged as a means of further validating and improving this model.

Vaccine safety in pregnancy and lactation

Several available vaccines have the potential to reduce maternal and fetal morbidity and mortality from preventable diseases. Thus, optimal protection against preventable diseases that pose a higher risk for disease and death in pregnant woman and their offspring should be balanced against the risk of malformations, abortions, stillbirth or other adverse outcomes that theoretically could affect the fetus as a result of vaccination in pregnancy. Maternal antibodies induced by vaccination dur-

spectre autistique,[3, 4] ainsi que les données tirées d'une évaluation quantitative des risques réalisée sur la base d'un modèle pharmacocinétique des vaccins contenant de l'aluminium établi par la FDA des États-Unis.

Le GACVS considère que ces 2 études[3, 4] comportent de graves failles. Leur argumentation de base est fondée sur des comparaisons écologiques de la teneur en aluminium des vaccins et du taux des troubles du spectre autistique dans plusieurs pays. En général, les études écologiques ne peuvent pas servir à affirmer l'existence d'une association de cause à effet car elles n'établissent pas de lien entre l'exposition et son résultat chez un individu mais seulement des corrélations entre l'exposition et les résultats sur des moyennes dans les populations. Leur utilité réside donc avant tout dans la formulation d'hypothèses. Dans ce cas particulier cependant, des problèmes supplémentaires limitent tout l'intérêt potentiel qu'elles auraient pu avoir: suppositions incorrectes sur des associations connues entre l'aluminium et des maladies neurologiques, incertitudes sur les taux de prévalence des troubles du spectre autistique ainsi que sur les calendriers de vaccination et, donc, sur le calcul des doses d'aluminium qui en résultent, dans différents pays.

Le GACVS a également examiné le modèle d'évaluation du risque lié à l'aluminium dans les vaccins, établi par la FDA des États-Unis. Les calculs de la FDA intègrent les dernières évaluations publiées sur les risques associés à l'aluminium, en tenant compte de l'absorption au niveau gastro-intestinal et au point d'injection. Il ressort de l'analyse de la FDA que la charge d'aluminium dans l'organisme après des injections de vaccins qui en contiennent ne dépasse jamais les seuils de sécurité réglementaires fixés aux États-Unis sur la base de l'aluminium ingéré, même pour les nourrissons de petit poids à la naissance. Le GACVS en conclut que cette évaluation globale des risques va encore dans le même sens que les données épidémiologiques et les informations tirées des essais cliniques sur l'innocuité de l'aluminium dans les vaccins. Des travaux sur la pharmacocinétique de l'aluminium dans les vaccins sont en cours et ils doivent être encouragés car ils constituent un moyen de valider et d'améliorer encore ce modèle.

Innocuité des vaccins au cours de la grossesse et de l'allaitement

Plusieurs vaccins disponibles permettent de réduire la morbidité et la mortalité maternelles et fœtales attribuables aux maladies évitables. Il faut donc comparer le bénéfice d'une protection optimale contre les maladies évitables constituant un risque élevé de morbidité et de mortalité pour les femmes enceintes et leur enfant, par rapport au risque de malformation, d'avortement, de mortinaissance ou d'autres conséquences indésirables qui pourraient théoriquement concerner le fœtus après une vaccination de la mère en cours de grossesse. Les

[3] Tomljenovic L, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *Journal of Inorganic Biochemistry*, 2011; 105: 1489–1499.

[4] Tomljenovic L, Shaw CA. Aluminum vaccine adjuvants: are they safe? *Current Medicinal Chemistry*, 2011; 18(17):2630–2637.

[3] Tomljenovic L, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *Journal of Inorganic Biochemistry*, 2011; 105:1489-1499.

[4] Tomljenovic L, Shaw CA. Aluminum vaccine adjuvants: are they safe? *Current Medicinal Chemistry*, 2011; 18(17):2630-2637.

ing pregnancy are actively transferred to the fetus and confer passive protection in the infant after birth. GACVS recently established a subgroup to review the safety profile of several important vaccines for pregnant and lactating women. In addition to the review of available data on influenza vaccines described below, the committee also reviewed the accumulated safety data for rubella-containing vaccines when inadvertently administered to pregnant women to complement the review conducted in June 2008. GACVS concludes that the data remain very reassuring for the use of vaccines during pregnancy, with no evidence of adverse fetal outcomes identified. Protection of mothers at risk and their young infants will be critical to attain the reduction of morbidity and mortality due to infections that affect many populations around the world.

Use of influenza vaccines during pregnancy

As the risk of influenza disease is increasingly recognized among pregnant women and a growing body of evidence supports the benefits to infants of maternal vaccination, the committee reviewed the safety data available for influenza vaccines derived from clinical trials, observational studies, and spontaneous reporting. The data confirm the safety of non-adjuvanted trivalent inactivated seasonal influenza vaccines in pregnancy. For example in the USA outcomes of pregnancy were assessed in 3719 vaccinated pregnant women compared with 45 866 controls in the Vaccine Safety Datalink during the period 1997–2002. From 1990–2009, an estimated 11.8 million pregnant women were vaccinated in the USA. In addition, a review of spontaneous reports found no maternal deaths, no unexpected pattern of adverse pregnancy events or fetal outcomes, and no increased risk of adverse pregnancy outcomes when compared to background rates. Extensive evaluation during the 2009 influenza A(H1N1)pdm09 pandemic supported the safety of adjuvanted and non-adjuvanted influenza vaccines when used in pregnant women; overall, the safety profile was comparable to seasonal influenza vaccine in non-pregnant adults, and there was no evidence of teratogenicity or any other negative impact on pregnancy outcomes. In addition, preliminary data from a few studies of influenza vaccine in pregnant women have confirmed not only the benefit of providing protection in this vulnerable population, but positive effects in their infants, including the reduction of low birth weights, and a significant decrease in influenza-related pneumonia in young children.

Causality assessment of Adverse Events following Immunization

Attribution of causality to AEFI, especially those considered severe, of public importance, and programmat-

anticorps produits par la mère grâce à la vaccination pendant la grossesse sont transférés activement au fœtus et, après la naissance, ils confèrent une protection passive au nourrisson. Le GACVS a récemment créé un sous-groupe chargé d'étudier le profil d'innocuité de plusieurs vaccins importants pour les femmes enceintes et allaitantes. En plus d'examiner les données disponibles sur les vaccins antigrippaux, comme il est décrit ci-dessous, le Comité a étudié, pour compléter l'étude faite en 2008, les données accumulées sur l'innocuité des vaccins à valence rubéole administrés aux femmes enceintes par inadvertance. Le GACVS en conclut que les données restent très rassurantes en ce qui concerne l'utilisation des vaccins au cours de la grossesse, aucune issue indésirable pour le fœtus n'ayant été identifiée. La protection des mères à risque et de leur nourrisson sera cruciale pour parvenir à réduire la morbidité et la mortalité causées par les infections qui touchent un grand nombre de populations dans le monde.

Utilisation des vaccins antigrippaux pendant la grossesse

Avec la reconnaissance croissante des risques de la grippe pour la femme enceinte et de plus en plus de données montrant que la vaccination de la mère est bénéfique pour le nourrisson, le Comité a examiné les données disponibles sur l'innocuité des vaccins antigrippaux, tirées d'essais cliniques, d'études d'observation et de notifications spontanées. Celles-ci confirment l'innocuité des vaccins trivalents inactivés, sans adjuvants, administrés contre la grippe saisonnière pendant la grossesse. Par exemple, aux États-Unis, l'issue de la grossesse a été évaluée chez 3719 femmes enceintes vaccinées par rapport à un groupe témoin de 45 866 femmes provenant de la base de données Vaccine Safety Datalink, de 1997 à 2002. On estime que, de 1990 à 2009, 11,8 millions de femmes enceintes ont été vaccinées aux États-Unis. En outre, une étude des notifications spontanées n'a mis en évidence aucun décès maternel, aucune évolution inattendue des événements indésirables au cours de la grossesse ou des conséquences pour le fœtus, et aucun risque accru d'issue indésirable de la grossesse par rapport aux taux de référence. Une évaluation de grande ampleur menée en 2009 au cours de la pandémie de grippe A(H1N1)pdm09 a montré que l'utilisation des vaccins antigrippaux avec ou sans adjuvants chez la femme enceinte était sûre; dans l'ensemble, le profil d'innocuité était comparable à celui du vaccin contre la grippe saisonnière utilisé chez les femmes qui ne sont pas enceintes, et il n'y avait pas d'indice d'effet tératogène ou d'autre impact négatif sur l'issue de la grossesse. En outre, les données préliminaires tirées de quelques études ont confirmé que, chez les femmes enceintes, le vaccin antigrippal non seulement conférait une protection mais qu'il avait aussi des effets positifs pour l'enfant, notamment en réduisant le risque de petit poids à la naissance et en faisant baisser nettement celui de pneumonie grippale du jeune enfant.

Évaluation du lien de causalité en cas de manifestations postvaccinales indésirables

L'imputation de la causalité des MAPI, en particulier dans les cas considérés comme graves, importants pour la santé publique

ically disruptive, are critical for ensuring vaccine safety. In 2005, WHO published an *aide-mémoire* to a systematic, standardized causality assessment process for serious AEFI (including clusters), providing a method for individual causality assessment to be used by staff of national immunization programmes, regulatory authorities and pharmacovigilance or surveillance departments.[5] After 7 years, several limitations had been identified during its use in the field, including: the need for more detailed guidance on the elements required to perform the assessment of causality, confusion over the terms used to classify the likelihood of association of the event to the vaccine, and the incomplete use of parameters for establishing causal association.

Following the GACVS decision to review the causality assessment system in December 2010, a working group was established to review the *aide-mémoire* and develop a method that would be simple, objective, adaptable and evidence-based when used by countries with different resources and capabilities. After concluding a thorough review of the most innovative methods available for determining causation for drugs and biologicals, an algorithmic scheme that incorporates additional elements of causation was designed. The guide was harmonized after the Clinical Immunization Safety Assessment (CISA) network's newly developed algorithm which is available in the USA[6] and the new definition of AEFI proposed by the Council for International Organizations of Medical Sciences (CIOMS).[7]

The new WHO proposed method allows the National Committees for AEFI case review and causality assessment to screen serious cases reported by their surveillance system for completeness and quality of information, ensuring the objectiveness of the assessment. Cases deemed incomplete are directed towards additional case investigation and review. A checklist containing the elements of causality assessment was included to guide the committee or the assessor to gather the evidence needed for case review, and when completed allows the application of an algorithm that helps determine if the AEFI could be consistent or inconsistent with an association with the immunization, or is deemed indeterminate due to lack of evidence. A repository of all AEFI cases sorted through this new document is considered critical and recommended to

ou susceptibles de perturber les programmes, est essentielle pour garantir l'innocuité des vaccins. En 2005, l'OMS a publié un aide-mémoire destiné à guider le lecteur dans l'application d'une procédure d'évaluation systématique et standardisée de la causalité des manifestations postvaccinales indésirables (y compris pour les grappes de cas). Il présentait une méthode d'évaluation de la causalité pour chaque cas, à l'intention du personnel des programmes nationaux de vaccination, des autorités de réglementation et des services de pharmacovigilance ou de surveillance.[5] Sept ans plus tard, son application sur le terrain a montré ses limites. En effet, on a besoin d'orientations plus détaillées sur les éléments nécessaires pour évaluer la causalité, il existe une confusion concernant les termes employés pour classer la probabilité du lien entre la manifestation et le vaccin, et les paramètres permettant d'établir la relation causale ne sont pas complètement utilisés.

Après la décision prise par le GACVS, en décembre 2010, de revoir le système d'évaluation de la causalité, un groupe de travail a été créé pour revoir l'aide-mémoire et mettre au point une méthode susceptible d'être simple, objective, adaptable et fondée sur des bases factuelles et utilisable par des pays n'ayant pas tous les mêmes ressources et les mêmes capacités. Après un examen approfondi des méthodes les plus innovantes permettant de déterminer les causes pour les médicaments et les produits biologiques, un algorithme intégrant des éléments supplémentaires pour établir les causes a été mis au point. Le guide a été harmonisé suivant le nouvel algorithme mis au point par le Clinical Immunization Safety Assessment (CISA) Network, disponible aux États-Unis,[6] et la nouvelle définition de MAPI proposée par le Conseil des Organisations internationales des Sciences médicales (CIOMS).[7]

La nouvelle méthode proposée par l'OMS permet aux comités nationaux chargés d'examiner les cas de MAPI et d'évaluer la causalité de vérifier la complétude et la qualité des informations concernant les cas graves rapportés par leur système de surveillance, et ainsi de garantir l'objectivité de l'évaluation. Les cas pour lesquels les informations sont considérées comme incomplètes font l'objet d'une enquête et d'un examen supplémentaires. Une liste de contrôle comportant les différents éléments de l'évaluation de la causalité a été ajoutée pour aider le comité ou l'évaluateur à rassembler les données nécessaires à l'étude des cas. Une fois cette liste passée en revue, il est possible d'appliquer un algorithme aidant à déterminer s'il existe ou non un lien de causalité entre la MAPI et la vaccination ou si, fautes de données probantes, il est impossible de se prononcer. Il est essentiel et recommandé d'instaurer un archivage de tous les cas de MAPI triés à l'aide de ce nouveau docu-

[5] *Aide-mémoire: Adverse events following immunization (AEFI): causality assessment.* Geneva, World Health Organization, 2005. Available from http://whqlibdoc.who.int/aide-memoire/a87773_eng.pdf; accessed July 2012.

[6] Halsey NA et al. Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*, 2012. Available online at http://www.ncbi.nlm.nih.gov/pubmed/22507656, accessed July 2012.

[7] *Definitions and application of terms for vaccine pharmacovigilance.* Geneva, World Health Organization/ Council for International Organizations of Medical Sciences, 2012. Available at http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf, accessed July 2012.

[5] *Aide-mémoire sur les événements indésirables post-vaccinaux (EIPV): évaluation de la causalité.* Genève, Organisation mondiale de la Santé, 2005. Disponible sur http://www.who.int/vaccines-documents/DocsPDF05/829.pdf; consulté en juillet 2012.

[6] Halsey NA et al. Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*, 2012. Disponible à l'adresse: http://www.ncbi.nlm.nih.gov/pubmed/22507656, consulté en juillet 2012.

[7] *Definitions and application of terms for vaccine pharmacovigilance.* Genève, Organisation mondiale de la Santé/Conseil des Organisations internationales des Sciences médicales, 2012. Disponible à l'adresse: http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf, consulté en juillet 2012.

allow for future signal detection and determining the need for additional epidemiological studies.

GACVS recognizes the boundaries of the newly developed method, mainly the limitations in the ability to associate novel, previously unknown AEFIs potentially associated with immunizations, and restrictions due to insufficient information available for individual cases. However, the new AEFI causality assessment system will provide a standardized and transparent method that allows stakeholders to understand the nature of the decision-making process, and pave the way for future evaluation of the guide to refine its effectiveness. GACVS has recommended that this new WHO AEFI causality assessment approach should be made public as soon as it is finalized, and that complementary materials and simple software be developed for use in countries to enable immunization staff to field-test the algorithm. Of the next steps deemed most important is the development of a booklet to codify the algorithm and train countries in its use. The committee encouraged the subgroup to further develop the product and endorsed the work process.

Core variables for AEFI monitoring

Collection of harmonized data on AEFI allows for better comparison and pooled analysis with findings from vaccine safety surveillance systems. In collaboration with a network of countries and independent experts, a preliminary list of core variables had been proposed. This list was subsequently compared with the reporting forms from the WHO Programme for International Drug Monitoring (Uppsala Monitoring Centre) to verify which variables are captured by the current reporting forms. Through this exercise, it became apparent that vaccine safety monitoring needs tools which are more specific to the type of variables required for proper AEFI surveillance and that the current web-based interface developed for reporting of suspected drug reactions (VigiFlow) should be adapted for AEFI reporting. To address these issues, the GACVS in December 2011 suggested developing a simpler and vaccine-specific user interface to enter AEFI data. A subgroup of GACVS was tasked to address those issues and presented the status of ongoing activities at the June 2012 meeting.

Collection of basic and advanced AEFI information

It is recognized that for the purpose of signal detection, data collection tools should remain as simple as possible. However, when signals are detected, or in cases of serious AEFI, additional data are essential to allow inferences to be drawn on the association with vaccines and to assess the need for further investigation and action. The subcommittee presented GACVS with 22 core variables that should be collected for any AEFI

ment, afin, à l'avenir, de détecter les signes et de déterminer s'il faut entreprendre des études épidémiologiques supplémentaires.

Le GACVS admet que la méthode qui vient d'être mise au point a ses limites, notamment en ce qui concerne la possibilité d'associer des MAPI nouvelles et inconnues à des vaccins et les restrictions dues à l'insuffisance des informations sur chaque cas. Cependant, le nouveau système d'évaluation de la causalité fournira une méthode standardisée et transparente permettant aux parties prenantes de comprendre la nature du processus de prise de décision, ainsi que de préparer le terrain à une évaluation future du guide, afin qu'il soit encore plus efficace. Le GACVS a recommandé de rendre publique cette nouvelle approche de l'évaluation de la causalité des MAPI proposée par l'OMS dès qu'elle aura été finalisée et de mettre au point des documents complémentaires et un logiciel simple, afin de permettre au personnel chargé de la vaccination dans les pays de tester l'algorithme sur le terrain. La rédaction d'une brochure pour codifier l'algorithme et la formation dans les pays à son utilisation ont été considérées comme 2 des prochaines étapes les plus importantes. Le Comité a encouragé le sous-groupe à développer encore le produit et a approuvé les travaux en cours.

Variables fondamentales pour le suivi des MAPI

Le recueil de données harmonisées sur les MAPI permet d'améliorer la comparaison et la méta-analyse par rapport aux résultats que donnent les systèmes de surveillance de l'innocuité des vaccins. Une liste préliminaire de variables fondamentales avait été proposée en collaboration avec un réseau de pays et d'experts indépendants. Cette liste a ensuite été comparée aux formulaires de notification du programme OMS de surveillance internationale des médicaments (centre collaborateur OMS pour la pharmacovigilance internationale, Uppsala) pour vérifier quelles étaient les variables prises en compte dans les formulaires actuels. Il est ressorti de cette comparaison que le suivi de l'innocuité des vaccins exigeait des outils plus spécifiques au type de variables nécessaires pour une surveillance correcte des MAPI et qu'il faudrait adapter à la notification des MAPI l'interface actuelle conçue sur le Web pour notifier les présomptions de réaction médicamenteuse (VigiFlow). À cet égard, le GACVS a proposé, en décembre 2011, que soit mise au point une interface utilisateur plus simple et spécifique aux vaccins pour entrer les données relatives aux MAPI. Un sous-groupe du GACVS a été chargé de se pencher sur cette question et il a présenté l'état d'avancement des travaux à la réunion de juin 2012.

Collecte des informations essentielles et détaillées

On sait que, pour la détection des signes, les outils de recueil de données doivent rester aussi simples que possible. Cependant, une fois les signes détectés ou en cas de MAPI grave, il est essentiel de disposer de données supplémentaires pour tirer des conclusions sur l'association avec des vaccins et pour déterminer s'il faut mener des enquêtes et prendre des mesures supplémentaires. Le sous-comité a présenté au GACVS 22 variables de base pour lesquelles des données doivent être collectées quelle que

(basic information) and an additional 33 variables of interest for a more detailed case review (advanced information). Basic information collected needs to be prioritized because the AEFI data collection, collation, transmission, analysis and feedback systems in different countries are heterogeneous. In addition, quantitative and qualitative aspects of data need to be considered. The suggested approach proposes a basic minimum of 22 variables with 10 identified as critical. This simple structure is expected to encourage countries that do not yet have an AEFI surveillance system in place to develop one. It is proposed that the reporting tool include the WHO-ART dictionary in order to standardize the terminology used to record signs, symptoms or a diagnosis, as well as a vaccine dictionary that will include details pertaining to all of the vaccines suspected. For the advanced information, details on the nature and frequency of reporting for events such as in campaigns or in routine immunization programmes, breast or bottle feeding, status of previous vaccination are proposed.

Vacciflow

"VacciFlow" will be developed as the adaptation of drug-specific VigiFlow 4.2 to facilitate the entry of vaccine-related AEFI data including immunization programme errors. Ideally "VacciFlow" will be used by both the national regulatory authority and the immunization programme staff. The possibility of incorporating this new interface with minimal computer capabilities and mobile phone technology was encouraged by GACVS. There will be 3 flexible levels created in "VacciFlow" enabling national and subnational level users to analyse and use the data available for action at each level. Automatic feedback to reporters on the status of the report will be built in. Adapting (modifying) existing AEFI reporting systems to adjust to the data proposed in this core set of variables will require an educational and dissemination effort in many countries. It is expected that the upcoming "VacciFlow" will be sufficiently simple and user-friendly to allow tailor-made adjustment for locally collected information. ■

soit la MAPI (informations essentielles) et 33 autres variables présentant un intérêt pour un examen plus détaillé du cas (informations détaillées). Les informations essentielles collectées doivent être hiérarchisées car les systèmes de recueil, de rassemblement, de transmission, d'analyse et de retour des données ne sont pas les mêmes dans tous les pays. Il faut aussi tenir compte des aspects quantitatifs et qualitatifs des données. L'approche suggérée propose un minimum de 22 variables, dont 10 sont présentées comme fondamentales. La simplicité de la structure devrait encourager les pays qui ne disposent pas encore d'un système de surveillance des MAPI à en mettre un en place. L'outil de notification devrait inclure le dictionnaire de l'OMS WHO-ART afin que la terminologie utilisée pour enregistrer les signes, les symptômes ou le diagnostic soit standardisée, ainsi qu'un dictionnaire des vaccins contenant des informations sur tous les vaccins soupçonnés de pouvoir entraîner des MAPI. En ce qui concerne les informations détaillées, on propose d'inclure des renseignements sur la nature et la fréquence de la notification dans le cadre d'événements tels que des campagnes de vaccination ou de programmes de vaccination systématique, sur le mode d'alimentation des nourrissons (allaitement au sein ou au biberon) ou encore sur les antécédents vaccinaux.

VacciFlow

Le logiciel « VacciFlow » sera mis au point en adaptant le logiciel VigiFlow 4.2, qui porte spécifiquement sur les médicaments, pour faciliter la saisie de données sur les MAPI liées aux vaccins. Ce logiciel tiendra également compte des erreurs des programmes de vaccination. L'idéal serait que «VacciFlow» soit utilisé à la fois par l'autorité nationale de réglementation et par le personnel du programme de vaccination. Le GACVS s'est dit favorable à l'intégration de cette nouvelle interface avec des moyens informatiques limités et dans les téléphones portables. «VacciFlow» comportera 3 niveaux flexibles permettant aux utilisateurs aux échelons national et infranational d'analyser et d'utiliser les données disponibles pour agir à chaque niveau. Le logiciel prévoira aussi un retour automatique des informations sur l'état de la notification aux personnes ayant transmis les informations. L'adaptation (ou la modification) des systèmes existants de notification des MAPI pour les ajuster aux données proposées dans cette série de variables de base exigera certainement un effort de formation et de diffusion dans de nombreux pays. « VacciFlow » devrait être suffisamment simple et convivial pour permettre l'ajustement des informations collectées au niveau local. ■

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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1) Par le serveur Web de l'OMS: A l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: **http://www.who.int/wer/**

2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à **listserv@who**.int en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh.

WORLD HEALTH ORGANIZATION
IMMUNIZATIONS, VACCINES AND BIOLOGICALS

IMMUNIZATION PRACTICES ADVISORY COMMITTEE (IPAC)
17-18 April 2012

Final meeting report and recommendations

IPAC Members present:
Shelley Deeks (Chair)
Robin Biellik
Xavier Bosch-Capblanch
Jonathan S. Colton
Francois Gasse
Najwa Khuri-Bulos
Folake Kio-Olayinka
Sanath Lamabadusuriya
Christopher Morgan
Jean Marc Olivé
Jane Soepardi
Robert Steinglass

Opening and Introduction

Dr Shelley Deeks (chair) opened the meeting and welcomed Dr Jean-Marc Olivé, an independent consultant with over thirty years' experience in EPI, to his first meeting.

Session I. Updates from SAGE and Global Advisory Committee on Vaccine Safety (GAVSC)

A. Updates from SAGE meeting (*Shelley Deeks, IPAC*)

Dr Deeks updated the committee on the November 2011 and April 2012 SAGE meetings, with particular focus on the sessions regarding polio, pneumococcal disease, hepatitis A and influenza. Programmatic considerations of polio, influenza, and hepatitis A vaccine were discussed among IPAC members. WHO will conduct further internal discussions to determine whether an IPAC subgroup needs to be developed to consider programmatic implications of the polio end-game strategy.

B. Updates from Global Advisory Committee on Vaccine Safety (*Patrick Zuber, WHO HQ*)

Dr Zuber reported on the topics reviewed during the December 2011 GACVS meeting. These are reported in WER 2012, 87, 53-60 and include the initiation of the work on vaccine safety during pregnancy and lactation; update on pandemic A(H1N1)2009 influenza vaccines; update on the global network for AEFI monitoring; update on rotavirus vaccine safety; and launch of the Global Vaccine Safety (GVS) Initiative as the implementation mechanism of the Global Vaccine Safety Blueprint.

The GVS Initiative is a collaborative effort administered by WHO. A planning group composed of representatives from interested organizations has been established to steer the initiative. Its main focus, as advised by GACVS and SAGE is on enhancing vaccines safety monitoring in all countries.

Session II. Programmatic Implications of Rotavirus age-limitations

A. Rotavirus Update from Global Advisory Committee on Vaccine Safety (*Patrick Zuber, WHO HQ*)

With respect to current rotavirus vaccines, GACVS concluded that Rotarix and RotaTeq continue to exhibit a good safety profile, but may be associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. The levels of risk observed are substantially less than those observed with the previous vaccine, Rotashield. The benefits of rotavirus vaccination without age restriction would greatly exceed the risks, particularly in developing countries with moderate and high mortality from rotavirus disease. Finally, active surveillance of intussusception in countries that plan to introduce rotavirus vaccines should be seriously considered.

B. Feedback from WHO Ad-Hoc Expert Consultation on Optimising Rotavirus Vaccines (RV) Schedules (*Najwa Khuri-Bulos, IPAC*)

Dr Najwa Khuri Bulos updated IPAC on the key conclusions of the consultation, which was held in February 2012. The objective was to review rotavirus vaccine schedules as previously recommended by SAGE in light of new studies from developing countries, and to decide if schedule modifications might be necessary based on this new evidence. This consultation was in preparation for the SAGE meeting in April 2012, where this topic was to be discussed.

Two major questions were reviewed extensively. The first addressed the effectiveness of rotavirus vaccines under different vaccination schedules and with different doses, given in various WHO mortality strata, taking into consideration age of the child, breast feeding status, concomitant vaccine administration and interval between vaccine doses. The second question addressed the evidence available on the benefits and risks of the current (and alternative) RV immunization schedules for children living in different WHO mortality strata.

The consultation concluded that there was no evidence to warrant a change in the current SAGE recommendations on dosing. It was noted that while "RV efficacy and effectiveness is lower in settings with high under-five mortality," there is "limited evidence to conclude that giving a third dose of RV1 is superior to the currently recommended two dose schedule".

The consultation concluded that "evidence available (although limited) and review of operational realities suggest that SAGE members should consider once more the merits and trade-offs (benefits and risks) associated with administration of rotavirus vaccines using a vaccination schedule without age-restrictions." Furthermore, the consultation recommended that SAGE consider removing age restrictions on the first and last dose of rotavirus vaccination and to consider recommending administering rotavirus vaccine concomitantly with other EPI vaccines wherever possible.

C. Feedback from SAGE on Rotavirus Vaccine Schedule (*Shelley Deeks, IPAC*)

At the April 2012 SAGE meeting, SAGE recognized that age restrictions around rotavirus (RV) vaccine dosing exclude the most vulnerable children who are often accessed and evaluated through outreach programs; by removing age restrictions, these programs can immunize children most vulnerable to disease, which will avert disease despite a possible small increase risk of intussusception. SAGE continues to recommend the first dose be administered with DTP-containing vaccines as soon as possible after 6 weeks of age, but recognises that late vaccination is better than no vaccination. SAGE further stated that countries should be empowered to make their own choice about ages based on local data and decision-making processes. The WHO RV vaccine position paper will be updated.

Discussion:

IPAC members noted that SAGE and GACVS have provided clear recommendations on the benefit and safety of RV vaccine, which should now be widely and clearly publicized. Several members noted that the age profile of onset of RVGE and compliance with vaccination schedules varies across countries. IPAC stressed the continuing importance of timely vaccination to prevent not only RVGE but also other infections. Based on SAGE's recommendations, the challenge will be to communicate the overwhelming benefit of timely RV vaccination to reduce morbidity and mortality; this will be enhanced by using this vaccine without narrow age limitations -- even as more cases of intussusception may be expected by lifting the age restrictions, by virtue of the epidemiology of intussusception.

In most countries intussusception is not a reportable condition. Without background rates, there is concern that improved surveillance for intussusception will result in increased reporting of co-incidental cases which may cast doubt on the role played by RV vaccine introduction. Some participants raised concern that use of the vaccine according to the new SAGE recommendations will be seen as an "off-label" use. Furthermore, as intussusception is a rare event, it may take several years to accumulate evidence on the dose- and age-specific role of RV vaccination in its etiology. Some members advised that countries and NITAGS will want to have evidence-based documents from WHO before agreeing to use RV vaccine "off-label". The planned update of WHO's position paper on RV was welcomed by members.

In light of the new information and recommendations concerning safety and timeliness, it was suggested that IPAC's role, consistent with its mandate, should be to discuss next steps related to introduction and roll-out of RV vaccine from a programmatic and operational perspective.

Recommendations and Decisions by IPAC

1. IPAC recommended that the previously agreed rotavirus vaccine training case scenarios be kept, but that additional training scenarios be developed to address relaxation of the age limitations for rotavirus vaccine, as was concluded at the SAGE April 2012 meeting.

Session III. Controlled Temperature Chain (CTC)

A. Progress with CTC: strategy & update (*Michel Zaffran*, *WHO HQ*)

The Controlled Temperature Chain (CTC) approach aims to take advantage of the fact that many vaccines are more stable than indicated by their current licenses. The key thrust of the strategy is to enable the use of certain vaccines outside the standard $+2^0$ to $+8^0$C range without requiring any reformulation and endorsed through a regulatory process. The regulatory approval will allow for 'on-license' use and is important for ensuring the vaccines remain potent and safe throughout their lifecycle. Furthermore, regulatory precedent for reflecting stability in vaccine licenses does currently exist in Canada, the United States, and the European Union.

Many countries have already been taking advantage of the existing stability in today's vaccines, using certain antigens outside the cold chain for limited periods of time, relying on the Vaccine Vial Monitor (VVM). However, although field studies have confirmed the potency of vaccines used in this way, this use is considered 'off-license' use, which is not condoned or supported by manufacturers and regulators.

This CTC work initially started using hepatitis B vaccine as a pathfinder. However, in-vitro potency data are not completely predictive of hepatitis B vaccine integrity; thus there is no direct correlation with clinical efficacy. It was determined that further data, in addition to in-vitro data, would be needed to demonstrate integrity of the vaccine after high temperature exposure before a license variation can be considered. The timing for this work therefore is longer than anticipated, and a re-licensed hepatitis B vaccine will not be available before 2014.

In the interim, the meningococcal A vaccine, MenAfriVac, emerged as a strong candidate for CTC use. As a result, the CTC pathway is currently being charted using the meningococcal A vaccine in a campaign setting, while work on hepatitis B vaccine continues.

The benefits from a CTC approach include reducing programmatic costs and constraints, such as diminishing the burden of ice pack freezing and surge capacity needs, increasing options for immunization strategies, decreasing human resources requirements and reducing the risk of freeze damage to vaccines.

B. Regulatory process for label variations (*Tong Wu, Health Canada*)

Since 2009, Canada has been providing on-license guidance for the use of vaccines after exposure to temperatures above +8ºC. This was done at the request of the provincial/territorial immunization programs, which identified significant amounts of vaccine having to be discarded after being inadvertently exposed to cold chain breaks.

Given that vaccines are complex biologicals, an in-depth scientific review is required in order to assess if and how a vaccine can be safely used at temperatures above +8ºC. These reviews are product specific, and require real time and temperature stability data. The specifications that are assessed should be linked to expected clinical outcomes and follow a 'worst case scenario' hypothesis, that is: if the vaccine is released right at the edge of its release specification, suffers the maximum amount of degradation possible, and is still required to meet the specification at the end of its shelf life. When conducting an assessment, Health Canada uses the following principle: Loss of potency during entire recommended storage period (regression method) + loss of potency during proposed period of CTC (regression method) must ≤ defined "expiry window" supported by clinical trials. This means that duration approved for CTC is shorter than what is supported by stability data.

C. Use of MenAfriVac in a CTC for campaigns (*Simona Zipursky, PATH*)

The need to keep vaccines in a +2º to +8ºC cold chain is a constraining factor for many immunization campaigns; those planned across sub-Saharan Africa to introduce the new meningococcal A vaccine, MenAfriVac® are a good example. However, data obtained from the vaccine manufacturer show that MenAfriVac®has been proven stable at temperatures of 40°C for several weeks. Collaboration among the vaccine manufacturer, PATH, WHO, and the Canadian and Indian regulatory bodies is underway in order to obtain a license variation for this vaccine. This variation will allow countries to use MenAfriVac® at ambient temperature, for limited periods of time, in a CTC.

This work involves four inter-related streams: (i) regulatory license variation; (ii) development and endorsement of operational guidance; (iii) country introductions; and (iv) operational research. IPAC's expertise was sought in area (ii) operational guidance and the request was made of IPAC to provide specific inputs to improve the draft field guidelines. The intent is to pilot these guidelines in the campaigns currently planned at the end 2012.

D. Sub-group perspective and next steps (*Francois Gasse, IPAC and working group lead*)

The IPAC working group provided input into the guidance document and CTC work stream. In order to ensure vaccine quality, maintaining the vaccine under the conditions specified on the label and approved by regulators (at +40°C or below) was an issue that needed to be addressed. The sub-group recommended that peak temperature chemical indicators accompany vaccines when stored or transported in cold boxes or vaccine carriers, while electronic loggers be reserved for large volume storage or transport settings. Further, the sub-group recommended that, when possible, vaccine carriers and cold boxes be used to transport vaccines even in a CTC. The version of the guidance circulated to IPAC reflects these comments, and the sub-group's position.

Discussion:

IPAC members were extremely supportive of the work accomplished on CTC and commended WHO/PATH Optimize and the sub-group on the exciting progress made in this area. The CTC strategy, if successful, would be a revolutionary change for immunization. The guidance document was felt to be clear and well written.

A range of general points were raised by IPAC members, encouraging WHO to a) share the best practices used by Health Canada with other National Regulatory Authorities (NRAs); b) consider reflecting the license variations granted by functional NRAs in the product inserts of pre-qualified products to help low-middle income countries in decision-making; c) continue exploring the development of new VVM types that reflect the higher stability of new vaccines; and d) continue working on improving the freeze stability of vaccines and support countries in preventing vaccine exposure to freezing temperatures.

Key technical inputs contributed by IPAC included the following:

- *Clarify the term CTC*. There needs to be a consistent definition and use of CTC terminology. This will protect it as a trustworthy brand, assuring that certain criteria must be complied with—e.g. CTC is the use of vaccines under monitored conditions, following a regulatory approval. The situation is monitored if there is a risk that the temperature could exceed the regulatory approval.
- *Clarify the scope of the guidance*. It is important to note that some countries have stocks of the meningococcal A + C vaccine; therefore it is essential to clarify that this is only for meningococcal A vaccine. It may be worth considering adding in the brand name for clarification.
- *Provide more guidance to support decision making*. The decision-making section would benefit from the use of a decision-making tree or algorithm.
- *Add a planning timeline example*. It would be useful to have a more comprehensive timeline provided as an example, starting at the decision-making process through to the campaign, including training and communications components etc.
- *Strengthen the AEFI section*. Further guidance in this area is needed, along with clear messages and protocols to follow. In addition, the language currently causes more alarm than is needed, based on the data. Special attention should be paid to community-level messaging around AEFIs.
- *Add aide-memoires*. Add aide-memoires for district and health centre levels.
- *Enhance guidance around supervision and monitoring*. Supervision guidance should include gathering information to assess the CTC in the country, which will help build the global evidence base.
- *Consider integrated campaigns*. As more and more campaigns are being done in an integrated manner, consider adding a section on this.

Some IPAC members expressed concern about assuring adequate training and use of temperature threshold indicators. While it is essential to ensure that the vaccine is not exposed above the specified peak temperature, IPAC members observed that threshold indicators could undermine the strong long-term reliance on VVMs in situations where threshold indicators signal that the vaccine must be discarded and VVMs signal that the vaccine is appropriate to use. The committee requested more in-depth discussion on the utility of temperature threshold indicators. Members also raised concern with the precision of the definition of CTC, as previous definitions were not limited to vaccines that had regulatory approval for non-standard storage and distribution.

A revised version of the guidance, incorporating IPAC's comments, will be circulated to the committee in June.

Recommendations and Decisions by IPAC

1. IPAC welcomed and supported the "*The Use of Meningitis A vaccine in a CTC during campaigns*" guidelines and recognized the great effort and amount of work completed to date.

2. IPAC requested a dedicated teleconference to focus further on the guidelines, review changes that have been made, and obtain more background information on temperature threshold indicators.

3. Further, IPAC requested WHO to clarify the definition of CTC in relationship to on- and off-label implementation of this concept.

Session IV. Topic Updates

A. Visual cue icon refinement (*Jon Colton, IPAC)*

Prof Colton presented on the finalization of the design of the visual cue icons. All recommendations from the September 2011 IPAC meeting were accomplished. The approved visual cues were refined to improve legibility (increased widths of numbers and lines; increased white space around numbers in calendar icon). Non-production, prototype labels were test printed by Fiocruz and Sanofi Pasteur and placed on vials. These were sent to the IPAC members prior to the meeting for review and comment, which were generally positive. The icons may be further refined, depending on the results of the pilot study(ies).

B. Visual cue pilot RFP (*Xavier Bosch-Capblanch, IPAC and working group lead*)

Dr Bosch-Capblanch presented the draft Request for Proposals (RFP) text entitled "*Process evaluation of visual cue vaccine vials introduction*", on behalf of the visual cue subgroup (Xavier Bosch-Capblanch, Folake Kio-Olayinka, Chris Morgan and Rudi Eggers). He pointed out that the visual cue design and issues around the health workers' understanding have been resolved or addressed. IPAC previously decided that the visual cue will be introduced in countries in two phases (pilot introduction and then scale-up). The pilot introduction study is a "process evaluation" to inform scaling up and not an 'effectiveness' study of the visual cue on wastage reduction or safety outcomes.

Several clarifications were requested, including how pilot countries would be selected, how the regulatory aspects of introducing the visual cue in vaccine vials label will be handled, and how proposals will be evaluated. These issues will be addressed in the next version of the RFP. It was also noted that it would be essential to clarify beforehand the potential use of the findings to inform decision-making and eventual scale up of the visual cues. This will be addressed in the protocol phase of the study in which a detailed analytical plan and decision framework will be requested from the bidder.

Members agreed to provide further written feedback on the RFP to WHO and the subgroup within seven days after circulation of the next draft.

C. Programmatic suitability for pre-qualification of vaccines (*Rudi Eggers, WHO HQ)*

Following the last IPAC meeting, the newly established PSPQ Standing Committee met to conduct a "dry-run" using existing vaccines to test the Standing Committee's procedures and documentation. The Standing Committee consists of five members: Alan Brooks (chair), Julie Milstien, Abdulreza Esteghamati, Jane Soepardi (IPAC member), Robin Biellik (IPAC member). Alan Brooks resigned his position and has been replaced by Julie Milstein as chair. Subsequent to the dry run, the PSPQ SC process has been streamlined further, and the first vaccine review

(PCV13 in a pre-filled syringe) is under way. It is expected that the first review will be finally decided by mid-March. In addition, the malaria vaccine (RTSS14) was presented to the PSPQ SC for an opinion.

Recommendations and Decisions by IPAC

1. IPAC endorsed in principle the "*Process evaluation of visual cue on vaccine vial introduction*" request for proposals, subject to minor revisions. IPAC encouraged WHO to proceed with the pilot in a timely manner.

Session V. Programmatic Considerations of Alternatives to Thiomersal-Containing Vaccines

A. Update from WHO Informal Consultation to develop further guidance on vaccines for the UNEP Inter-governmental Negotiating Committee Meeting 4 (INC4), and Update from SAGE conclusions (*David Wood, WHO HQ*)

Dr Wood informed IPAC on the outcomes of a WHO scientific meeting conducted in April 2012, the purpose of which was to generate evidence feeding into deliberations of the Intergovernmental Negotiating Committee Meeting (INC4), an international body preparing a global legally binding instrument on mercury reduction. [1] The proposed treaty concerns the immunization community because thiomersal, a mercury-based preservative, is used in most multi-dose vaccine formulations. Key conclusions of the consultation were that a) the global burden of thiomersal among mercury-based products is extremely small; b) replacement of thiomersal with an alternative preservative may affect the quality, safety and efficacy of a vaccine; c) re-submission would require major work in re-testing and re-regulation with no guarantee of success; and d) there are no viable alternative preservatives available in the near- or mid-term.

Experiences by vaccine procurement agencies (UNICEF and PAHO) demonstrate that while single-dose vials are procured for newer vaccines such as DTP-Hep B-Hib, multi-dose vials (most of which are thiomersal-preserved) remain a critical part of immunization programs, and this perspective is also reported from countries. There would be a high risk of disruption to routine immunization programmes and mass immunization campaigns if multi-dose vials are not available. The consequences would be a predictable and sizable increase in mortality, for very limited environmental gain. There is insufficient existing manufacturing capacity to remove thiomersal and switch to single-use vials; and such a switch would require a substantial increase in costs and resources for implementation of immunization. There are some risks to vaccine access during the treaty negotiations: if countries opt for thiomersal-free vaccines, then they are likely to face interruption to vaccine supply, particularly for the most basic routine vaccines. In addition, IPAC was informed that environmental regulatory requirements may increase if the treaty is ratified, thus creating potential difficulties in access to thiomersal as a raw material in vaccine manufacture.

During their meeting deliberations in April 2012, SAGE expressed grave concern that current global discussions may threaten, without scientific justification, access to thiomersal-containing vaccines; reaffirmed that thiomersal-containing vaccines are safe, essential and irreplaceable components of immunization programmes; supported urgent global communications at the highest levels; and supported on-going dialogue between the health sector and the environment sector at global and national levels to facilitate a common understanding of the critical role of thiomersal-containing vaccines. Noting the potential threat to thiomersal-

[1] The documents from the WHO Informal Consultation to develop further guidance on vaccines for the UNEP Inter-governmental Negotiating Committee Meeting 4 (INC4) are located at: http://www.who.int/immunization/sage/meetings/2012/april/presentations_background_docs/en/index.html

containing vaccines, SAGE requested WHO to produce a report on the security of the supply of such vaccines and also encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.

B. Impact assessment of thiomersal-free vaccines on supply chain *(Anthony Battersby, WHO consultant)*

Mr Anthony Battersby presented an analysis which evaluates the financial, programmatic and environmental impact of removing thiomersal from vaccines. This research was based on a survey of manufacturers and modelling based on procurement patterns by UNICEF and PAHO, as well as available data from selected countries. The report highlighted that global production of pharmaceutical-grade thiomersal is sourced from one single producer at approximately 2,434 kg per annum, 64% of which goes to vaccines. This represents a negligible proportion of the environmental burden of mercury.

Development costs and time to shift to thiomersal-free vaccines are considered substantial, with clinical trials estimated to cost at least $1M per vaccine, with the outcome of trials and future vaccine stability unknown.

The likely increase in cost varies inversely with cost of vaccine, so that the cost increase to DTP is several hundred percent over current costs, and some vaccines such as influenza, are disproportionately affected. The annual cost of PAHO or UNICEF supplied vaccine is estimated to rise from $522 million to $855 Million. At country level, Kenya's vaccine costs would potentially rise from $45 million to over $55 million, with the cost of its air freight bill for international vaccine shipments rising by an estimated $750,000 per year; with a commensurate increase in carbon dioxide emissions.

Volume implications for cold chain storage are significant, varying from 165% to 324%, with major impact on central and peripheral stores. Workload implications go beyond expansion in funding, and affect storekeepers, clinic session staffing, training needs, and service provision. Outreach operations may also be significantly affected, with no current alternatives to multi-dose vials for use in extended outreach, birth dose outreach (e.g., hepatitis B vaccine) or campaigns (such as those for prevention of meningococcal). Waste management implications are of the order of a tripling of impact with a shift to all single-dose vials, increasing vial waste from 2,350 m^3 (based on 2011 PAHO and UNICEF procurement data) to between 3,850 m^3 and 7,600 m^3.

Overall removal of thiomersal would almost certainly lead to severe vaccine shortages. It would also entail: major impact on manufacturing, distribution, vaccine costs and environmental waste; greater workload for logistic and nursing staff; a transition period of the order of 10 years; and a high risk of serious program disruption. Absence of thiomersal would also seriously interfere with the manufacture of particular vaccines such as pertussis and seasonal and pandemic influenza vaccine.

C. Discussion Points *(Chris Morgan, IPAC and lead focal point)*

Dr Morgan synthesized the key evidence presented and proposed language for IPAC to consider as a committee statement, with emphasis on programmatic concerns.

Discussion:

IPAC members discussed the safety assurances relating to thiomersal, noting that a recent update of evidence for safety had been considered by SAGE and GACVS. Members discussed alternative technologies to thiomersal, including mechanical approaches to drawing multiple doses in an aseptic manner as well as alternative preservatives, noting that no satisfactory option is currently feasible. Members noted that other important stakeholders, including GAVI, PATH and a representation of manufacturers, continue to align with the WHO position, and

members discussed the need for communications to involve a broad range of partners, including those beyond the health sector. Discussions identified the need to develop a long-term vision, with a strong basis in programmatic requirements, for future vaccine formulations, presentations and delivery systems.

It was noted, however, that the evidence presented was based on interviews and modelling and therefore, concrete figures on burden of cold chain and costs may be subject to great variability.

IPAC concluded it is essential that thiomersal-containing vaccines be exempted from the legally binding global instrument being drafted to reduce or abolish mercury-containing products. The programmatic issues for countries to consider are significant. The consequences for immunization programs of removing thiomersal from vaccines include the risk of losing access to some vaccines currently in high use at low cost (e.g., TT, DTwP, and hepatitis B vaccines). Immunization services would be severely disrupted if multi-dose vials that require thiomersal were no longer available. Implications include multi-fold increases in the costs of vaccines, and their transportation and storage, in addition to increased workload of logistic and nursing staff and the increased cost and complexity of waste management. Evidence from one study elaborating a theoretical scenario presented in IPAC suggested that the annual vaccine costs may be expected to rise by over 60% and shipping costs to rise in the order of 120%.

Members noted the need to make credible information readily available to countries to respond to community and professional concerns regarding the effect of the non-removal of thiomersal. It was stressed that communications need to include deaths averted through the use of vaccines that contain thiomersal and the potential consequences in terms of deaths and disease as a result of disruptions in vaccination programs.

Recommendations and Decisions by IPAC

1. IPAC concluded that the abrupt removal of thiomersal-containing vaccines would be extremely disruptive with disastrous consequences for vaccination programs and infant, child, and maternal health, likely resulting in increased mortality and morbidity. As a result, IPAC concluded that it is essential that thiomersal-containing vaccines be exempted from the global mercury-free treaty. IPAC noted that there are severe programmatic consequences of a shift away from thiomersal-containing vaccines, including interruption to vaccine supply and dramatic increases in program costs and resource requirements for countries to manage such a change.

2. Although IPAC recognises and supports the global initiative to reduce exposure to mercury in the environment, IPAC supports the position expressed by SAGE that thiomersal-containing vaccines are safe, essential, and irreplaceable components of immunization programs, especially in developing countries, and that removal of these products would disproportionately jeopardize the health and lives of the most disadvantaged children worldwide. Thiomersal-containing vaccines are estimated to avert at least 1,400,000 childhood deaths each year.

3. IPAC called for an intensified and unified effort at global and national levels to improve communication strategies to inform decision-makers and the wider public about the negative effects of a rapid transition away from thiomersal, using a wide set of partnerships beyond the immunization and health sectors.

4. IPAC recommended that WHO build upon the opportunity presented by the global initiative to remove mercury from the environment to heighten attention to improving vaccine formulations, presentations and packaging, logistics, program delivery, vaccine wastage, and waste disposal systems. IPAC calls for an intensive research investment into programmatic improvements (e.g., new technologies for maintaining sterility when

withdrawing doses from a multiple dose vial, new requirements for vaccine handling, logistics and waste disposal, etc.). Furthermore, as countries will come under increasing pressure to reduce environmental exposure to mercury, IPAC supports continued research into effective, feasible and affordable alternatives for new vaccine preservatives.

5. IPAC requested feedback from INC4 consultations at IPAC's October 2012 meeting.

Session VI. Hepatitis B birth dose implementation

A. Summary of progress since April 2011 (*Robin Biellik, IPAC member and working group lead)*

The implementation of the hepatitis B vaccine birth dose was discussed at the April 2011 IPAC meeting. At that meeting, IPAC members provided inputs on the draft WHO background paper developed by Burnet Institute entitled "*Best practices and needs for the delivery and monitoring of hepatitis B vaccine birth dose*." Subsequently, three external peer reviewers also provided extensive comments.

Incorporating the feedback received from IPAC and external peer reviewers, Ms Priya Mannava and Dr Chris Morgan of Burnet Institute substantially revised the paper, which is now entitled: "*Practices to improve coverage of Hepatitis B birth dose vaccine*." Substantive revisions include the extension of the literature search through March 2012, a major reorganization and re-examination of the evidence in the form of a systematic review, with evidence graded in accordance with WHO standards, and significant streamlining of the language with better alignment for the target audience. The support of the AusAID's Compass: Women's and Children's Health Knowledge Hub was acknowledged.

In April 2011, IPAC further recommended that appropriate guidance materials on the implementation of hepatitis B vaccine birth dose be developed. CDC Atlanta agreed to lead in developing a management manual in collaboration with Burnet Institute and WHO. The document, which is still in its conceptual stage, will include a policy brief, job aides and a programme manager's problem-solving guide. A session of the IPAC Hepatitis B Birth Dose Working Group (Robin Biellik, Chris Morgan) has been scheduled for 19 April 2012 to define the programme of work.

Dr Biellik emphasized that Dr Morgan would maintain his role as a WHO consultant during this session, and would recuse himself from IPAC deliberations on the paper.

IPAC members were requested to:

- endorse the updated *Practices to improve coverage of Hepatitis B birth dose vaccine* document for WHO publication;
- confirm that it constitutes a satisfactory evidence base for the development of complementary operational materials on planning and implementing Hepatitis B birth dose; and
- Provide input on the proposed contents / outline for those operational materials.

B. Revisions to document on implementation practices (*Priya Mannava and Chris Morgan, Burnet Institute, Melbourne*)

Dr Morgan, acting in his role as WHO Consultant, presented the revised version of the review of practices to improve coverage with hepatitis B birth dose vaccine. The presentation noted that effective practices to improve hepatitis B birth dose coverage included:

- service delivery arrangements to increase access to skilled childbirth care, integration of vaccination with maternal and newborn care (detailing some specific practices to enable this), linkages with private providers and special measures to reach infants born outside health facilities;
- health workforce considerations addressing attitudes, specific training, and options for task shifting to expand available vaccinators;
- medical technologies that allow storage of vaccine close to the location of birth, consideration of Uniject™ presentations of the vaccine and the need to maintain supply of monovalent formulations;
- health information practices for birth registration, pregnancy tracking and accurate definition of the birth dose (as within 24 hours of birth) in national and regional monitoring;
- financing arrangements that provide adequate funding and minimise costs to families;
- addressing community concerns including planning communications to address the potential of coincidental newborn deaths; and
- leadership and governance practices such as clear national policy, guidance that accurately defines the birth-dose, strong central communications, and consideration, where appropriate, of use of the vaccine in controlled temperature chain or the accreditation of additional vaccinators.

The presentation also noted the importance of harmonising references to hepatitis B birth dose vaccination, with accurate definition of timeliness in global, regional and national guidelines when addressing the newborn period. Dr Morgan also noted potential linkages to other technical consultations within WHO, such as those for community-based postnatal care.

C. Update on Hepatitis B vaccine birth dose guidance materials (*Nancy Glass, CDC Fellow)*

In 2006, the WHO Western Pacific Regional Office (WPRO) produced an operational field guide entitled "*Preventing mother-to-child transmission of Hepatitis B*". The CDC has agreed, in collaboration with the Burnet Institute, WHO HQ and WPRO, to develop a management manual that builds on the WPRO manual and is applicable in the global context. The proposed title for the manual is "Implementation and Strengthening of the National Perinatal Hepatitis B Vaccination (Birth Dose) Program: Guide for EPI Program Managers" and will contain:

- a policy brief for national programme managers responsible for advocating for hepatitis B birth dose;
- job-aides on how to introduce birth dose; and
- a problem-solving guide for programme managers addressing low hepatitis B vaccination coverage in facility-based and home-births.

An outline of the manual listing the proposed chapters and annexes was distributed at the meeting for comments and suggestions.

Discussion:

IPAC members universally commended the Burnet Institute for the rigorous revisions to the document "*Practices to improve coverage of Hepatitis B birth dose vaccine*", referring to the document as an excellent review which is more complete and well-structured than the earlier version. IPAC members provided a series of comments and suggestions to further improve the document prior to finalization. Members expressed that the analysis of best practices constitutes a "scoping review" rather than a "systematic review". The authors agreed to take all comments and suggestions into account at the Working Group meeting on 19 April.

Recommendations and decisions by IPAC

1. IPAC endorsed in principle the "*Practices to improve coverage of the hepatitis B birth dose*" document with modifications, including the substitution of the term "systematic review" by "scoping review", a brief description of the quality of evidence attached to

the description of findings, and a 'toning down' of some of the recommendations statements (*Vote: unanimous consensus*).

2. IPAC confirmed that this document should be used as part of the evidence-base for the development of complementary operational materials on planning and implementing a hepatitis B vaccine birth dose guideline (*Vote: unanimous consensus*). IPAC noted that the document, while an essential piece of the evidence base on hepatitis B birth dose practices, is not suitable in isolation as a basis to set policy direction.

Session VII. Multi-dose Vial Policy

A. Country Implementation of multi-dose vial policy (*Diana Chang Blanc, WHO HQ*)

The objectives of this analysis were to consolidate information from regions and countries on the implementation of the multi-dose vial policy (MDVP) in WHO member states and to identify key deviations in national policy application from the global WHO policy. Country implementation status and deviations from the current global MDVP help provide context prior to revisions of the current policy.

National MDVP data were collected from 75% of 194 WHO member states; nearly 60% of member states have an established national MDVP. Of countries with an established MDVP, 58% of these policies have at least one deviation from the global MDVP. The most common deviations of national policies from the global MDVP are modified discard time limits for open vial use in a subsequent immunization and application of MDVP to outreach sessions. Of countries with an established MDVP, 39% articulate a modified time limit. The 6 hour limit for reconstituted vaccines was relatively unchanged; however, the 28 day limit for liquid vaccines was reduced to 14 days or less, primarily clustering around 7 days. It should be noted that these modified discard time limits were most commonly reported by countries in the European and West African regions. In terms of limiting the application of the MDVP to fixed immunization sites only, this was not common, but was most frequently reported in South-East Asia (5 countries) and Europe (8 countries). In conclusion, a revision to the WHO global MDVP would impact many Member States, but the policy if well-articulated should pose no problem for countries to adapt.

B. Trends in multi-doe vaccine vial use in UNICEF procuring countries, 2000-2011 (*Jodi Liu, WHO consultant*)

Trends in multi-dose vaccine vial use were evaluated as part of developing the evidence-base for a revision to the MDVP. The objectives of this study were to identify national trends in multi-dose vaccine vial use and to assess factors influencing the change in the use of various vial sizes in UNICEF procuring countries during 2000 to 2011.

The evolution of multi-dose vial use contains micro-patterns but no clear overall pattern was observed over 2000-2011 with DTP-based, hepatitis B, and measles-containing vaccines in UNICEF procuring countries. Over the study period, shifts from larger to smaller multi-dose vials, and vice versa, have occurred. DTP procurement shows preference for 10 dose over 20 dose vials, although the number of procuring countries has decreased over time. Two countries switched from 1 to 10 dose presentations of DTP-Hib. DTP-HepB/Hib procurement has largely been dictated by global supply availability and has shifted from 2 to 1 to 10 dose vials. With the increasing use of pentavalent vaccine, hepatitis B procurement has shifted from 10 to 1 dose vials to accommodate hepatitis B vaccine birth dose. No trends were observed with DTP-HepB and measles-containing vaccines, which are most commonly used in 10 dose vial presentations. However, recognition of country interest for 5 dose vials of measles vaccine has been increasing.

The use of multi-dose vials is affected by global supply and country-driven preference, which may be influenced by a combination of factors such as price, funding sources, cold chain requirements, wastage and safety concerns, programmatic feasibility, and historical usage. Although the use of different vaccine presentations has changed over the past decade, multi-dose vials remain commonly used in UNICEF procuring countries and remain a vital part of immunization programmes.

C. Update on multi-dose vial policy revisions (*Diana Chang Blanc, WHO HQ*)

Ms Chang Blanc updated IPAC on key steps undertaken towards the revision of MDVP since the September 2011 meeting. An issues paper and an activity plan have been drafted to which working group members have contributed (Robert Steinglass, Francois Gasse, Jon Colton, Najwa Khuri-Bulos, Thierry Gastineau). About fifty percent of activities in the work plan have advanced, with the two preceding presentations representing key outputs.

Remaining activities will take additional time to undertake, so an interim action will be to update individual prequalified web pages to include applicability of MDVP, product by product, to facilitate interpretation by country. This will require screening of all prequalified products for proper categorization.

To date, there are no compelling scientific reasons or programmatic benefits to alter the 6 hour or 28 day discard points. Furthermore, the study on MDVP implementation in Member States demonstrates that most countries apply these limits; about twenty surveyed countries from two regions concentrated around ≤ 7 day discard.

The three substantive issues remain the outcomes of the visual cue pilot, the placement change of the vaccine vial monitor for certain vaccines and the need to further define 'appropriate cold chain conditions'. Work in these areas will continue to proceed.

Discussion:

IPAC members noted the lack of data on the implementation of the policy at operational level and their impact on vaccine wastage, particularly as reliable vaccine wastage calculations are difficult to retrieve at country level. Brazil has recently published an article on vaccine wastage, but the country does not apply the MDVP. There are still limited data on whether the application of MDVP leads to wastage reduction and cost savings, as is often presumed. The Fiji wastage study currently under development may provide more information. There is growing recognition that 5-dose vials, as opposed to 10 dose or 20 dose vials, can bring programmatic value in certain settings.

Members remarked on the inter-relationship between the issue of thiomersal and MDVP, and the need to maintain a long-term perspective on the revision because of the changing landscape. As countries shift to one-dose presentations, MDVP may lose its relevance over time. When drafting the policy, WHO was encouraged to proceed with the assumption that visual triggers (VVM, visual cue) will be in force.

Discussion on the scientific basis behind the 28 day time limit was raised, with some promoting the idea to abolish the time-limit altogether as it is based on estimated vaccine supply delivery cycles at peripheral level rather than scientific necessity. However, most countries apply the 28 day time limit, so changing a policy that is well-understood in the field would need to be weighed against any marginal benefit that could be gained from the change in message and practice.

Members were requested to provide any additional feedback on the MDVP issues paper within the next seven days.

Recommendations and Decisions by IPAC

1. IPAC recognized the importance of the work conducted on MDVP since its September 2011 meeting. IPAC is looking forward to feedback on future outputs.

2. IPAC recommended that WHO take a long-term perspective for MDVP revision and give careful consideration to the programmatic issues impacted by or inter-related with MDVP.

Session VIII. Immunization in Practice (IIP)

A. Revisions to Immunization in Practice (*Jhilmil Bahl, WHO HQ*)

The last version of the Immunization in Practice document was published in 2005. It now is only accessible at http://www.who.int/immunization_delivery/systems_policy/training/en/index1.html.

A detailed table of contents was shared with IPAC members in February 2012 and members gave very extensive feedback which will be incorporated in the revision. The IPAC meeting session focused on issues for which WHO will seek further guidance from IPAC members, including disease and vaccine listing, how to handle different presentations of the same antigen, trade-offs between print media and internet, and proper cold chain conditions.

A session of the IIP Working Group (Folake Kio-Olayinka, Jean-Marc Olivé, Francois Gasse) has been scheduled for 19 April 2012 to focus on the Microplanning module. The timeline for development of IIP is early 2013, with draft versions available in late 2012.

Members were requested to provide any additional feedback on the IIP table of contents within the next seven days.

Discussion:

Meeting participants widely recognized IIP as a useful field guide and resource for health workers as well as partner staff. Some members stressed the importance of keeping the guide simple and not too bulky. Others leaned towards a more comprehensive guide as sometimes the handbook is the only resource available in the field and used by staff at all levels.

Discussion turned to the idea of producing a comprehensive 'modular' set on the web, with support to countries who choose to 'print on demand' those modules most relevant to them. Having a web-based version would also make the update process easier as polices will continue to change in the coming years. While this idea was considered valuable, there remained insistence that a print-based core version was still required as sub-national levels do not have adequate internet connectivity to download large versions of material.

Members observed that 'Immunization in Practice' will incorporate several practice issues that are being discussed in IPAC (e.g., visual cue, controlled temperature chain, multi-dose vial policy); it is therefore critical for WHO to approach the development of this document collaboratively, engaging widely IVB staff, IPAC and key partner agencies.

Members suggested conducting a 'market survey' of field users and asking what they would like included in the updated guide and in which format. In terms of next steps, WHO agreed to execute this; additionally, WHO will conduct further discussion in the department on the best format for the guide, taking into account feedback provided by IPAC members.

Recommendations and Decisions by IPAC

1. IPAC reiterated strong support for "Immunization in Practice" and recognition of the need for this reference manual.

Annex A: IPAC working group composition

	IPAC	WHO region	WHO focal point
Controlled Temperature Chain	Francois Gasse* Thierry Gastineau Jane Soepardi Debbie Kristensen		Michel Zaffran
Hep B birth dose	Robin Biellik* Chris Morgan		Diana Chang Blanc
Immunization in Practice	Francois Gasse Folake Kio-Olayinka Jean-Marc Olivé		Jhilmil Bahl
Programmatic Suitability of Vaccine Candidates for WHO Prequalification PSPQ	Robin Biellik Jane Soepardi		Rudi Eggers Nora Dellepiane
Rotavirus Vaccine: consequences of age limitations on vaccination programme	Robin Biellik Robert Steinglass*	Nadia Teleb (EMRO)	Jhilmil Bahl
Rotavirus Vaccine: Vaccine safety-related	Shelley Deeks Najwa Khuri Bulos		Ana-Maria Henao Restrepo
Routine and Supplemental Doses	Vance Dietz Folake Kio-Olayinka*		Tracey Goodman Tony Burton
Visual Cue (to transition to MDVP)	Robert Steinglass* Francois Gasse Najwa Khuri-Bulos Jonathan Colton	Richard Mihigo (AFRO) Oommen John (SEARO)	Rudi Eggers
Multi-dose Vial Policy	Robert Steinglass Francois Gasse Najwa Khuri-Bulos Jonathan Colton Thierry Gastineau	Martha Velandia (PAHO)	Diana Chang Blanc
Visual Cue Pilot	Xavier Bosch-Capblanch* Folake Kio-Olayinka Chris Morgan		Rudi Eggers
Vaccine Presentation and Packaging Advisory Group VPPAG	Robert Steinglass Debbie Kristensen Osman Mansoor		Solo Kone
Vaccine Safety	Najwa Khuri- Bulos		Patrick Zuber

* Lead focal point

REPORT ON THE IMMUNIZATION AND VACCINES RELATED IMPLEMENTATION RESEARCH (IVIR)

Advisory Committee Meeting
Geneva, 25-26 September 2012

Executive Summary

(Preliminary draft)

- The sixth meeting of the IVIR advisory committee was held 25-26 September 2012 in Geneva, Switzerland. The name of the advisory committee has now been changed from QUIVER (Quantitative Immunization and Vaccines Related Research) to IVIR (Immunization and Vaccines related Implementation Research) so that it can incorporate immunization systems issues as well as quantitative methods in evaluating vaccines.

- WHO is in the process of developing an Implementation Research priority setting framework. They have set up an ad hoc working group and are in the process of prioritizing the research questions. IVIR is positive about the priority setting approach and methods used. However, the members feel that more thought should be given to whether or not to shorten the list of proposed research questions to be prioritized (currently 86 priority questions) and reformat the questions to reduce the burden on the respondents. In addition, IVIR believes that a wide number of stakeholders should be involved, particularly from the countries and each of the six WHO regions.

- The Johns Hopkins School of Public Health International Vaccine Access Center is using Value of Statistical Life (VSL) to value a fatality or injury prevented through vaccination in monetary terms. IVIR members believe that Cost Benefit Analysis (CBA)/Value of Statistical Life (VSL) and Cost-Effectiveness Analysis (CEA) address different questions and that VSL has not been as widely used in the health sector. They believe that there are technical challenges to the measures that have not been fully addressed. The committee believes that VSL may provide valuable complementary information but should not be used as the basis for priority setting in vaccines at this time. In theory, the VSL method is appropriate to decide whether a vaccine should be introduced, but empirical evidence is lacking, particularly in low- and middle-income countries (LMICs). The IVIR-AC recommends case studies using both CBA/VSL and CEA for economic evaluation of vaccine introduction using similar datasets in LMICs.

- WHO established a working group to assess yellow fever disease burden. Improving evidence on yellow fever will help inform decisions about vaccination as well as GAVI decisions about what to invest. The working group is tasked with providing information on unpublished sources of yellow fever data and to provide input into the methods used to estimate burden in Africa. Imperial College London was commissioned to coordinate and carry out the work. The working group proposed two approaches to estimate burden of disease: (1) estimate the annual risk of infection from the age distribution of observed cases; and (2) estimate the basic reproduction number from reported outbreak sizes. Preliminary estimates are expected to be presented to WHO and partners in late October with final estimates by the end of 2012. Next steps will be the evaluation of YF control strategies, support policy-making and peer-review publication. It was noted that it will be important to distinguish between yellow fever and jaundice possibly due to other causes.

- Work on the broader benefits of vaccination addresses requests from external stakeholders as well as in-country decision-makers, such as Ministers of Finance, for outcomes of economic evaluations beyond traditional measures (e.g., cost per QALY/DALY). The intended outcome is to develop tools and methods that could capture broader impacts of vaccination, in a way that is useful to stakeholders and feasible to measure. So far, this work has involved two expert consultations (Toronto 2011 and Geneva 2012), a stakeholder survey, and a literature review. In addition, four groups have responded to a request for proposals to develop innovative tools and have begun conducting their proposed packages of work. IVIR members recognize that measurement of broader economic impact of vaccines is important to estimate and thinks that the proposed theoretical framework is appropriate. However, it is more difficult to estimate indirect effects of vaccines – i.e., the specific mechanisms to deal with confounding have not yet been worked out and there are deficiencies in basic data. IVIR recommends that there should be a continued effort to try to find better mechanisms to measure these causal relations. It is also important to think about including variables that measure broader impact in the design of RCTs to improve the likelihood that indirect effects can be evaluated.

- WHO is continuing to support an investment case for measles and rubella eradication. IVIR is encouraged by the investment in properly modeling eradication before the measles end game is reached. However, they continue to emphasize the need to consider heterogeneity in vaccine uptake, which is a key driver during the eradication phase. This requires models that do not simply aggregate entire populations, as well as exploration of the behavior of vaccine refusers and hard-to-reach groups within individual countries. It is also important to conduct an assessment of risks associated with elimination campaigns, issues associated with first dose vs. second dose, and costs of outbreaks. IVIR suggests that data from the experience of the Americas in eliminating measles and rubella could be evaluated and used for some of these risk assessment analyses.

- WHO has developed a cervical cancer prevention and control costing (C4P) tool. IVIR reviewers believe that the methods used in the WHO C4P tool are appropriate. They feel that the costing tool could be very helpful for national program managers in planning for the introduction of HPV vaccination, as well as screening and treatment once that module is completed. They suggest some modifications that could further enhance the tool: (1) include an optional module for capturing societal costs (user and indirect/productivity costs); (2) provide a sensitivity or scenario analysis, including allowing for different vaccination schedules; (3) include more monitoring and evaluation costs, particularly for cancer registries for the screening and treatment module; (4) include an optional module for local data collection for countries that have decentralized health systems; and (5) add more information on cost calculations to the user guide.

- A proposal to use emulation in order to incorporate transmission dynamics (herd immunity) into static models of immunization (such as WHO-CHOICE's PopMod, PAHO's TriVac, and LiST) was presented. The plan is to use PopMod as an exemplar, and incorporate herd effects from a dynamic model of rotavirus vaccination into PopMod. An emulator would then be used to allow PopMod to model parameter sets that had not been explicitly used in the original dynamic model. IVIR members believe that both static and dynamic models have benefits and drawbacks. The proposed approach is to merge the emulator with the static model. This approach has promise but also has some drawbacks. IVIR members suggest that the model be pilot tested. They also feel that there should be some exploration of what would be required to provide the kind of modeling tool that will incorporate the benefits of static and dynamic modeling.

- WHO commissioned a study on the burden of disease of varicella and herpes zoster. IVIR members believe that the proposed methods to investigate the burden of disease of varicella and herpes zoster are appropriate but are concerned about the lack of data, especially in African countries. For this reason, they suggest that the working group evaluate other existing sero-prevalence data, as well as data from Latin American countries that have introduced varicella vaccine. Even in the absence of hard data, modeling can play a role in estimating the impact of vaccination. IVIR members also suggested some medium-term solutions to the lack of data: (1) include zoster in existing surveillance systems; and (2) test for varicella antibodies in existing serum samples in Kenya and other countries.

POLIO ERADICATION ENDGAME (2013-2018)

STRATEGIC PLAN & LEGACY PLANNING

Global Polio Eradication Initiative

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1. PURPOSE

On 26 May 2012 the World Health Assembly (WHA) declared the completion of poliovirus eradication to be a programmatic emergency for global public health and called for the development of a comprehensive polio endgame strategy.[1] In response, the Global Polio Eradication Initiative (GPEI) has developed this Endgame Strategic Plan in consultation with national health authorities, scientific experts, global health initiatives, donor partners and other stakeholders. This Plan outlines the strategic approach to the eradication of all remaining polio disease - due to both wild and vaccine-related polioviruses –, the management of poliovirus risks in the post-eradication era, and the development of a process for transitioning the GPEI infrastructure as the programme comes to completion. Particular attention has been given to aligning this Plan with the goals, objectives and major activities of the Global Vaccine Action Plan (GVAP).[2]

This Endgame Strategic Plan outlines at a high level the necessary activities to complete the polio eradication initiative over the period 2013-2018. The timeline is based on the epidemiology of polio globally at end-2012, the recent rate and trend in OPV campaign quality improvements in the remaining polio-infected areas, new understanding of the risks posed by vaccine-related polioviruses, and, the recent development of new strategies and tools for managing post-eradication risks. The Plan runs parallel to the GPEI Emergency Action Plan 2012-2013 which outlines specific activities to complete wild poliovirus eradication in specific geographies.[3] Beyond 2013 this Plan will be complemented by new bi-annual operational plans that outline the specific activities and tactics needed to achieve the Plan's outcomes based on the evolving epidemiology of polio and the priorities for managing the vaccine-related and post-eradication risks. With full implementation of this Plan, polio will be the first disease of humans to be eradicated from the face of the Earth in the twenty-first century.

This document also frames the process for planning the polio 'Legacy', building on the polio programme's achievements and experience, to sustain a polio-free world after programme closure and to ensure that the assets, learnings, capacities and workforces developed in the fight against polio are applied to other major public health challenges.

2. STATEMENT OF INTENT

The goal of this Plan is to complete the eradication and containment of all wild, vaccine-related and Sabin polioviruses, such that no child ever again suffers paralytic poliomyelitis.

[1] Resolution WHA65.5 'Poliomyelitis: intensification of the global eradication initiative'
[2] Resolution WHA65.17 'Global vaccine action plan'
[3] EAP available at:
http://www.polioeradication.org/resourcelibrary/strategyandwork/emergencyactionplan.aspx

3. CONTEXT

In January 2012, a fourth WHO Region (South East Asia) became polio-free as India passed the milestone of one year without a single case. As India was reaching this milestone, however, case numbers doubled in 2011 in the three remaining polio-endemic countries: Afghanistan, Pakistan, and Nigeria. Given the increasing evidence from recent outbreaks of the terrible consequences of failure, but also the potential for success as shown by India, in May 2012 the WHA declared the completion of polio eradication a programmatic *emergency for global public health*.[4] In all three remaining polio-endemic countries, national emergency action plans were established to reach every child with the polio vaccine; and in each country oversight bodies were established that answer directly to their heads of state to scrutinize implementation and ensure accountability for the quality of key activities. The core GPEI partners restructured their polio programmes to reflect this emergency and a massive surge of technical assistance was deployed to the highest risk areas for polio to assist governments with strategy implementation. By mid-2012 thousands of additional polio workers were applying new tactics, including lessons from India, to reach every child in the remaining infected areas; by end-2012 independent analyses were concluding that these course-corrections were improving OPV campaign coverage such that the worst-performing infected areas were now on track to stop transmission by end-2014[5].

The World Health Assembly (WHA), the annual meeting of the Ministers of Health of all Member States of the World Health Organization (WHO), first committed to polio eradication when it adopted resolution 41.28 in 1988 calling for the worldwide eradication of the disease by the year 2000. That marked the launch of the GPEI, spearheaded by national governments, WHO, Rotary International, the US Centers for Disease Control and Prevention (CDC) and UNICEF. At that time, more than 125 countries were endemic with the disease and each year more than 350,000 children were paralyzed for life by polio. Since 1988, the GPEI has reduced the global incidence of polio by more than 99%, three of six WHO Regions have been 'certified' polio-free (the Americas Region in 1994, the Western Pacific in 2000 and the European Region in 2002), and one of the three wild poliovirus serotypes (type 2) has been eradicated (last isolated in 1999). Through the GPEI, more than 10 billion doses of oral polio vaccine (OPV) have been administered to more than 2.5 billion children worldwide; more than 10 million people are today walking who would otherwise have been paralysed; and, over 1.5 million childhood deaths have been prevented through the administration of Vitamin A during polio campaigns.

As progress towards wild poliovirus eradication accelerated in the late 1990s, new risks to a polio-free world became apparent. Vaccine-derived polioviruses (VDPVs) were – rarely – found to be able to regain the ability to both circulate and paralyze, causing polio outbreaks due to circulating VDPVs (cVDPVs) and – even more rarely – VDPVs were shown to persist for years in some individuals with primary immunodeficiency syndromes (i.e. as 'iVDPVs'). It has since been confirmed that cVDPVs can become biologically equivalent to wild polioviruses, causing severe paralysis, bulbar polio, and death, and can circulate indefinitely in areas with immunity gaps. By 2005, expert polio eradication and immunization advisory bodies concluded that addressing these risks in a comprehensive manner,

[4] Notably outbreaks in adults in DR Congo 2010-2011 caused by type 1 wild poliovirus
[5] Global Good analyses – Nigeria & Pakistan 2012.

and eliminating all paralytic polio disease, would ultimately require stopping all use of oral poliovirus vaccines (OPV) globally as part of the polio eradication endgame. In May 2008, in line with guidance from WHO's Scientific Advisory Group of Experts on immunization (SAGE), the WHA endorsed the principle of synchronized OPV cessation globally, requesting acceleration of the programme of work on post-eradication risk management, including if and when appropriate, establishing a timeline for the eventual cessation of the use of OPV in routine immunization programmes.[6]

Throughout the GPEI, commentators and stakeholders have highlighted that key achievements of this public-private partnership could and should be built on for the broader global good. The GPEI has faced extraordinary challenges - technical, programmatic, financial, geopolitical - but has developed capacities to meet those challenges and has learned lessons that can be applied to other global health initiatives. After more than 20 years of implementation, the principal achievement that stands out is the capacity to reach the "fifth child" (i.e. the 20 percent of all children globally who are not reached with other health services, even routine immunization). This achievement has translated into an expanded global surveillance and response capacity and the ability to deliver basic services to the most marginalized and vulnerable populations in the world. These capacities have wider utility beyond the polio programme. A central element of the polio 'legacy' must be to garner the programme's potential to contribute to improving routine immunization coverage and the delivery of other health interventions, , and to conduct surveillance and response activities for other important diseases. With sufficient funding and support, other global health programmes can benefit from the experience, lessons learned, and assets of the polio programme for the greater global public good.

[6] Resolution WHA61.1: 'Poliomyelitis: mechanism for management of potential risks to eradication'

4. ENDGAME STRATEGIC PLAN – MILESTONES & MAJOR CHALLENGES

The ultimate milestone of the endgame strategic plan is global certification of wild poliovirus eradication by end-2018. Achieving this milestone, and the overall goal of this Plan, requires interrupting wild poliovirus transmission by end-2014 and stopping all routine immunization with type 2 oral polio vaccine in a globally synchronized manner at some point during the period 2015-2016 (Table 1). There are major challenges to achieving each of these milestones.

Table 1: Key Dates

DATE	MILESTONE
End-2014	Interruption of residual wild poliovirus transmission
During 2015/6	Synchronized switch of trivalent OPV with bivalent OPV globally
End-2018	Global Certification
During 2019	bOPV Cessation

Most immediately, and significantly, three of the four polio-infected countries at end-2012 – Afghanistan, Pakistan, and Nigeria – have never interrupted the transmission of indigenous wild polioviruses. Furthermore, viruses from these endemic areas, particularly Nigeria, have regularly re-infected polio-free areas leading to importation-associated outbreaks and, in four previously polio-free countries, the re-establishment of persistent transmission. Although no such international spread has occurred in 2012 as of end-October, importations will remain a significant and constant threat until all wild poliovirus is interrupted globally. At end-2012, independent analyses of the impact of the GPEI Emergency Action Plan 2012-2013 concluded that the combination of innovations being applied in the remaining endemic areas to improve programme oversight and accountability, field operations, and community demand was translating into improved OPV campaign coverage trends such that all of these countries were on track to achieve the population immunity thresholds needed to stop transmission by end-2014. This plan summarizes the national and international actions detailed in the GPEI Emergency Action Plan to sustain this progress while addressing emerging threats, including in the areas of security, suspension of vaccination, and political change.

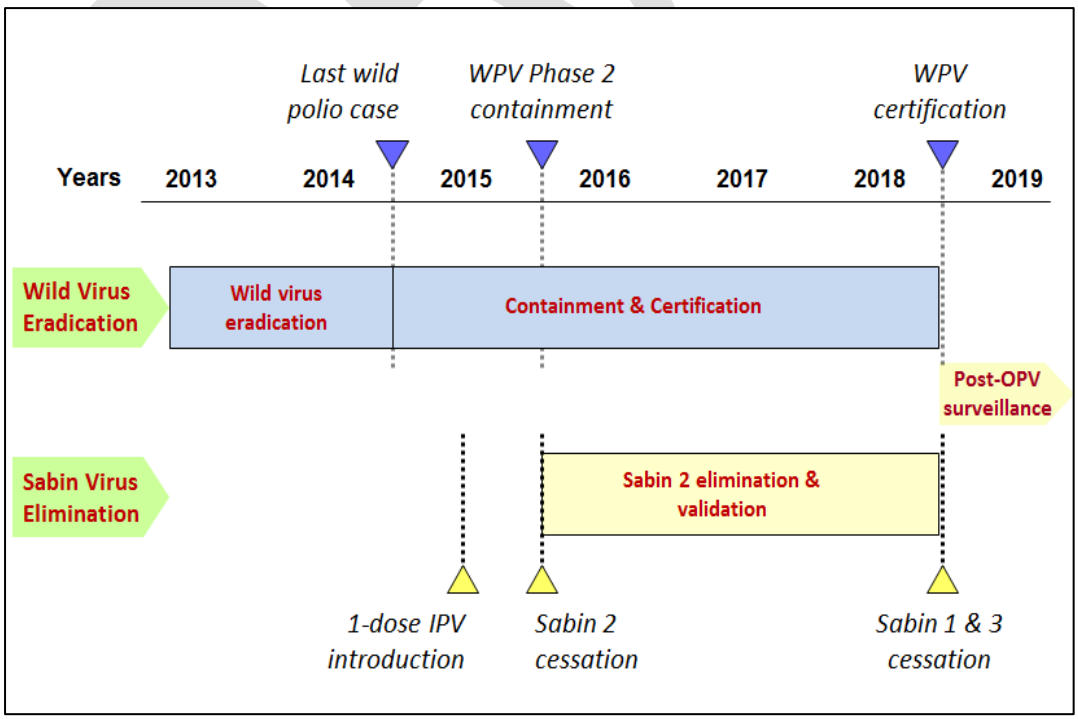
Achieving the globally synchronized cessation of routine immunization with type 2 oral poliovirus vaccine (OPV) faces a combination of logistical, communications, vaccine supply and programmatic challenges across a much greater geographic area given that over 125 countries were using trivalent OPV as of end-2012. The recent availability (2009), and proven efficacy of bivalent OPV against the remaining wild polioviruses type 1 and 3 serotypes is central to the new endgame strategy. While a sufficient and secure international supply of this product will by end-2013 be available for an eventual tOPV-bOPV switch globally, all countries relying on national tOPV production will need to develop and license a bivalent product. More complicated will be ensuring the availability of sufficient supplies of inactivated poliovirus vaccine (IPV) – at an affordable price – to allow all countries to introduce at least 1 dose of this product into their routine immunization programmes in advance of the tOPV-bOPV switch. As daunting are the logistical challenges of synchronously switching all OPV-using countries from tOPV to bOPV, withdrawing the tOPV field stocks, and safely destroying or containing residual vaccine virus. Accompanying this logistical work will be a

significant communications effort for the parents whose children will receive the new vaccine schedule, and training of the health workers who must implement it. This Plan outlines the strategic approach to OPV2 cessation and the activities required to address the associated challenges. Operational plans for each of these aspects will be updated and refined as the programme of work on post-OPV risk management is implemented.

The global certification of wild poliovirus eradication – and verification of the elimination of type 2 vaccine-related viruses – will require ensuring highly sensitive poliovirus surveillance, and full application of relevant poliovirus biocontainment requirements, across the entire world. Chronic gaps in surveillance sensitivity will need to be addressed in recently infected countries as well as those which have long been certified as polio-free, overcoming complacency, weak health systems, geography, insecurity and other challenges to identifying and investigating paralyzed children. International consensus will need to be confirmed on the final biocontainment requirements for the safe handling of residual polioviruses (e.g. for vaccine production, research, diagnostics); the necessary inventorying, destruction and containment activities will then need to be implemented and verified in all countries. As importantly, international consensus will be required on the criteria and processes for reintroducing live poliovirus vaccines to respond to any reintroduced or emergent polioviruses after OPV cessation. This Plan summarizes the certification process and major criteria, and explains the approach that will be taken to achieve the necessary surveillance sensitivity globally and implement containment.

Figure 1 illustrates the timelines and key dates for each of the two main work streams – completion of wild poliovirus eradication and elimination of Sabin polioviruses – needed to achieve the goal of the Polio Endgame Strategic Plan.

Figure 1: The Endgame Milestones



5. OUTCOMES AND MAJOR ACTIVITIES

OUTCOMES

The Polio Endgame Strategic Plan is designed to produce four major outcomes to complete the eradication and containment of all polioviruses:

1. Population immunity in infected and high risk areas above the thresholds needed to interrupt circulating polioviruses and prevent re-establishment of imported or emergent viruses.

2. Global poliovirus surveillance and response capacity to rapidly detect and interrupt any emergent poliovirus.

3. Sabin 2 polioviruses removed from routine immunization programmes in all OPV-using countries.

4. Appropriate biocontainment globally of all wild polioviruses, vaccine-related polioviruses and Sabin strain type 2 poliovirus.

Table 2 summarizes the relationship between these outcomes and the major activities outlined in sections 5.1-5.5 of the Plan.

Table 2: Outcomes and Major Activities

Outcome	Major Activities
High population immunity	- routine immunization systems strengthening - national & subnational immunization days - IPV introduction - community engagement & social mobilization
Surveillance & response capacity	- outbreak response & mop-ups - stockpiles for emergency response - acute flaccid paralysis surveillance - environmental surveillance - new diagnostics & special studies
Sabin 2 poliovirus removal	- OPV cessation (type 2)
Poliovirus containment	- biocontainment of residual polioviruses - certification of eradication & containment

MAJOR ACTIVITIES

5.1 ROUTINE IMMUNIZATION

Routine Immunization Systems Strengthening

Strengthening routine immunization systems to achieve the Global Vaccine Action Plan (GVAP) coverage targets is fundamental to the polio endgame. Improvements in routine immunization coverage against poliovirus are essential to minimize the risk of cVDPV emergence following OPV cessation and to optimize the impact of IPV. Given the inherent weaknesses of health systems in many OPV-using countries GVAP envisages the strengthening of both fixed site delivery of routine vaccination programmes and sustainable outreach activities.

The GPEI will seek to contribute to specific GVAP objectives through a two-pronged approach that is coordinated with global health partners, particularly the Global Alliance for Vaccines & Immunization (GAVI), and exploits the GPEI infrastructure and processes to assist national authorities and the broader immunization community to improve coverage.

First, in all countries with a polio staff presence (over 60 countries), there will be an increased emphasis on using these staff and related GPEI capacities and experience to contribute directly to the GVAP objectives and activities related to strengthening immunization systems (GVAP objective 4) and ensuring individuals and communities understand and demand vaccines (GVAP objective 2). Particular attention will be given to those GVAP activities which build on the training and experience of GPEI staff such as strengthening monitoring and surveillance systems, improving the capacity of managers and frontline workers, strengthening infrastructure and logistics, building advocacy capacity, creating incentives, and engaging individuals and communities.

Secondly, in those geographies where the GPEI has deployed and maintained a strong human resource infrastructure which extends down to the subnational level (i.e. recently endemic and re-established transmission areas), the GPEI emphasis will also extend to include key activities under the GVAP objective of extending the benefits of immunization equitably to all people. In these contexts the GPEI experience, staff and capacities will be applied to the development and implementation of existing and/or new approaches to tackle inequities in immunization coverage. This will include using GPEI staffing, microplanning, experience in reaching marginalized groups, and effective monitoring to drive up DTP3/Penta 3 coverage.

> **TARGET**: By 2016, >50% of the time of polio-funded field personnel will be devoted to specific, measurable GVAP activities to help national authorities strengthen routine immunization systems and services.

> **TARGET**: By end-2018, DTP3/Penta3 coverage should be a minimum of 70% in the worst-performing Local Government Areas (LGAs), districts or agencies of the northern states of Nigeria and India, Pakistan, southern provinces of Afghanistan, Angola, Chad, eastern DR Congo, Somalia and south Sudan.

OPV Cessation

Due to the long-term risks of vaccine-associated paralytic poliomyelitis (VAPP), iVDPVs and cVDPVs, the use of specific oral polio vaccine (OPV) serotypes will be phased out globally from all routine immunization programmes in a synchronized manner. Given that type 2 wild poliovirus has been eliminated globally for over 10 years, and that the greatest burden of VDPV-associated disease is due to the Sabin type 2 virus, OPV2 cessation is a central, prominent and near-term goal of the polio endgame. This serotype will be eliminated by replacing all trivalent OPV with bivalent OPV (types 1 & 3) with a target date of late-2015 (at latest 2016) for a globally-synchronized cessation of all tOPV use.

The most critical pre-requisites for a tOPV-bOPV switch are that any persistent cVDPV2 outbreaks (e.g. Nigeria, Somalia at mid-2012) have been stopped and that there is proven capacity to detect and stop any new outbreaks. All countries should have the capacity to detect and interrupt cVDPV outbreaks within 6 months of an index case. An additional pre-requisite will be the availability of an adequate supply of the appropriate vaccines to allow for a globally-coordinated tOPV/bOPV switch, including availability of sufficient bOPV and 'affordable' IPV options (see below). Additional pre-requisites include international consensus on stopping the use and delivery of tOPV formulations globally, and the availability of stockpiles of mOPV2 to respond to possible post-switch cVDPV2 outbreaks. Cessation of bivalent OPV is targeted for 2019 (i.e. as soon as feasible, following global certification).

> **TARGET**: By end-2016, 100% of tOPV-using countries have replaced tOPV with bOPV for routine immunization.
>
> **TARGET**: By end-2019, 100% of countries have stopped all bOPV use.

IPV introduction

To boost population immunity against polioviruses prior to a tOPV-bOPV switch, and to maintain a polio-primed population thereafter, all countries are recommended to introduce at least 1 dose of IPV into their routine immunization programmes prior to or at the time of OPV2 cessation. This will help maintain population immunity against type 2 poliovirus, thereby substantially reducing the consequences of a subsequent circulating poliovirus - in terms of paralytic disease - and facilitating the containment of outbreaks. For countries at particular risk of cVPDV emergence, this approach may need to be complemented with additional measures (e.g. pre-cessation tOPV campaigns to boost immunity; introduction of two routine IPV doses). Recognising that the risks associated with eventual bOPV cessation may be similar to those associated with OPV2 cessation, it is recommended that countries plan to continue at least one dose of IPV for at least five years after bOPV cessation. As this will continue till at least 2024, this will need to be managed and funded through routine immunization programmes, given the need to mainstream operations. IPV may also have a role to play in helping to interrupt transmission in endemic countries, when administered alongside OPV (see SIA section 5.2 below).

Lessons learned in the introduction of new vaccines in low and middle income countries over the past decade, e.g. of *Haemophilus influenzae* type b, pneumococcal, rotavirus or HPV vaccines will be beneficial to IPV introduction. Countries will need to perform proper planning and preparation using existing checklists for cold chain, logistics and vaccine management, health care worker training and supervision, waste management and injection safety and adverse events following immunization (AEFI) monitoring.

The introduction of IPV into low and middle income countries will require a combination of volume purchasing of existing IPV products and the realization of low-cost IPV options that have been identified in clinical and pre-clinical studies and have the potential to achieve a market price of <US$1.00/dose. Two approaches will be pursued to achieve the development of low-cost/dose IPV options in the near-term: licensing of intradermal (ID) fractional (1/5th) dose IPV and development of new, adjuvanted intramuscular (IM) IPV products.[7] As countries may have different preferences with respect to the ID versus the adjuvanted IM option, and there is insufficient evidence at this time to recommend one of these approaches over the other as a supplementary dose at the time of OPV2 cessation, both options are being pursued. At end-2012, both approaches faced substantial regulatory and/or development challenges which could potentially be addressed in the near-term (24-48 months) with intensive support from the international community, the development of a multi-dose policy for IPV, and rapid mapping of regulatory pathways. Recognizing that the development of these new, low-cost IPV options may not meet the optimal timeline for a tOPV-bOPV switch, the GPEI is working with manufacturers, GAVI and stakeholders to develop by mid-2013 a strategy that would allow initial introduction in low and low-middle income countries using existing IPV products at substantially reduced prices, with a subsequent transition to more sustainable, low-cost products as they became available. By 2017 there should be feasible options for safely producing IPV in developing countries settings (e.g. Sabin-IPV) to ensure that all countries have the opportunity to produce IPV for their routine childhood immunization.[8]

> **TARGET**: By end-2015, at least 1 IPV product available for < US$1/dose; at least 2 such products available by end-2016.
>
> **TARGET**: By end-2015, 100% of OPV-using countries have introduced > 1 dose of IPV into the routine immunization schedule.

5.2 SUPPLEMENTARY IMMUNIZATION ACTIVITIES (SIAs)

Supplementary immunization activities (SIAs) build on routine immunization programmes to establish very high population immunity in order to interrupt both endemic polio transmission and outbreaks following importations. In polio-free areas SIAs can also help to maintain population immunity at sufficient levels to prevent the circulation of a poliovirus following an importation. This section outlines the fundamental elements of the SIA strategy for the polio endgame.

[7] Resik et al Cuba study, JID, 2010 demonstrated that one fractional dose (1/5th or a full dose), after multiple OPV doses may be sufficient to establish immunity base (seroconversion and priming).
[8] SAGE meeting, 10-12 April 2012: http://www.who.int/immunization/sage/previous_april2012/en/index.html

National & Subnational Immunization Days (NIDs & SNIDs)

An intensive schedule of supplementary immunization activities will be conducted to interrupt any residual wild poliovirus transmission, to maintain high population immunity in areas at highest risk of importation and/or persistent circulation, and to reduce the risk of VDPV emergence prior to OPV cessation. Geographically the most intensive schedule of NIDs and SNIDs will be conducted in endemic areas (i.e. 6-8 rounds per year in northern Nigeria, Pakistan, southern Afghanistan), areas of recurrent importations from these endemic areas (i.e. 2-4 rounds per year in parts of West Africa, Chad, Sudan and South Sudan), and areas of recurrent cVDPV emergence (e.g. 2-4 rounds per year in northern India, Somalia, eastern Ethiopia, eastern DR Congo, and Yemen). In areas where 2 or more countries have historically shared a common poliovirus reservoir or route of international spread, these activities will be internationally synchronized with special cross-border coordination and activities to optimize coverage in border areas.

The GPEI will continue to intensify its risk analysis and modeling on an ongoing basis to help refine the SIA calendar to achieve and sustain immunity levels needed to interrupt transmission and remain polio-free. For endemic areas, the intensity of SIAs will be scaled-back only after at least 18 months following the last confirmed detection of a circulating wild poliovirus (i.e. after 2 high seasons without wild poliovirus detection); for re-infected areas, the intensity of SIAs will be scaled-back only after at least 12 months following the last confirmed detection of circulating wild poliovirus. Following the tOPV-bOPV switch (see section 6.1), a baseline schedule of 2 SIAs per year will be continued in the areas of highest risk of types 1 and 3 VDPV emergence until the time of bOPV cessation.

As OPV campaigns are the core strategy for boosting population immunity above the threshold for stopping polio transmission in endemic areas, it is essential that a sufficiently high quality of campaigns is achieved and maintained in the endemic countries. This requires professional campaign management; clear accountabilities; appropriate and tailored tactics for insecure and conflict affected areas; and, the utilization of proven innovations and best practice in campaign planning and implementation to ensure that campaigns reach every last child. The combination of tactics introduced under the GPEI Emergency Action Plan 2012-13 will be sustained and expanded as needed to address persistent gaps in SIA coverage, including the deployment of the technical assistance surge through partner agencies, review and refinement of microplanning in the highest risk areas, greater scrutiny of vaccinator selection and training and retention rates, reworking of vaccination team supervision strategies, introduction of direct payment mechanisms for vaccinators and supervisors, and enhanced community mobilization. Annex 1 summarizes the major actions being employed in each of the remaining endemic countries, under the GPEI Emergency Action Plan 2012-13, to improve SIA performance and accountability to achieve the population immunity levels needed to stop transmission. These actions are categorized across six thematic areas:

- Leadership to ensure a whole of government/society approach,
- Oversight to guarantee accountability for programme and partner performance
- Microplanning for missed children
- Institutionalizing best practice for vaccination team performance
- Social mobilization to enhance community demand

- Surge of technical support to assist for worst-performing areas

Pre-, intra- and post-campaign monitoring will be used to ensure real-time course corrections in SIA planning, implementation and assessment. Standardized dashboards will be systematically applied in all polio-endemic areas to assess SIA preparedness at district level, with immediate deferment and urgent surge support to areas failing to meet the defined standard. Building on the best practices of India, intra-campaign monitoring will be utilized to ensure more effective end-of-day review meetings and targeting of remedial or catch-up activities in priority areas. Lot Quality Assurance Sampling (LQAS) and independent monitoring will be used to assess campaign coverage in all accessible areas and guide catch-up activities.

A combination of scientific and operational research will inform decisions on the potential utility of expanding the age groups targeted during OPV SIAs in endemic areas as well as the types of polio vaccines administered. Recent data from polio outbreak response activities suggests that expanding the target age group for OPV beyond 60 months of age in SIAs may accelerate the interruption of polio transmission due to a number of factors, particularly improved coverage among the very young. Similarly, there is increasingly strong evidence that a supplementary dose of IPV can substantially boost mucosal immunity in OPV-vaccinated populations, potentially accelerating eradication. Although extending these approaches to endemic areas has substantial communications and logistical implications, both can be evaluated for use in endemic reservoir areas where transmission persists into late 2013.

> **TARGET**: by end-2013, LQAS confirmed coverage of > 80% in all very high risk LGAs/districts of northern Nigeria and southern Afghanistan.
>
> **TARGET**: by end-2013, LQAS confirmed coverage of > 90% in all very high risk LGAs/districts of Pakistan.

Outbreak Response & Mop-Ups

A more aggressive approach to outbreaks of both wild and vaccine-derived polioviruses will be implemented with a goal of stopping any poliovirus within 120 days of an index case. Building on experience from more than 100 wild and vaccine-derived poliovirus outbreaks over the last 10 years, the new response tactics will include implementing a minimum of 5 response rounds (each covering a minimum of 1 million people), expanding the target age group for the first 2 rounds (i.e. to < 15 years of age or the entire population, depending on the epidemiology), and reducing the interval between the first 3 rounds (i.e. from 4-6 to 2-3 weeks). Joint national and international rapid assessments will be conducted at 3 and 6 months following the index case to assess quality of outbreak response and plan any course corrections. Together, this represents a marked step-up in the response to polio outbreaks.

Whereas outbreak response activities have historically been driven by isolation of a poliovirus from a paralyzed child, during the endgame period environmental data will also be used to guide outbreak response planning and implementation. For known infected areas, the detection of a positive

environmental sample will guide the geographic extent as well as the duration of a response. In previously polio-free areas, the detection of a positive environmental sample will trigger both a virologic and an epidemiologic investigation to guide heightened surveillance or an immunization response.

The vaccine of choice for outbreak response will depend on the nature of the virus (wild vs. VDPV), and the phase of the eradication programme (i.e. prior to or following the tOPV-bOPV switch). Prior to the tOPV-bOPV switch the vaccine of choice for a wild poliovirus outbreak (i.e. type 1 or 3) will be bOPV; the vaccine of choice for a cVDPV will be bOPV for type 1 or 3 cVDPVs and tOPV for type 2 cVDPVs. To reduce the risks associated with hoarding or stockpiling of tOPV following the tOPV-bOPV switch, in that period the vaccine of choice for a type 2 cVDPV would generally be mOPV2.

TARGET: By mid-2013, 100% of polio outbreaks stopped within 120 days of an index case.

Stockpiles for Emergency Response

Prior to the tOPV-bOPV switch, OPV will be the vaccine of choice to respond to all wild and VDPV outbreaks (see above). During this period, global OPV supply will be managed to ensure a sufficient buffer stock (i.e. a minimum of 50 million bOPV doses) is maintained for this purpose. Following the tOPV-bOPV switch, bOPV will be the vaccine of choice for responding to all type 1 or type 3 wild poliovirus outbreaks and will be available through the buffer stock strategy. After the tOPV-bOPV switch, monovalent OPV2 will be the vaccine of choice for responding to any cVDPV2 outbreak or a WPV2 release from a laboratory or production facility; the detection of an ambiguous vaccine-derived poliovirus (aVDPV) may trigger a pre-emptive IPV response in the immediate area.[9]

A stockpile of over 500 million doses of mOPV2 as bulk, will be available by 2015 for this purpose. After the tOPV-bOPV switch, provision will be made for rapid access to stand-alone IPV (up to 10 million doses) for countries and areas contiguous with, but outside of the area of, an outbreak to rapidly reinforce population immunity. Ideally this can be achieved through careful management of the global IPV buffer stock. Following bOPV cessation (target date 2019) a combination of monovalent OPVs and IPV (per above) will be used for responding to any wild or vaccine-derived poliovirus regardless of serotype (i.e. the same strategy for type 2 viruses will apply to all viruses). A stockpile of 300 million doses of mOPV1 and 300 million doses of mOPV3 will be established by 2018 for this purpose.

5.3 COMMUNITY ENGAGEMENT & SOCIAL MOBILIZATION

Securing the buy-in of the most marginalized and disaffected communities to campaigns is vital to complete polio eradication. Persistent pockets of vaccination refusals can potentially derail the

[9] Ambiguous vaccine-derived polioviruses (aVDPVs) are vaccine-derived polioviruses that are either isolated from people with no known immunodeficiency, or isolated from sewage whose ultimate source is unknown.

global eradication effort. The closer the programme moves to eradication the more critical it is to be able to access socially disaffected groups. In addition, the new polio endgame brings new communication challenges requiring the development of new strategies to address IPV introduction and OPV cessation.

Reaching the most marginalized children requires understanding and overcoming local social, cultural, political and religious barriers. Rapid social research will be used to help build understanding of why the programme continues to miss children, with findings quickly operationalized to better inform the response. In May 2012 a new tool was developed to investigate areas with evidence of chronically missed children. Already the data generated is guiding the targeting of locally-specific interventions. Quarterly reporting against a set of global communication indicators, with social data now collected right down to settlement level in the highest risk areas is helping drive more systematic evidence-based planning and implementation of a mix of communication and social mobilization interventions.

Public advocacy

Mobilizing decision makers and administrative structures involves a range of activities at various levels to ensure that polio eradication is fully on the political and administrative agenda. This involves persuading influential people and organizations to advocate and organize support. As polio has now been largely restricted to three countries with large and predominant Muslim populations a greater effort is underway to ensure the right mix of international and locally respected Islamic voices support polio efforts.

Health professionals, including private practitioners and medical associations, must be fully aligned with programme to publicly reinforce the call for vaccination and allay any fears and concerns. For example, the Nigerian Medical Association members have been sensitized on the importance of reporting suspected polio and involved in OPV campaigns to accompany teams to high risk areas and visit houses or settlements that have been historically resistant to polio immunization.

In all endemic and polio priority countries, plans will include the holding of local government meetings, official memos and press briefings to demonstrate public commitment; systematic use of mass media to raise visibility of polio activities through news coverage, talk shows, soap operas, celebrity spokespersons, discussion and other entertainment education programmes; and regular meetings and question and answer sessions among government representatives, local and community organizations and leadership to discuss campaign plans and allay fears.

Community engagement and mobilization

Community mobilization through involvement, engagement and participation is critical to build support for polio campaigns at local levels, and to help mitigate the consequences of any crisis that may arise from rumours and misinformation. Local community leaders (political, social and religious, influential people) will be mobilized to play an active role in planning, organizing and promoting campaigns, and engaging community members to discuss and personalize the risks associated with polio and actions that can be taken to protect the community. Community mobilization will be

organized by local government and partners (including UNICEF, Rotary and local NGOs) through: community group meetings; traditional and new media, such as a town criers, film showings and theatre groups; grassroots organizations; schoolchildren; religious institutions; and traditional healers.

Social Mobilization networks

Based on the highly successful 9000 strong social mobilization network model in India (SMNet), dedicated networks are now being scaled up in the highest risk areas for polio transmission in Afghanistan, Nigeria and Pakistan with thousands of volunteers recruited in 2012. These local men and women are empowered to address local concerns about polio and routine immunization to ensure communities have the right information, delivered through locally appropriate channels, to enable parents to make the right decisions to protect their children. This is already having an effect, as evidenced by higher rates of awareness of campaigns, increased conversion of refusals and reduced numbers of missed children in polio reservoirs in Pakistan, Afghanistan and Nigeria. Social research consistently cites social mobilizers and community health workers to be among the most credible, trustworthy sources of information.

Promotion and advertising

Leading up to and during campaigns promotional materials and advertising remind communities that polio is still a problem and that they should vaccinate their children. Appropriate promotional materials, such as leaflets, pamphlets, banners, flags, and radio and television spots will be used strategically, as has been used in India to achieve awareness levels as high as 98%. To build awareness in Pakistan a national media strategy featuring Shahid Afridi, one of Pakistan's most famous cricketers, was launched in 2012. The private sector in the endemic countries will continue to be engaged to provide support.

Point of service promotion

Wherever polio or routine vaccination is provided at a fixed service point it will be promoted with visible promotional signs and symbols to emphasize the availability and accessibility of support and advice and to visibly reinforce the value of the intervention. When OPV doses are provided house-to-house, this visibility will be provided through promotional signs and symbols on vaccination team clothing, caps, bags or even vaccine carriers. In Nigeria, to ensure vaccinators are able to present themselves to caregivers both courteously and professionally a new Inter-Personal Communication skills kit was produced and special training conducted in several high risk states in 2012.

5.4 SURVEILLANCE

Sensitive surveillance systems are essential to polio eradication. They enable the identification of any residual viruses and are a crucial basis for certification of eradication. This section outlines the steps that will be taken to further build and maintain a comprehensive polio surveillance system for eradication.

Acute Flaccid Paralysis Surveillance

The detection and investigation of Acute Flaccid Paralysis (AFP) cases remains the core strategy for detecting both wild and vaccine-derived polioviruses, to guide SIA strategy, to facilitate certification and to validate the absence of circulating VDPVs. There will be three major priorities during the endgame period. For the three regions that are certified polio-free - the Americas, Europe and Western Pacific - the priority will be to revitalize AFP surveillance to achieve certification-standard performance in all areas with an AFP policy by 2015 to ensure the capacity to detect and respond to any cVDPV emergence following the tOPV-bOPV switch.[10] This will be achieved through heightened political commitment to the goals of the endgame, through allocation of additional resources where needed – including for laboratory capacity - and through WHO Regional Offices support to countries in revitalizing AFP surveillance.

For the three regions not certified polio-free at end-2012, the priority will be to close remaining gaps in AFP surveillance sensitivity (particularly in northern Nigeria; west, central and Horn of Africa; Pakistan; and, Afghanistan) by 2014 in advance of a global tOPV-bOPV switch and then to sustain certification-standard performance at the national and subnational level through regional and global certification. Particular attention will be given to ensuring documented active (at least monthly) AFP surveillance at all major reporting sites, expanding networks of community informants and, potentially, establishing rewards for polio-confirmed AFP cases.

In areas where performance is sub-optimal, the focus will be on staff training and instituting appropriate management and accountability structures, in-depth analysis of surveillance data, and use of technology. In areas with extraordinary challenges, in addition to the above, special activities will be put in place, to include targeted AFP community searches, 6-monthly active case searches and case searches during vaccination campaigns. Regional and national plans will elaborate specific activities and budgets and there will be more systematic regional risk assessments and response.

> **TARGET**: By end-2014, 100% of countries in certified Regions achieving and sustaining certification-standard surveillance.
>
> **TARGET**: By end-2013, 100% of countries in non- certified Regions achieving AFP detection rates of 2 cases per 100,000 population <15 years, at province/state level.

Environmental Sampling

The systematic sampling of sewage for polioviruses will be geographically expanded to identify any residual transmission in endemic areas, to provide early indication of new importations into

[10] Certification-standard performance is defined as the achievement of a non-polio AFP rate of at least 1 case of non-polio AFP / 100.000 population < 15 yrs, with adequate stool specimens collected from at least 80% of cases; specimens are defined as 'adequate' if 2 specimens are collected within 14 days of onset of paralysis, at least 24 hours apart, arriving in the laboratory in good condition; all specimens must be analyzed in a laboratory that is accredited by WHO.

recurrently re-infected areas, and to document the elimination of Sabin viruses following the tOPV-bOPV switch and eventual bOPV cessation. Additional endemic sampling sites in Nigeria and Afghanistan, as well as new sites in highest-risk areas/routes for importation would be in place by mid-2014. Based on the number of countries/areas at particular risk of a VDPV emergence, or which have a national tOPV production facility, this will be complemented by an additional 15-20 cities with sampling sites globally, prior to the tOPV-bOPV switch in 2015.

> **TARGET**: By end-2015, environmental sampling sites established in an additional 15-20 cities globally to help monitor OPV2 cessation and the elimination of type 2 vaccine-related polioviruses.

Special Surveillance

AFP and environmental surveillance will be complemented by special surveillance studies with four specific objectives. First, there will be expanded use of serologic surveys to more rapidly assess and validate population immunity levels, stratified by age group, in any areas with persistent poliovirus transmission on at least an annual basis. Secondly, large-scale stool surveys and expanded contact sampling will be used to more rapidly rule out ongoing poliovirus transmission in recently re-infected and/or endemic areas which are no longer reporting polio cases. Thirdly, special studies will be scaled-up among patients with primary immunodeficiency syndromes to more systematically detect iVDPVs in both industrialized and middle-income countries. Finally, special environmental surveillance studies will be conducted for species C enteroviruses in areas with recurrent cVPDV emergences and/or risk factors for cVDPV emergence.

> **TARGET**: By end-2013, seroprevalence surveys underway in all areas of residual wild poliovirus transmission.

New Diagnostics

Laboratory testing requirements have the potential to evolve significantly with the phase-out of all routine OPV use. The increased use of environmental surveillance, together with the tOPV-bOPV switch, presents an opportunity to introduce new diagnostic techniques and algorithms into the Global Polio Laboratory Network (GPLN). Incremental introduction of new diagnostic techniques for environmental surveillance will take place through 2014. Additional changes will be implemented at the time of the tOPV-bOPV switch and again at the time of complete OPV cessation. The current challenges of finding wild polioviruses and cVDPVs amongst a background of OPV will be removed and alternative assays could be developed with a focus on more rapid detection and characterization of polioviruses, including possible direct detection without cell culture. The core technology to achieve this is expected to be worked out by 2014. These changes may also allow for increased flexibility in where assays are performed and increase options for supporting polio surveillance long-term. A rapid immunity assessment tool, under development, will help more easily and accurately measure population immunity.

5.5 CONTAINMENT & CERTIFICATION PROCESSES

Appropriate biocontainment of polioviruses is a fundamental step towards global certification and minimizing the long-term risks associated with poliovirus stocks. This section outlines the biocontainment requirements and the process for global certification.

Biocontainment of Residual Polioviruses

Following global interruption of wild and vaccine-derived polioviruses and cessation of OPV use, facility-based polioviruses will represent the only remaining source for reintroduction to human populations.[11] These risks can be eliminated in most areas through the destruction of wild poliovirus and OPV/Sabin infectious and potentially infectious materials, as the majority of countries will have no need for live viruses in the post-eradication era. However, a small number of poliovirus facilities (10-20) will be necessary to ensure continued essential international functions, including IPV production, OPV stockpile maintenance, vaccine quality assurance, diagnostic reagent production, virus reference functions, and crucial research.

Dates for the destruction of poliovirus materials and implementation of safeguards will differ for wild and Sabin polioviruses and be linked to global WPV interruption, the tOPV-bOPV switch, and global OPV cessation. The first stage of biocontainment is to complete laboratory survey and inventory activities in all polio-free countries and prepare for implementation of containment activities prior to global certification. These activities have largely been completed globally with the exception of persistent polio-infected countries. By the time that wild poliovirus transmission has been interrupted for one year – interruption targeted for end-2014 - Phase II containment activities will have been initiated in all countries in preparation for containment of all wild polioviruses by mid-2016. Sabin type 2 polioviruses will be controlled at the time of the tOPV-bOPV switch. At the time of global OPV cessation all remaining Sabin polioviruses will be contained.

The development and finalization of the Global Action Plan for the Laboratory Containment of Wild Polioviruses (GAP III) will be used to establish international consensus on the timeframe and mechanisms for ensuring that the containment requirements for laboratory stocks of wild poliovirus and VDPVs are appropriate to the risks. A finalized GAP III will also address the need to establish consensus on the relevant biosafety levels for handling Sabin and Sabin-derived polioviruses during the OPV cessation phase. International agreement on long-term containment standards for all polioviruses (i.e. Sabin as well as wild poliovirus strains) will need to be established by 2014.

> **TARGET**: by end-2014, international agreement on long-term containment of polioviruses and post-eradication use of OPV.
>
> **TARGET**: by end-2015 phase 2 biocontainment activities implemented for wild polioviruses.

Certification of Wild Poliovirus Eradication & Containment

The primary requirements for certifying a WHO region as free of wild poliovirus are (a) the absence of any wild polioviruses for a minimum of 3 years in all countries of the Region, (b) the presence of certification-standard surveillance in all countries, and (c) the completion of Phase I bio-containment activities for all facility-based wild poliovirus stocks.[12] Certification at the Regional level is done by Regional Certification Commissions (RCC) which report in turn to the Global Certification Commission (GCC). At its meeting in August 2012, the GCC indicated that it could in 2013 consider evidence that type 2 wild poliovirus has been eradicated, based on its absence for more than 10 years and regional surveillance sensitivity. The consideration of this evidence would be the first stage of a formal process to 'conclude' that type 2 wild poliovirus has been eradicated, a critical step in the process of OPV2 cessation. It is anticipated that a 4th WHO Region – Southeast Asia – can be certified polio-free by mid-2014, contingent on the timely submission of full documentation by all relevant National Certification Committees (NCCs) and their acceptance by the South East Asia Region (SEAR) RCC. If Nigeria, Pakistan and Afghanistan interrupt all wild poliovirus transmission by end-2014, the remaining two WHO Regions – Africa and the Eastern Mediterranean – could potentially be certified by end-2017, with global certification occurring as early as the following year.

A number of programmatic challenges and policy issues will need to be addressed for global certification of wild poliovirus eradication and validation of the elimination of all vaccine-related viruses, including: the revitalization of certification-standard surveillance in the three Regions which have already been certified (i.e. the Americas, the Western Pacific and Europe); verification of bio-containment of all wild and, eventually, Sabin polioviruses; and, establishment of formal criteria for verifying the absence of circulating vaccine-derived polioviruses (cVDPVs) globally.

TARGET: by end-2013, reconstitution of global and all regional certification mechanisms.

TARGET: by end-2014, full documentation submitted to the South East Asia Regional Certification Commission.

[12] See footnote 10 for the definition of certification-standard surveillance.

6. GEOGRAPHIC DISTRIBUTION OF POLIOVIRUS RISKS

The poliovirus risks that must be addressed during the endgame are not geographically homogeneous but instead are concentrated in certain areas, depending on whether they pertain to wild or vaccine-derived polioviruses. These risks constitute both national and international hazards and will require additional, sometimes tailored, measures to mitigate them.

6.1 WILD POLIOVIRUSES

In 2013-2018, wild poliovirus risks will be concentrated in a combination of developing and industrialized countries. Initially, the greatest risk will be in *areas with ongoing or recent wild poliovirus transmission*. Based on the global epidemiology of polio at mid-2012, these will be northern Nigeria, FATA/KP Pakistan, southern Afghanistan and, potentially, bordering areas of neighbouring countries which regularly become re-infected due to population movements, such as the countries bordering Lake Chad and west African countries bordering Nigeria. These areas will require particularly intensive AFP and possibly supplementary surveillance activities to detect and respond to any residual transmission as detailed in the GPEI Emergency Action Plan 2012-2013 and summarized in Annex 1 and section 5 of this Plan.

As the endgame period progresses, countries retaining wild polioviruses for the purposes of *Salk-IPV production and/or essential QA/QC, laboratory or research functions* may constitute the greatest residual wild poliovirus risks. At mid-2012, five countries have active Salk-IPV production sites: Belgium, Denmark, France, the Netherlands, and Sweden. The number and location of countries which retain wild polioviruses for essential QA/QC, laboratory and research functions will be finalized with completion of the Phase 1 biocontainment activities globally. These areas will require full application of the *primary*, *secondary* and *tertiary* biocontainment safeguards to minimize the risk of inadvertent or intentional wild poliovirus re-introduction. For wild poliovirus type 2, these safeguards will need to be in place by 2015; for wild poliovirus types 1 and 3 it is anticipated that these safeguards will need to be in place by 2018.

6.2 VACCINE-DERIVED POLIOVIRUSES

In 2013-2018, VDPV risks will also be concentrated in a combination of developing and industrialized countries. The greatest risk will be due to *circulating vaccine-derived polioviruses (cVDPVs)* prior to, at the time of, and immediately following the tOPV-bOPV switch. While all OPV-using countries are potentially at risk of generating cVDPVs, especially those with low-moderate coverage, the risk appears to be geographically concentrated in certain areas with recurrent cVDPV emergence. As of mid-2012, these areas included northern Nigeria, southern Afghanistan, south-central Somalia and bordering areas of Ethiopia, eastern DR Congo, southern Madagascar, Yemen, and, possibly, western Uttar Pradesh, India. These areas will require particularly intensive efforts to boost routine immunization coverage prior to the tOPV-bOPV switch and to enhance AFP and surveillance activities to detect and respond rapidly to any newly emergent cVDPVs. Additional strategies will be considered to reduce the risk of a cVDPV emergence at the time of a tOPV-bOPV switch in such areas, including the conducting of a tOPV mass campaign immediately prior to the switch and adding a two

dose routine IPV schedule for at least a transition period. It is assumed that any cVDPVs that emerge at the time of OPV cessation can be rapidly interrupted using monovalent OPV (mOPV) campaigns and, if necessary, ring vaccination with IPV.[13] It is further assumed that any such time-limited mOPV responses would at most very rarely, if ever, give rise to new cVDPVs, particularly in the period immediately following OPV cessation. The experience to date with OPV response campaigns in low coverage areas supports this assumption.

Vaccine-related polioviruses that have not genetically evolved to where they have become VDPVs because they differ from the corresponding OPV strain by >1% of nucleotide positions by genetic sequencing, can still rarely cause sporadic cases of vaccine associated paralytic polio (VAPP). A WHO evaluation estimated that the global burden of VAPP is between 250-500 cases per year. The risk of VAPP is directly related to susceptibility to the type-specific poliovirus causing the VAPP; thus, already immune individuals are not at risk. VAPP cases may occur in either immunologically normal or immunodeficient individuals who are either recipients of OPV or contacts of OPV recipients. VAPP cases are manifest as single, sporadic cases and do not cause polio outbreaks. Cessation of OPV use will eliminate all risk of VAPP cases permanently.

Although less well characterized, the risk of *chronic iVDPVs* (i.e. with persistence of VDPV shedding for >36 months) appears to be concentrated primarily in industrialized countries where treatment is more often available for individuals with primary B-cell immunodeficiency syndromes (i.e., having defects in antibody production). These iVDPVs could theoretically reintroduce poliovirus into the wider population. However, since OPV was introduced in the 1960s none of the 30 recorded cases of prolonged iVDPV excretion (i.e. > 6 months) have been shown to cause secondary cases. All 4 of the chronic iVDPVs that have been detected as of mid-2012 occurred in high-income countries with high polio immunity and hygiene levels. As of mid-2012, only 2 chronic iVDPVs were either known or suspected to be continuing to shed virus – one each in the United Kingdom and the United States. A three-pronged strategy is being developed to manage this risk. First, enhanced identification and systematic screening of individuals with primary B-cell immunodeficiency syndromes will be used to identify potential iVDPVs. Secondly, immediate contacts will be recommended full vaccination to reduce the risk of infection and spread. Thirdly, the development and testing of polio antiviral compounds is being accelerated to identify a minimum of 2 compounds with the capacity to clear iVDPVs. As of mid-2012, one such compound was in Phase 1 trials and 3 additional compounds were under assessment.

[13] Defined as the vaccination of all susceptible individuals in a prescribed area around an outbreak

7. MAJOR RISKS TO THE ENDGAME

The immediate risk to the endgame strategic plan is failure to interrupt wild poliovirus transmission. As indicated by the recent interruption of wild poliovirus in India, the strategies to interrupt transmission outlined in this plan will work if fully implemented to a sufficiently high standard. The risks to interrupting transmission are chiefly operational and financial. This section examines these risks under four principal headings and outlines approaches to mitigate these risks.

Operational

- Inadequate management of large-scale eradication operations
- Failure to reach the last children in reservoir areas due to:
    - Geographic barriers to access
    - Insecurity

Without adequate management of eradication operations, no matter the funding, the Endgame will not achieve its goals. Clear management plans, including accountabilities must continue to be strengthened in all infected countries, and managers must be held accountable for meeting the targets enshrined within these plans. The risks are too high to allow poor management to derail eradication efforts. Annex A outlines how each of the remaining endemic countries has structured its polio programme management and operations to interrupt transmission of wild poliovirus.

The GPEI has gained invaluable experience from eradicating polio in conflict-affected and insecure areas. Common principles exist, particularly that people living in conflict-affected areas are highly motivated to improve their children's futures and can be readily engaged in the delivery of basic health services. Major humanitarian actors can also provide valuable assistance in negotiating access. A range of tactics has been developed and employed to access children and boost immunity more rapidly in insecure areas. Whilst not underestimating the challenges posed by insecurity and conflict, with appropriate investment of resources and attention, and the introduction of tailored strategies, conflict and insecurity should not pose an insurmountable barrier to achieving eradication.

Financial

- Insufficient pledges against the US$ 5.5 billion budget
- Insufficient cash flow

All activities outlined in this strategic plan must be fully funded, sufficiently in advance to allow implementation as scheduled and at a high standard. The GPEI projects a financial requirement of US$ 5.5 billion for the 2013-2018 Endgame period.[14] The larger the gap in financing, the more planned activities would need to be cut and the higher the consequent risks of failure to complete eradication. In the worst-case scenario, insufficient financing would result in unmet eradication targets, polio would re-establish itself in previously polio-free countries and the virus would take a stronger hold in the endemic countries. The GPEI is developing a resource mobilization strategy for the endgame period (see Section 9.2 below). The GPEI will work closely with donors to ensure predictable cash flow to enable planned activities to go ahead as scheduled.

[14] See section 8 'Financial Resources 2013-2018

Political

- Inability to establish and/or sustain political support in worst-performing districts/communities
- Inability to sustain national and state/provincial commitments and oversight in key geographies due to political change and competing priorities.

Political alignment with the goals of polio eradication at all levels is an essential enabling factor to the success of the Endgame. The political commitment at the national and sub-national levels in the remaining endemic and reinfected countries must be sustained and deepened. This commitment is essential to mobilize the local resources, access and accountability needed to improve the programme's reach to all children and sustain efforts beyond the interruption of wild poliovirus transmission. Structures and mechanisms have been established in each of the endemic countries to ensure that the strong political support for the polio programme at a national level is continued down to the state and district levels. For each of the endemic countries, this is outlined in Annex, along with accountabilities. The potential impact of political change cannot be fully mitigated; however, the development and sustained implementation of polio advocacy campaigns in key geographies can help to address this risk.

Societal

- Development of substantial resistance to, or boycott of, polio campaigns in key geographies
- Persistent suspension of polio campaigns (e.g. in parts of Pakistan and Somalia)

Alignment with the goals of the polio programme at the sub-national level is an essential element in ensuring communities buy-in to the vaccination campaigns. Appropriate community leaders need to be engaged. These are often traditional or religious or tribal leaders. Working to ensure alignment is a priority, as outlined in section 6.3.

The worrying suspension of campaigns in parts of Pakistan and Somalia threatens to create new vulnerable areas. Political leadership and commitment to negotiate is needed to overcome these bans.

8. FINANCIAL RESOURCES 2013-2018

8.1 INDICATIVE BUDGET

The financial requirements for the 'Endgame' are projected to be US$ 5.5 billion for the period 2013-2018, taking into account the Endgame Milestones outlined in Section 4.[15] This reflects substantial work under various scenarios and is the consensus position of the core GPEI partners, in consultation with the relevant global, regional and country stakeholders. The proportion across key budget categories will be adjusted as progress against key milestones is evaluated. Adjusting the estimated year of interruption will increase/decrease costs accordingly.

The key budget drivers are:

- The cost of OPV campaigns
- Technical assistance to countries
- Surveillance and Laboratory costs
- Outbreak Response capacity & stockpiles
- IPV introduction
- Containment & Certification costs
- Surge Capacity
- Research and Product Development
- Programme Support Costs

The financial requirements for the period will be presented in an accompanying Financial Resource Requirements (FRR) document with corresponding costs and underlying assumptions per major budget category. The FRR information will be reviewed and updated every 4 months.

Please see Annex B for a table outlining the projected costs per budget category. – ***TO BE ADDED***

8.2 RESOURCE MOBILIZATION

The financial needs of the endgame strategic plan will be met by implementing a resource mobilization, communications and advocacy strategy aligned with the endgame strategic plan and jointly developed by GPEI partners with the guidance of the relevant executive groups in the GPEI architecture, particularly the Polio Partners Group and the Polio Emergency Steering Committee. The resource mobilization strategy that is under development will aim to ensure that traditional donors maintain or increase their commitments, that new and non-traditional donors are courted and activated, that polio-affected countries increase their domestic financial contributions and that innovative mechanisms for funding are identified and exploited. A specific task force is being formed to drive this strategy.

Sustainable financing will require renewed commitments from governments and development partners as well as additional countries joining as development partners. The participation of in-

[15] This does not include the nationally funded elements of the polio eradication campaigns in India.

country civil society organizations is also critical. National governments should play a lead role through their Ministries of Health in coordinating with immunization partners, through national Interagency Coordinating Committees (ICCs), the identification and quantification of resource needs and in tracking the effective and efficient use of these resources.

TARGET: By May 2013, secure pledges to fully fund US$ 5.5 billion 2013-2018 period.

8.3 FINANCIAL MANAGEMENT AND EFFECTIVENESS

The GPEI has continually evaluated costs throughout implementation and sought opportunities to ensure good stewardship of available resources. In recent years, reviewing the costs associated with SIAs in countries such as Chad and DR Congo led to substantial reductions in operational costs. Currently, the GPEI partners are considering other ways to optimize costs and ensure maximum value for money including a project supported by external consultants to evaluate the key drivers of costs and performance across the global GPEI program (GPEI Value for Money project). The primary goal of this project is to identify areas where results can be delivered more cost-effectively, ideally by cost shifting within the current budget. An important secondary goal of the project is to promote greater transparency on major GPEI cost categories. A report detailing partnership findings and next steps will be available by November 2012.

9. PLANNING FOR THE POLIO LEGACY

INTRODUCTION

During more than 20 years of operations the GPEI has mobilized and trained millions of volunteers and health workers; reached into households untouched by other initiatives; mapped and brought health interventions to communities previously unreached; and, established a standardized, real-time global surveillance and response capacity. All these activities have been done for the cause of polio eradication. However, in doing so the GPEI has also been able to benefit other health work, principally through its surveillance and response capability for other VPDs and the delivery of basic health services by its vaccination teams. As the programme enters its final stages there is a need for the global health community to plan for a future beyond polio eradication. This is to ensure not only a World safe from polio but also to ensure that investments made in the cause of polio are fully exploited. These are two principal goals of the Legacy work:

- First, to mainstream the longterm polio immunization, surveillance, response and containment functions in order to protect a polio-free World.
- Second, to ensure the knowledge, capacities, processes and assets that the programme has created are utilized for other health initiatives.

This section maps out how this will be accomplished through first outlining the work needed to mainstream the major elements of the GPEI's activities; detailing the GPEI's major achievements and the contribution of the polio workforce to other health activities;, and, outlining a process and timeframe for consultation, planning and shaping the post-polio era.

9.1 MAINSTREAMING LONG-TERM POLIO FUNCTIONS

Organizations involved in polio eradication will need to plan to integrate activities undertaken for polio eradication into separate and ongoing functional structures and transition staff, as needed. This mainstreaming of technical operations under polio will be an essential part of the legacy of polio. This mainstreaming covers a number of categories.

- Ensure continued integration of polio immunization activities into national and international routine immunization programmes.

- Fully integrate polio surveillance and response activities into national and global mechanisms under the International Health Regulations (IHR 2005).

- For countries intending to maintain poliovirus stocks, ensure appropriate containment of polioviruses according to agreed international and national standards, regulations and protocols.

9.2 ACCOMPLISHMENTS

This section highlights specific GPEI achievements that could have benefit and applicability to other global health initiatives.

After more than 20 years of implementation, one major achievement stands out. The GPEI has reached and regularly accessed the chronically unreached, marginalized and most vulnerable populations in the world. This in turn has led to two major dividends – the delivery of basic health services, and a truly global surveillance and response capacity for both health and humanitarian emergencies.

Resolving serious problems of access

The polio programme has gone further than any other programme in being able to develop sustained access to the most marginalized children and communities: the 'fifth child' (the most inaccessible 20 percent of all children). The polio programme has developed the knowledge, capacities and systems to overcome the logistic, geographic, social, political, cultural, ethnic, gender, financial and other barriers/bottlenecks to working with the most marginalised, deprived and security compromised children and vulnerable populations in the world. Elements that allowed the GPEI to do this include the success of social mobilization programmes, the training and deployment of vaccination teams, improved micro-planning, mapping that made use of innovations such as GPS/GSI. This capability has enabled the polio workforce to provide other basic health services including anti-helminthics, Vitamin A supplements, measles mortality reduction activities, delivery of bed-nets amongst other basic health services.

Integrated Disease Surveillance and Response (IDSR)

Polio eradication efforts have led to the creation of a global surveillance and response capability for VPDs. Through the creation of its integrated AFP surveillance and laboratory capability, the GPEI receives regular and credible reporting on any instance of acute flaccid paralysis (AFP) and is able to respond appropriately. This unprecedented surveillance capability came from the need to identify, notify and investigate many tens of thousands of AFP cases worldwide every year. This has also facilitated surveillance and response for other diseases including measles, tetanus, meningitis, yellow fever and other VPDs, and assisted in the global response to humanitarian emergencies such as SARS and the South-East Asian Tsunami of 2004.

Contribution to other health work

The sharing of assets and learnings with other global health initiatives is an essential element of the polio legacy. This could include strengthening routine immunization (including modifying polio tools and innovations to benefit RI), best practice in data management, community engagement and mapping, and building a motivated and trained health workforce for the global public good. The polio workforce already contribute to this work and will continue to do so through the Endgame. Through the process outlined below, planning will take place for transfer of assets and best practice to the broader global health community.

9.3 PLANNING FOR THE POST-POLIO ERA

The first step in the process is to map the polio assets. This exercise will take place through the end of 2012 and into the first quarter of 2013. This is intended to outline what has been created through polio eradication, both tangible and intangible assets, establish what activities and contributions polio-funded staff are making beyond the polio programme, and to look at what capacities could be at risk with the intended eventual closure of the polio eradication programme. This exercise will examine the following four areas and will be undertaken by the GPEI spearheading partners in consultation with national governments and other key stakeholders:

1. POLICY AND STRATEGY PROCESSES (examples)

- Multi-year strategic plans and planning processes
- Technical advisory bodies and policy processes (national, regional & global)

2. PARTNER AND DONOR PROCESSES (examples)

- The GPEI architecture – managing a global public-private partnership
- Interagency Coordinating Committees (ICCs)
- Financial Resource Requirements (FRRs) & cashflow management

3. OPERATIONAL AND TACTICAL PROCESSES (examples)

- Social Mobilization
- Global surveillance and response capacity
- Mapping Communities
- Data management
- Vaccination Teams
- Building a trained and motivated health workforce

4. OVERSIGHT AND MONITORING PROCESSES (examples)

- Performance indicators
- Global and Regional Certification Commissions (GCC/RCCs)
- Independent Monitoring Board (IMB)

The second major element of planning for the post-polio era is the consultative process. The purpose of this is threefold. First, to tell the polio story to a broader community that understands what polio eradication is, but may not grasp the full extent of the programme's potential to benefit other health initiatives. This exercise will feed into the second, which is to have broad stakeholder consultation on what the assets created through global polio eradication efforts could be used for beyond polio. This is not meant to be a prescriptive exercise but is instead intended to stimulate discussion around the potential benefits of these assets to other programmes and initiatives. A priority in this process will be to get input from national governments on how polio assets could benefit their health priorities (e.g. measles campaigns). These consultations will take place throughout2013. This consultative stage will examine whether polio assets and learnings are able to

contribute to strengthening of health systems, benefits to immunization and fighting other vaccine-preventable diseases. The third element of the consultative process will be to examine funding issues and potential sources of funding for the assets of the GPEI that could be used more widely than polio. The spearheading partners within the GPEI will lead this process, according to the timeline laid out below. This includes the WHO governing bodies process as the high level forum for making decisions on priorities.

ACTIVITY	PURPOSE	TIMEFRAME
Map Assets	To have a full picture of the polio infrastructure	January– April 2013
Stakeholder Consultations	To understand risks/benefits of the polio infrastructure	Throughout 2013
WHO Regional Committees	WHO Member State input	Q3-Q4 2013
WHO Executive Board	Review proposals	January 2014
World Health Assembly	Decisions on Legacy	May 2104

The final major element of planning for the post-polio era is a responsible and well-managed ramp-down of polio eradication efforts. This process will include addressing the issues surrounding the long-term future of the polio workforce. The consultative process on wider use of polio assets will address the issue of how to manage tangible assets and any transfer of staffing to other programmes and funding to continue assets with wider applicability to other vaccine-preventable diseases.

10. GOVERNANCE AND OVERSIGHT

Global Governance

The World Health Assembly issues the resolutions that determine the scope and direction for the Global Polio Eradication Initiative. The Polio Oversight Board, comprised of the heads of agencies of WHO, UNICEF, Rotary International, the US CDC and the Bill & Melinda Gates Foundation, meets quarterly to provide operational oversight and ensure high-level accountability across the GPEI partnership.

The Global Polio Partners Group is a multi-stakeholder body with representatives from donor and technical agencies, foundations, NGOs, polio-affected countries and the spearheading partners. The group provides input and guidance on strategy and implementation, ensures stakeholder voices are heard by the GPEI at the level of the Polio Oversight Board and undertakes both advocacy and diplomatic activities to mobilize resources for the polio programme. It is expected that the PPG will continue its role throughout the Endgame. As the focus of the GPEI evolves over the endgame period, as necessary, oversight arrangements will evolve to reflect changing realities.

National Governance

In Nigeria and Pakistan, the 2 most endemic countries at mid-2012, a Presidential and Prime-Ministerial oversight body were established, respectively, to ensure full implementation of the national emergency action plans, close oversight of LGA and district SIA performance, introduction of course-corrections as needed, and appropriate accountability for the quality and coverage of eradication activities. These bodies will be sustained for at least 12 months after the last wild poliovirus cases in each country.

Global & Regional Certification Commissions

Once wild poliovirus transmission appears to have been interrupted in a Region (i.e. 12 months after the last circulating wild poliovirus is detected), the work of the relevant Regional Certification Commission will intensify. The work of the Global Certification Commission (GCC) will intensify 12 months after the last wild poliovirus is detected globally.

Global Oversight and Technical Advisory Bodies

Independent oversight of eradication activities is provided by the Independent Monitoring Board (IMB). The GPEI responds to the IMB's recommendations and guidance in managing eradication efforts. The Strategic Advisory Group of Experts on immunization (SAGE) provides crucial technical guidance on immunization, ensuring a sound basis for policy decision making. SAGE is supported by the SAGE Polio Working Group.

The SAGE will continue its polio advisory role throughout the endgame period. The IMB will continue to evaluate progress towards the goal of the interruption of transmission.

Regional and National Advisory Bodies

Technical Advisory Groups (TAGs). Regional or national TAGs comprise experts in related fields of polio eradication, and regularly convene to review a region or country's polio epidemiology and put forward appropriate strategies to more rapidly achieve eradication.

11. ROLES AND RESPONSIBILITIES

11.1 Roles of GPEI Partners

National governments:

National governments are both the owners and beneficiaries of the GPEI. Polio-affected countries undertake the full range of activities detailed in their country plans and summarized in this GPEI Strategic Plan. Achievement of country milestones will require polio-affected countries to hold ensure accountability at national, subnational and district level, and with other GPEI partners, to plan, implement and monitor the activities to reach every child with polio vaccine. The remaining endemic countries Afghanistan, Nigeria and Pakistan are the focus of surge efforts under the Emergency Action Plan.

At the same time, national governments in the three WHO regions already certified as polio-free, and polio-free member states in the three remaining endemic Regions, have a critical role to play in maintaining high population immunity and sensitive surveillance for AFP and to fully implement internationally-agreed processes to manage the long-term risks after WPV eradication.

National governments play a critical financing role in the eradication initiative. Of note, the proportion of the GPEI budget that is funded by domestic resources of polio-affected countries has increased from less than 10% in 2003-2005 to more than 30% in 2007-2009. This increase is driven largely by India, but also by Nigeria, Pakistan and Bangladesh. Other major in-kind contributions from polio-affected countries - such as the time of volunteers, health workers and others in SIA planning and implementation - have an estimated dollar value similar to that of international financial contributions.

Coordination amongst GPEI partners

The GPEI partners have created new structures and processes for international support, coordination and interagency leadership under the Emergency Action Plan. This includes the leadership role of the Polio Emergency Steering Committee (PESC) which oversees a number of groups designed to assist countries in their eradication efforts, drive operational innovations and mobilize resources. Whilst these structures will continue under the EAP, the GPEI is working to include coordination with other global health initiatives. This will be particularly important as the legacy planning takes place. The GPEI will develop structures to facilitate broader cross-agency cooperation. The GPEI is also developing an accountability framework to ensure that responsibilities and appropriate accountabilities for the spearheading partners are clearly defined during the endgame period.

Donor partners:

Since the 1988 WHA resolution to eradicate polio, funding commitments to the GPEI have totalled US$9 billion. In addition to contributions by national governments to their own polio eradication

efforts, 45 public and private donors have given more than US$1 million, with 19 of these having given US$25 million or more.

Donors to the GPEI include a wide range of donor governments, private foundations (eg Rotary International, the Bill and Melinda Gates Foundation, the UN Foundation), multilateral organizations, development banks, non-governmental organizations and, corporate partners. Donor engagement in polio-affected countries, to ensure optimal planning, implementation, monitoring and financing of country activities, will be a necessary complement to their engagement at the global level. In addition to financing, donor partners play an important advocacy role, both with polio-affected countries and donor peers. Some donor governments also provide access to technical expertise from within their national institutions, including through participation in global, regional and country-level technical advisory groups.

ANNEX A – COUNTRY UPDATES

This annex outlines how each of the remaining endemic countries has made improvements to its polio programme under six thematic areas since the launch of the Emergency Action Plan in 2012, in order to accelerate the interruption of transmission of wild poliovirus. For further information on each of the endemic countries please refer to national plans and the Emergency Action Plan.

NIGERIA (to be completed)

Leadership for a whole of government/ society approach

- **State and Provincial Task Forces** – Following a directive from the Presidential Task Force earlier this year, State Task Forces will be Chaired by the Deputy Governor. Local Government Area Task Forces have been established and should be chaired by the LGA Chairmen or Deputy. It is expected that the LGA Chairmen or a senior representative chair the evening review meetings during IPDs – The involvement of state and LGA leadership and over- sight is tracked through the Abuja Commitments and reported publically each quarter.

- **Traditional Leader Engagement** – Much has been done to engage and mobilize the revered traditional leadership to support polio eradication in Nigeria. His Eminence the Sultan of Sokoto has called publically for traditional leaders to support the programme and Emirs, District Heads, Village Heads and Ward Heads are actively involved. These leaders sensitize communities to upcoming rounds, are responsible for suitable selection of locally appropriate vaccinators, and resolve non-compliance and reporting if areas in their control are poorly covered.

Oversight of Programme and Partner Performance

- **President Task/Prime Ministerial Task Forces and other monitoring mechanisms** – Presidential Task Force on Immunization meeting regularly. Chaired by Minister of Health for State Dr. Pate who is responsible for reporting to the President.

- **Dashboard** – A new innovation operational in September. Tracks a number of pre-implementation indicators at the LGA and State level. Provides clear evidence to the programme of areas that are not ready for implementation, allowing local or state authorities to provide additional support or postpone implementation in certain areas. The dashboard now also tracks in-process indicators daily to the state and national operations room allowing much closer tracking of how campaigns are proceeding.

- **LQAS monitoring** – Has been scaled up considerably since its introduction in late 2009 and in the last IPD conducted in July 124 LGAs were evaluated using this methodology. The LQAS has proven very effective in Nigeria and has helped identify gaps in Independent Monitoring and identify more accurately good or poor performing areas.

Microplanning for Missed Children

- **House-by-house approach** – Based on learnings from the Indian polio programme, Nigeria has moved from a focus on children and settlement to household. This promotes a bottom-up approach with involvement of local health staff and traditional leadership. Walk through

of finished plans and verification strengthened. This results in a rationalized workload, greater accountability of teams, and easier supervision.

- **Nomad/Migrant** – Considerable work is underway to better map nomadic populations and engage with local leaders to ensure these populations are covered during IPDs and by routine services. A Recent pilot in July conducted in 41 LGAs in states with large nomadic populations and most at risk of polio infection found more than 8000 additional settlements not included on July micro-plan. 15% of these settlements had never been visited by a vaccination team. The study also found evidence of recent missed transmission with nine AFP cases with onset of paralysis in the last six months found not reported. Plans to scale up to other LGAs with large nomadic populations in coming months.

- **Improved Mapping** – GIS project underway in four states: Kano, Jigawa, Sokoto and Zamfara. Ward and LGA level maps completed with plans to scale up in November to remaining polio infected states.

Vaccination Teams to Institute Best Practice

- **Optimizing Recruitment, Training, IPC Skills, Retention** – Ward Selection Committees led by local traditional leaders established to ensure that locally acceptable vaccinators and supervisors are selected. Focus on retaining vaccinators, recorders and team supervisors to ensure over time capacity is built and teams are able to build trust with community. New coordinated training package for all new surge staff being developed with a focus on adult learning techniques and strong IPC skills.

- **Direct Disbursement Mechanisms** – Long-established. Nigeria is a leader in this regard. Little problems with payment of vaccinators

- **Restructuring Vaccination Teams** – Restructuring of vaccination teams and re-alignment to feasible daily targets was the first step in improving team performance.

- **Supervision** – Surge support Group Supervisor as well as field volunteers. Too early to demonstrate impact but managing this surge is one of the key priorities of the Nigerian programme.

- **Special Vaccination Teams (cross border, migrant/nomadic, transit)** – Newly reinvigorated emphasis on cross border coordination with teams who cover border areas expected to coordinate coverage and meet in the field to ensure settlements or households are not missed. Transit teams strengthened with better micro-plans that allow for greater supervision. Teams expected to cover markets, busy transit or bus stops, hospitals, large medical centres and water points. Evening teams being used at busiest points where children can be found: evening markets, hospitals and evening koranic schools.

- **Permanent Polio Teams in High Threat Settings** – Under discussion. Nigerian programme looking to rapidly learn from Afghanistan experience and deploy in areas where security threats are greatest or where access is hindered from terrorist activities.

Social Mobilization for Community Demand

- Intensifying Community Engagement
    - Intensified Ward Communication Strategy
    - Volunteer Community Mobilizer network/Other Partnerships

    - Engagement of traditional/Religious leaders
- Sustaining high level commitment
- Increasing awareness & demand for immunization
- Building capacity at State/LGA level
- Measuring what we do
- Significant scale up of community engagement approaches
    - Launch of Tsangaya 'koranic' school project
    - Integrated Ward Communication Strategy & Volunteer Community Mobilizer Network
    - Focused & increased engagement of traditional/Religious Leaders
- Expanded Human Resource capacity
    - Volunteer Community Mobilizers
    - LGA/state communication consultants
- Training & capacity development
- Abuja commitments with more focus on LGA

Surge for worst-performing areas

- Delivery of surge (>3900 staff) focused on most under-performing LGAs
- Short-term support of Surveillance Medical Officers from the India programme

PAKISTAN (to be completed)

Leadership for a whole of government/ society approach

- Key national cross-sectoral leads reporting to PM
- Head of state has appointed single focal person
- Single focal person per province

Oversight of Programme and Partner Performance

- Prime Minister's Cell for Polio Eradication established and maintained through change of PM.
- Domestic contributions: 3-year financing from the Islamic Development Bank (US$ 227 million)
- District Commissioners and UC Medical Officers now held responsible for overall implementation as outlined in Augmented National Emergency Action Plan launched.
- Accountability and management training for nation and provincial staff and frontline workers.
- Regular use of LQAS to complement other campaign monitoring techniques and cross-check against epidemiology.
- Real time reporting of preparedness indicators (300+ staff in districts and UCs).

Microplanning for Missed Children

- working with UN country team to ensure vaccination in camps for internally displaced and refugees, vaccination at transit points, etc.
- Access: working across sectors – military, political, administration, civil society - to help reach children in areas of insecurity.
- Regular cross-border planning and activities with Afghanistan.

- Expansion of age group and increased use of SIADs in newly-accessible areas or displaced and high-risk population groups in sanctuary areas.

Vaccination Teams to Institutionalize Best Practice

- Direct payment mechanism: to motivate frontline workers as well as ensure transparency and accountability. Requires use of ID cards, thus ensuring workers are minimum age.
- Joint SOPs on operational and comms workers

Social Mobilization for Community Demand

- Deployment of CommNet
- Consultation of national experts on FATA access issues and creative solutions

Surge for worst-performing areas

- Delivery of surge in technical assistance (>900): Union Council level polio workers and social mobilization network. Surge prioritized to clearly identified, worst-performing districts and UCs.
- Government appointed medical officers in high-risk UCs

AFGHANISTAN (to be completed)

Leadership for a whole of government/ society approach

- Inter-ministerial task force established.
- Head of state has appointed single focal person.

Oversight of Programme and Partner Performance

- Presidential action: signed Emergency Action Plan.
- District EPI Management Teams trained and active in the 13 high-risk districts
- Increased technical support to high-risk districts, including full-time District Polio Managers.
- Focus on management training to overcome administrative and managerial obstacles.

Microplanning for Missed Children

- Delivery of increased technical assistance (34)
- Improved access in Southern Region: through negotiation with parties in conflict and community leaders, special fixed site vax teams, religious leaders' support.
- Regular cross-border planning and activities with Pakistan.

Vaccination Teams to Institutionalize Best Practice

- Permanent polio teams in 8 of 13 high-risk districts.

Social Mobilization for Community Demand

- New communication strategy rolled out in September: 'Polio eradication is MY responsibility' theme, based on the role of different parts of society in eradication.

Note for the Record

5th Meeting of the SAGE Polio Working Group

World Health Organization, Geneva, September 3 - 4, 2012

Introduction

The fifth meeting of the SAGE Polio Working Group (WG) was held on 3 and 4 September, 2012 at the World Health Organization in Geneva, Switzerland. The meeting was attended by the following WG members: Elizabeth Miller (Chair), Peter Figueroa, Jacob John, Francis Nkrumah, Walter Dowdle, Walter Orenstein, Antoine Kabore, Kimberly Thompson and Nicholas Grassly; Hyam Bashour was unable to attend.

Jay Wenger, Bill and Melinda Gates Foundation, and Julian Bilous attended several meeting sessions as an invited expert. Participants from WHO were Bruce Aylward , Jackie Fournier-Caruana, Philippe Duclos, Tracey Goodman, Hamid Jafari, Roland Sutter, Rudi Tangermann, and Chris Wolff.

On the first day, the WG interacted in separate sessions with teams representing four manufacturers of inactivated polio vaccine (IPV) from Glaxo-Smith-Kline, SANOFI, the Serum Institute of India, and the Staten Serum Institute (Denmark). Manufacturers responded to a series of questions previously provided to them by the WG (see Annex III).

This note presents a summary on main findings, conclusions and recommendations from the 5th WG meeting, and summarizes presentations and discussions on main agenda items (see agenda in Annex I).

1 Background and objectives of the fifth meeting

The main objective of the fifth SAGE Polio Working Group meeting was to prepare for renewed interaction with SAGE on the planned cessation of OPV2 (replacing tOPV with bOPV for routine immunization) through:

(a) detailed review of the current status of the GPEI, of key pre-requisites for OPV2 cessation, and of the GPEI draft 'Endgame and Legacy' strategic plan 2014-2018;

(b) direct interaction with IPV manufacturers, to learn more about available IPV products, prices and supply options, particularly in view of the need to develop 'affordable' IPV options for low and low-middle income countries as IPV will be the only poliovirus vaccine available for routine immunization after OPV cessation;

(c) discussion of 4 main questions related to OPV2 cessation: on IPV introduction, ID vs IM application of IPV, timing for implementing OPV2 cessation, and on the duration of IPV use following final cessation of routine OPV.

2 Summary of main findings, conclusions and recommendations

Following discussions at the 5th meeting, the WG agreed on the following main findings, conclusions and recommendations.

2.1 *Cessation of OPV2 is central to the new 'polio endgame'.* OPV2 cessation should be a central, prominent and near-term goal of the new 'polio endgame.' Wild poliovirus type 2 has been eradicated for >10 years and OPV2 cessation will eliminate the generation of new outbreaks due to type 2 Sabin viruses and nearly 50% of vaccine-associated paralytic poliomyelitis. OPV2 cessation is a seminal step in the polio endgame culminating in the eradication of all wild polioviruses, the cessation of all routine OPV use (to end vaccine-associated paralytic polio and vaccine-derived poliovirus outbreaks), and the end of all poliomyelitis disease.

2.2 *Use of IPV to manage risks associated with OPV2 cessation.* OPV2 cessation will expose the global population to a new, exceptional era in the history of vaccination, in which there will

be a low, but real risk of type 2 polio outbreaks due to circulating vaccine-derived polioviruses, long-term VDPV excretors and reintroduction from containment failures (the last WPV type 2 cases, which occurred in northern India in 2002-2003, were associated with the introduction of a laboratory strain).

The risks of new cVDPV2 emergences extend into the period immediately following OPV2 cessation, because some OPV2 viruses may be circulating silently in populations with relatively low population immunity at the time of cessation. The possibility of sustained transmission of a type 2 virus increases with increasing population susceptibility following cessation of all routine and supplemental use of OPV2. IPV, which is trivalent and includes serotype 2, will be the only poliovirus vaccine available for type 2 protection. At least 1 dose of IPV should be introduced into routine immunization programmes prior to or at the time of OPV2 cessation to yield the following expected benefits:

a) the prevention of paralytic polio in individuals successfully vaccinated with IPV who get exposed to a cVPDV type 2, Sabin type 2 (VAPP) or wild poliovirus type 2;

b) improved immunological response in individuals previously vaccinated with IPV when receiving mOPV2 (and potentially IPV) vaccination given in response to a WPV2 or cVDPV2 outbreak that occurs after OPV2 cessation;

c) reduced transmission of cVDPV2 or WPV2 should they be introduced (i.e. there is evidence to suggest that IPV reduces the titer of fecal virus excretion and duration of shedding and is equivalent to OPV in decreasing oropharyngeal shedding);

d) boosting of immunity to wild polioviruses type 1 and 3 in vaccine recipients, which may further accelerate wild poliovirus eradication.

For countries at particular risk of cVPDV emergence, the suggested minimum 1-dose IPV policy may need to be complemented with additional measures (e.g. pre-OPV2-cessation boosting with tOPV SIAs to maximize population immunity to serotype 2 or introduction of a 2nd IPV dose, potentially with catch-up campaigns).

2.3 *Target price for an affordable IPV.* Based on consultation with manufacturers, volume purchasing, guaranteed procurement and other such approaches can substantially reduce the price of current IPV products below that currently available to Unicef (i.e. US$2.75/dose) and can play a role in facilitating the early introduction of IPV for OPV2 cessation. Such approaches cannot achieve a target price substantially below US$1.00/dose for an 'affordable' IPV product for low-income settings due to inherent costs in the production of the current vaccine.

Volume purchasing of whole dose IPV, potentially subsidized to achieve a more affordable near-term price, may be an important part of a global IPV introduction strategy for low and low-middle income countries. The affordable IPV options that have been identified in clinical and preclinical studies, but which current manufacturers have not yet fully developed or licensed, must also be realized to ensure sustainable solutions for low and low-middle income countries. The recommendation to include at least one dose of IPV in routine immunization (with additional use as needed) reflects a risk management perspective independent of cost considerations. However, the lower the price of IPV, the more cost-effective IPV becomes as an option. Based on the interaction with manufacturers, the WG expects the international community to collaborate with manufacturers to work toward a target price of $0.50/dose of IPV for low-income countries.

2.4 *Fractional dose, intradermal (ID) or adjuvanted, intramuscular(IM) IPV as "low cost" IPV options.* Following an extensive review of potential strategies for achieving a low cost trivalent IPV product for OPV2 cessation in the near term, two viable approaches emerged for reducing the cost substantially below US$ 1 per dose: intradermal (ID) fractional (1/5th) doses

and adjuvanted intramuscular (IM) IPV. Both approaches face substantial regulatory and/or development challenges but these can be addressed in the near-term (24-36 months) with appropriate, intensive support from the international community, the development of a multi-dose vial policy for IPV, active engagement by manufacturers, and rapid mapping of regulatory pathways and options.

2.5 *Need to make both fractional intradermal (ID) and adjuvanted intramuscular (IM) options available.* As countries may have different preferences with respect to the ID vs. the adjuvanted IM dose-sparing options, and based on limited evidence about the related risks, costs, and benefits, both options should be pursued. Some immunization program managers identified a potential preference for ID administration if IPV were to be given at an immunization contact during which other IM injections are already given (e.g. DPT, PCV); other immunization programs may prefer not to introduce a new delivery technology.

WHO has been collaborating with the manufacturers of needle-free injection devices for several years, which has resulted in the engineering of two new intradermal devices that are currently being investigated in clinical trials. If successful, these devices could be used to administer fractional-dose IPV intradermally.

2.6 *Need to continue IPV for at least 5 years beyond bOPV cessation.* Recognizing that as the risks associated with eventual bOPV cessation may be similar to those following OPV2 cessation, countries should plan to continue IPV vaccination for at least 5 years after bOPV cessation (i.e., after stopping all routine use of OPV). This issue will be reviewed as additional information becomes available, particularly the experience with OPV2 cessation.

2.7 *Target synchronous OPV2 cessation by 2015-2016.* As a fundamental step in the polio endgame, synchronous OPV2 cessation should be targeted for the near-term (i.e. 2015 or 2016). Additional consideration of the time frame will be reported back to SAGE in April 2013 following further review of the prerequisites for OPV2 cessation, including the development of affordable IPV options, long-term biocontainment policy, and post-OPV outbreak response policy.

3 Next steps and action points

The WG agreed to the following main next steps and action points:

a) **Follow-up letter to manufacturers:** the WHO secretariat should write a follow-up communication to IPV manufacturers who had been invited to the WG meeting, to request them to summarize the information they had provided to the WG during the interaction on 3 September. Manufacturers should be asked to describe the strategies which a company is able and willing to pursue to work towards developing an 'affordable' IPV product, to comment on the time-frame for this development work, and most importantly, to provide, as much as possible, specific information on the price per dose that this development may eventually result in.

b) **Background paper for SAGE:** the WG requests that the secretariat provide an expanded background paper, to be provided to the WG and then to SAGE (and to be included in the SAGE 'yellow book'), in order to summarize as completely as possible the scientific evidence to underpin the recommendation for a 1-dose IPV strategy.

c) **WG conference call end-October:** the WG should hold a pre-SAGE conference call (end-October / early November) to finalize WG recommendations and the WG presentation to SAGE at their November meeting.

d) **IPAC presentation on IPV delivery through IM vs. ID injection:** the outcome of the recent 5th WG meeting, as well as the assessment of implications of adding a dose of IPV either through

IM (full or adjuvanted dose) or through ID injection (fractional dose), should be presented to the SAGE Immunization Practices Advisory Committee (IPAC) at their meeting in early October.

e) **Regional consultations:** the 'polio endgame', including plans for OPV2 cessation, should be explained and discussed at the regional and country level, including at regional EPI manager's meetings (EMR: 18 September; this discussion has happened at the time of writing - 6/20/12, see ANNEX IV; AMR/PAHO: 17 October; SEAR: mid-December)

ANNEX I Presentations and discussions on other agenda items

The following are brief summaries of presentations and key agenda items from the 5th meeting.

3.1 *Current status of the GPEI and outcomes of VDPV meeting.*

B. Aylward reported on *major developments in the Global Eradication Initiative since the last WG meeting* in early February 2012. Key development in terms of polio epidemiology was that in end-February 2012, India was formally removed from the list of countries with wild poliovirus transmission; the last wild poliovirus case in India was detected in January 2011.

Also, type 3 wild poliovirus cases are only reported from northern Nigeria and Pakistan. The only area reporting type 3 WPV in Asia is a small circumscribed area of Khyber agency, North-West Pakistan.

Following the report of the GPEI's Independent Monitoring Board (IMB) in the fall of 2011 and the subsequent discussion on the status of the GPEI at SAGE in November 2011, the World Health Assembly declared polio eradication as an *emergency for global public health* on 25 May 2012. Since then, efforts have been targeted at the remaining priority countries to establish and improve accountability structures for government and partner agency staff, to identify and recruite more than 6500 additional partner agency staff (WHO: technical assistance, UNICEF: social mobilizers) at the local level in highest risk areas, and to establish multiple new strategies to improve the quality of SIAs to identify and vaccinate children missed by SIAs.

Activities in the three endemic countries Afghanistan, Pakistan and Nigeria have received effective support from the highest political level, including from the Heads of State.

As of 11 September 2012, the majority of the 136 cases reported in 2012 were reported from the endemic countries (Nigeria: 84, Pakistan: 30, Afghanistan: 17, with only 5 cases reported from Chad), while the number of cases reported at this time last year was 379, reported from 11 countries.

Nigeria currently is the only country in the world where the number of cases has considerably increased compared to last year (from 26 in 2011 to 84 cases this year).

Type 2 vaccine-derived poliovirus (cVDPV2) from the known foci of transmission in northern Nigeria and south-east DR Congo had been reported last in April 2012; however, cVDPV2 - with evidence of prolonged undetected transmission - was recently also reported from both sides of the Kenya-Somalia border.

The large remaining financing gap of around 600 million USD to implement the 2012-13 emergency plan is a continued serious problem, which has already led to the cancellation of planned SIAs in more than 30 countries at risk of importation and spread.

*Discussions about OPV2 cessation at SAGE and the WHA. I*n April 2012, SAGE re-affirmed the need for sequential cessation of OPV vaccine serotypes, starting with type 2 (i.e. synchronous replacement of tOPV with bOPV for routine immunization, or OPV2 cessation), and, to mitigate possible associated risks, had recommended for countries to consider to introduce 1 dose of IPV into their routine immunization schedules prior to OPV2 cessation.

While promoting the concept of introducing a universal 1-dose IPV policy in the context of OPV2 cessation, SAGE recognized and accepted that it was highly probable that IPV uptake would be low in low-coverage countries. SAGE requested that WHO and the GPEI continue to work towards making low-cost options for IM and IM IPV available within 1 year, and decided that, while OPV2 cessation was urgent, 2014 was too early as the target date for OPV2 cessation.

In a resolution on polio eradication in May the WHA endorsed the concept of OPV2 cessation, but expressed alarm over current IPV prices, limited IPV supply options, and lack of clear cost-benefit

assessments. The WHA requested WHO to work with partners and manufacturers to enhance IPV affordability and availability.

The Global Certification Commission (GCC), in August 2012, welcomed the benefits of an early cessation of OPV2 use, and recommended a formal process for Regional Certification Commissions (RCCs) to 'conclude' (not certify) that wild poliovirus type 2 was eradicated, based on time since WPV2 was last seen (>10 yrs), and on the quality and sensitivity of surveillance in the Regions. The GCC recommended that Phase I of lab containment of WPVs needs to be completed globally, prior to OPV2 cessation. The GCC is willing to consider evidence to conclude WPV2 was eradicated as early as mid-2013.

3.2 *Development of the Polio Endgame and Legacy Strategy*

A. Freeman introduced the current draft strategic plan for the polio endgame and legacy options. This document is currently being developed in close consultation with GPEI spearheading partners and other initiatives (i.e. GAVI), as well as with WHO Regional Offices; further consultations about this project will be held with the IMB in October and with SAGE in November.

The document will be drafted using three main sections: a) the endgame strategic plan, including the eradication of polio, and management of associated risk, b) the legacy, i.e. to define the broader global health benefits of the global polio programme, as well as c) the financial requirements 2014 to 2018 (i.e. a 2014 to 2018 indicative budget).

Key assumptions of the document will be that WPV transmission will be interrupted globally by end-2014, OPV coverage reaches the necessary thresholds, full financing and effective implementation will be feasible, VDPVs can be eliminated, and affordable IPV will be available for low-income settings.

Major thematic areas, timelines and milestones for the 'Endgame' section will include a) routine immunization, b) SIAs, c) surveillance, d) communications and social mobilization, e) lab containment and f) the certification process. Geographical considerations and risks to be considered will relate to wild poliovirus and vaccine-derived poliovirus. Long-term poliovirus risks during the endgame will be managed with a long-term IPV policy, effective response activities to cVDPV using IPV, and the use of polio anti-viral compounds.

The 'legacy' part of the document will include a discussion of the polio infrastructure (human resources, capacities and infrastructure, social mobilization and knowledge), as well as a discussion of 'broader benefits' of polio eradication - including an expanded global surveillance response capability.

3.3 *Affordable IPV for routine immunization: new study results contributing to policy discussions*

R. Sutter provided updates on new study results that are relevant to the ongoing policy discussions. Three main policy-relevant questions to address were:

- whether recent results from the Indian study on intestinal immunity confirm that IPV boosts intestinal immunity in infants and children with a history of multiple OPV doses;
    - preliminary analyses from this high-quality trial (few drop-outs, high compliance with study procedures and completion of questionnaire data) suggest that a single dose of IPV can significantly decrease excretion in all age groups, but that the greatest benefits are seen in older children because their intestinal immunity has waned; full analysis of the results is expected in the next 3 months;
- whether or not data from the Cuba study (phase 2) show a difference between intestinal immunity induced by fractional-dose IPV compared with full-dose IPV;

    - preliminary conclusions include that full-dose IM IPV and fractional-dose ID IPV (1/5 of a full dose) induce a similar immune response, and that tOPV (live virus) can accelerate intestinal immune response in IPV-vaccinated infants (regardless whether vaccinated with a full or fractional IPV dose);

- what evidence can be derived from Hungarian VAPP on the one-dose efficacy of IPV against VAPP;
    - data from Hungary suggest a highly significant reduction of VAPP following the introduction of one dose of IPV.
    - the WG noted however that other data from a WPV1 outbreak in Senegal suggested potentially lower effectiveness of a single dose of IPV.

3.4 *ID vs. IM administration of IPV in context of OPV2 cessation*

J. Bilous reported on findings of 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 also included interviews with EPI managers from Asia (India), and Africa (one West and one East African country).

Main conclusions were that:

- ID administration of IPV may be preferred in countries where multiple IM injections are already being given to infants at the time suggested for scheduling the IPV dose (i.e. the 3rd DTP contact at 14 weeks of age);
- training and supervision will be more intensive for ID administration;
- vaccine wastage rates may be higher for ID, but cost of wastage lower;
- countries which already have been successful at introducing several other new vaccines will be most successful in introducing IPV; however, these countries generally have well-performing EPI programmes and will be least likely to be affected by cVDPV following OPV2 cessation;
- large countries without a history of successful nationwide new vaccine introduction will encounter greater difficulties.

3.5 *Towards affordable IPV - recent efforts by the BMGF*

Jay Wenger, the director of the polio team at the Bill and Melinda Gates Foundation, provided an update on the foundation's current program of work on IPV, including findings and the BMGF position related to four main areas of interest:

- the potential contribution of IPV to polio eradication,
- IPV product options for GAVI-eligible countries and lower middle-income markets,
- the affordability of IPV and supply potential for GAVI-eligible countries and lower middle-income markets, and
- factors enabling affordable IPV for GAVI-eligible countries and lower middle-income markets.

Probably the most critical issues for the BMGF are the 'affordability factors' defining IPV affordability and supply potential.

The BMGF feels that a key factor for success will be clear SAGE recommendations on IPV use in polio eradication, including on

a) the role of IPV in routine immunization as part of OPV2 cessation,

b) its role in routine immunization as part of OPV cessation overall, and

c) the role of IPV during campaign use to help interrupt WPV transmisison.

In this context, the BMGF encourages the WG to identify the additional studies or efforts needed in case any of the previous 3 questions cannot yet be answered due to insufficient data.

The second-most critical factor will be for the GPEI to gain sufficient financial support for IPV, including clarification of whether GAVI will be willing to open a 'funding window' for IPV.

Lastly, once SAGE recommendations on IPV use have been made, country acceptance and uptake will depend on establishing a dedicated technical capacity to support countries in the adoption of IPV.

J. Wenger assured the WG that the BMGF is committed to support the availability of IPV for GAVI-eligible and lower middle-income countries, at the lowest possible prices.

3.6 *Surveillance strategies to accompany OPV2 cessation*

H. Jafari described to the WG the surveillance goals and priorities to accompany and support the 'polio endgame,' including the AFP surveillance and environmental surveillance (ES) systems. The main objectives of surveillance will be to ensure prompt and reliable detection of and response to any wild poliovirus and Sabin 2 virus following OPV2 cessation (i.e. discontinuation of tOPV), and to any VDVP or Sabin virus following cessation of all OPV.

Main surveillance strategies for the 'endgame' will be the AFP system, supplemented by environmental surveillance, as well as, when and where appropriate, special targeted studies, including serosurveys, large scale stool surveys and expanded sampling of case contacts.

For AFP surveillance, certified WHO Regions (Americas, European and Western Pacific Regions) will need to revitalize their AFP system to meet performance standards through global certification. Non-certified Regions (Eastern Med., S.-E. Asian and African Regions) will need to close any remaining AFP quality gaps prior to OPV2 cessation, and subsequently sustain AFP quality at the national and sub-national levels through regional and global certification.

Environmental surveillance of waste or sewage water samples is used to supplement AFP in selected areas; the method can potentially detect infection / transmission before paralytic cases occur. However, ES has to be targeted appropriately and is most successful in detecting polioviruses, i.e. excretion from high-risk population groups, where such groups reside and can be sampled in areas with converging sewage systems.

The GPEI plans to expand ES to

a) identify residual WPV transmission in endemic areas,

b) provide early indication of new importations, and

c) document elimination of Sabin virus following OPV2 cessation and eventual bOPV cessation.

By mid-2014, additional ES sampling sites will be placed in Nigeria and Afghanistan, and other areas at high risk of WPV importation and spread. Also, an additional 10 to 20 sites globally will be established based on history of recurrent cVDPV emergence.

In summary, surveillance systems for poliovirus will be adapted to support the goals and priorities of the 'polio endgame,' including regional and global certification of wild poliovirus eradication and verification of VDPV elimination. To achieve the surveillance objectives, targeted environmental surveillance will be further expanded, and special surveillance activities will be used; also, new diagnostics will be developed to more rapidly detect polioviruses.

3.7 *Poliovirus laboratory containment as pre-requisite for OPV2 cessation*

C. Wolff noted that the main objective of the Global Action Plan III (GAP III) for laboratory poliovirus containment, the key policy document, is to minimize the risk of reintroducing facility-based wild and Sabin polioviruses into communities following wild poliovirus eradication and OPV cessation.

GAP III relies on two main containment strategies: risk elimination through the destruction of unneeded poliovirus materials, and risk management - activities to manage the risk and consequences of a possible inadvertent poliovirus release through effective management and so-called 'safeguards.'

Primary safeguards minimize risk through facility design, management and oversight (i.e. biosafety level requirements, legal frameworks, national and international accreditation). Secondary safeguards minimize the consequences of poliovirus release through locating facilities in areas with sufficiently high anti-polio immunity, and tertiary safeguards minimize consequences through locating wild poliovirus facilities in areas with low probabilities of poliovirus spread (i.e. with high standards of hygiene and sanitation).

Main implications of / requirements for OPV2 cessation (i.e. replacement of tOPV with bOPV for routine immunization) are:

- finalization of Phase I of lab containment (national survey and inventory);
- determination of all facilities retaining WPV type 2 infectious or potentially infectious materials, and those retaining Sabin 2 materials;
- establishment of national regulatory environment in WHO Member States to encourage destruction of unneeded type 2 poliovirus materials and to facilitate safe handling of type 2 materials that are retained.

The following will be important next steps to assure progress in lab containment commensurate with plans for OPV2 cessation:

- continue completion of lab inventories to finish Phase I containment in polio-free countries (particularly India);
- finalize containment procedures required for phased OPV cessation (serotype containment);
- begin process of Sabin 2 containment;
- finalize GAP III with approval of WHO governing bodies; and
- begin work with Member States on national regulatory frameworks.

3.8 *Outbreak response strategies post-OPV*

The GPEI has gained experience in responding to more than 100 outbreaks of wild poliovirus (WPV) and of circulating vaccine-derived poliovirus (cVDPV) during the last decade. The intensity and dynamics of response will change with increasing time from the cessation of OPV use, as both population susceptibility and public health response capacity change.

Key principles of response, as recommended by the Advisory Committee on Polio Eradication (ACPE) and endorsed in a WHA resolution, remain to

a) within 7 days of the report confirming the outbreak, to rapidly conduct an assessment and develop a response plan, to
b) conduct a large, high-quality and sustained immunization response within 4 weeks of the confirmation of the outbreak, and
c) to implement a surveillance response through immediate enhancement of surveillance and detailed investigation.

The immediacy, speed and scope of outbreak response has been strongly predictive of the duration of the outbreak and number of immunization rounds needed to control it. Outbreaks for which a quality response immunization was conducted within less than 6 weeks of onset of the index case continued for only half as long as those for which the first immunization round was conducted more than 6 weeks after onset of paralysis of the index case. Similarly, the duration of outbreaks for which response campaigns included children over the age of five years was shorter than outbreaks for which the immunization response targeted five-year olds only.

Based on lessons learned in responding to outbreaks during the last decade, the following key principles are suggested for outbreak response post-OPV cessation:

- Speed – response within less than 6 weeks of index case onset and less than 4 weeks of notification;
- Flexibility – short intervals (2-3 weeks) between rounds, targeting of wider age groups (< 15 years);
- Technical support – initial assessment within 48 hours of report, deployment of teams within 7 days;
- Sustaining response – minimum 5 response rounds
- 'Closing out' – assessment of response quality at 3 months following the first case, and of surveillance quality at 6 months, or when the outbreak appears to be over, to assure transmission has been reliably interrupted.

OPV remains the main vaccine of choice for response even after its routine use has been stopped, since it will be available in stockpiles, is easily used in large-scale campaigns, rapidly triggers and boosts intestinal immunity, and has a proven track record in outbreak response.

Following OPV2 cessation, mOPV2 will be used for type 2 cVDPV outbreaks, and bOPV or mOPV for outbreaks of WPV or cVDPV type 1 and 3. Stand-alone IPV may play a role for responding in contiguous areas affected by the outbreak. Following cessation of all OPV use (i.e. post bOPV cessation), outbreak response will be conducted with the appropriate mOPV from stockpiles, possibly with stand-alone IPV.

ANNEX II

Draft Agenda

Fifth Meeting of the SAGE Polio Working Group

WHO, Geneva, *Salle D,* 3-4 September, 2012

Monday, 3 September, 2012

8:00 – 8:15	Registration	
8:15 - 8:30	Welcome and opening remarks	E. Miller
8:30 – 9:00	Current status of the GPEI and outcomes of VDPV meeting	B. Aylward
9:00 – 10:00	Affordable IPV for routine immunization: new data strengthening the case, and I.D. vs I.M. IPV administration	R. Sutter J. Bilous
10:00 - 10:30	Towards affordable IPV - recent efforts by the BMGF	J. Wenger
10:30 – 11:00	*Coffee break*	
11:00 - 11:30	Poliovirus lab containment: GAP III, finalizing facility requirements, and implications for tOPV-bOPV switch	C. Wolff
11:30 - 12:30	IPV products, prices and supply: WG interaction with SANOFI *(closed session)*	
12:30 - 13:30	*Lunch break*	
13:30 - 14:30	IPV products, prices and supply: WG interaction with *GSK*	*(closed session)*
14:30 - 15:30	IPV products, prices and supply: WG interaction with *Serum* Institute of India (SII)	*(closed session)*
15:00 – 15:30	Coffee *break*	
15:30 - 16:30	IPV products, prices and supply: WG interaction with Staten Serum Institute (Denmark)	(closed session)
16:30 - 17:00	WG discussion	

Tuesday, 4 September 2012

8:30 - 8:45	Recap - day 1	E. Miller
8:45 - 9:30	Surveillance strategies to accompany the switch: AFP, expanding environmental surveillance and targeted studies	H. Jafari
9:30 - 10:00	Outbreak response strategies post-OPV: mOPV stockpile and WHO use, potential role of IPV	C. Wolff
10:00 - 10:30	*Coffee break*	
10:30 - 11:00	The GPEI 'Endgame and Legacy' strategic plan 2014-2018	A. Freeman
From 11:00	*Internal WG discussion on key questions to prepare for renewed interaction with SAGE on the tOPV-bOPV switch (closed session)*	
11:00 - 12:30	*1 - IPV introduction:* should SAGE strengthen its IPV recommendation given the additional information now available on VDPV risks and IPV impact, price, supply and route of administration?	
12:30 – 13:30	*Lunch break*	

13:30 – 14:30	*2 - ID vs IM application of IPV:* how should SAGE balance its recommendations vis-a-vis ID vs IM IPV use for the purposes of a tOPV-bOPV switch?	
14:30 – 15:30	*3 - Timing for tOPV-bOPV switch:* in view of the additional information suggesting that the pre-requisites are likely to be in place, can SAGE now make a specific recommendation on the timing of a tOPV-bOPV switch?	
15:30 - 16:00	*Coffee break*	
16:00 - 17:00	*4 - IPV post-bOPV cessation:* should SAGE recommend 1 routine IPV dose following final cessation of bOPV?	
17:00 - 18:00	Final WG discussion to prepare for November meeting of SAGE	E. Miller

ANNEX III - Letter and questions to IPV manufacturers

Dear ....

On behalf of Dr Elizabeth Miller, Chair of the SAGE Polio Working Group, I would like to invite you to the Working Group meeting on the afternoon of 3 September, 2012.

In planning for the 'tOPV-bOPV switch' (i.e. cessation of type 2 OPV use), and eventual bOPV cessation, the WG would appreciate your frank perspectives on key issues related to IPV that may affect planning for these critical phases of the polio 'endgame'.

The following are main issues which the Working Group would like to discuss with you:

(a) what are the quantities of whole dose IPV could your company potentially provide for low-income markets over the coming 5 years, and under what conditions?

(b) how would volume purchasing translate into price reductions for whole dose IPV from your company?

(c) how would fractional dosing and the use of adjuvants impact IPV price, and what would your company require to develop such products?

(d) how does your company envisage the development challenges and timlines for a low-cost, low-IPV dose hexavalent product for low-income settings, and what would your company require to develop such a product?

We would appreciate if you could prepare 15 to 20 minute presentations on these main discussion issues. In preparing for the inter-action with the Working Group please also note the attached more detailed list of relevant questions.

The information you provide and all discussions will be treated as confidential, unless you explicitly inform us otherwise.

Please confirm at your earliest convenience that you will be able to participate in the planned session between the Working Group and your company which has been tentatively scheduled for ..... p.m. on 3 September, 2012.

With best regards,

.....

Detailed background questions.

1) Current IPV:

a) what is your current production capacity and what would be your timelines for scale-ups to 50, 100 and 200 million doses per year?

b) what are the key factors affecting your decisions re scale-up/expansion?

c) what is your current 'best price' for stand-alone IPV for low-income settings and what would be your rough 'best price' for 10 million doses year? 25, 50, 100?

d) how would volume purchases and guaranteed minimum purchases affect your price? what other approaches could help you offer a best price?

2) ID IPV: your perspectives on

a) the licensing pathway for ID (requirements, timelines, feasibility based on discussions to date - if any - with your regulators),

b) the impact of ID on your company's cost and price of ID per dose; specifically what would be your 'best price' for ID IPV? How - if at all - would volume purchases affect your company's price?

3) 'Low-cost' IM IPV (SAGE's specific request): your perspectives on

a) potential approaches to developing a low-cost (as well as low price) IM IPV standalone vaccine for low-income settings,

b) specifically, what would be the potential dose reduction with adjuvanting of IPV?

c) what is the feasibility of developing an adjuvanted IM IPV (timelines, regulatory path)?

d) what would be the potential cost-savings/price reduction for an adjuvanted standalone product?

4) Hexavalent IPV:

a) do you have a development plan for a 'low-cost' hexavalent product targeted for low-income/GAVI settings?

b) if not, what would you need to initiate such a development project?

c) how would the price of such a hexavalent compare to your current pentavalent product?

d) what approach would your company take to a hexavalent product (e.g. WP vs aP; IPV antigen content?)

e) what is your company's best and worst case development timelines for a low-cost hexavalent product?

ANNEX IV

New Polio end game strategy (tOPV-bOPV switch)

Comments from National EPI managers & chairmen of NITAG, WHO Eastern Mediterranean Region, 27th EPI managers meeting, 20 September, Egypt

As per SAGE request (April 2012 meeting), the "new proposed polio end game" was discussed during the 27th inter-country meeting of national EPI managers in the WHO Eastern Mediterranean Region. This meeting was held from 17 to 20 September in Sharm El Sheikh and was attended by the national EPI managers and the chairmen of the NITAGs in the 23 EMR member states, as well as by several partners.

So far, 10 EMR countries have introduced at least one dose of IPV into their national routine immunization schedule, and one country is in the process of doing it. The remaining 12 countries include the 7 GAVI-eligible EMR countries (Afghanistan, Djibouti, Pakistan, Somalia, Sudan, South Sudan and Yemen) and 5 low-middle income countries (Egypt, Iran, Iraq, Morocco & Tunisia).

The tOPV-bOPV switch session was conducted first in plenary, with all countries, and several issues were raised, mainly concerns about the IPV price. Different prices were raised for the full IM IPV: 1) currently prices paid by some countries in the Region (self procuring MIC and HIC) are around 3.2 to 3.5 USD 2)UNICEF price currently around 2.5 USD and 3) participants were informed about the new SII offer to UNICEF of 1.5 USD. SII initiative was well received from the country representatives and they consider it as a positive sign towards lower prices in the future (competition between producers), but still this is considered by MIC as beyond their current financial capacities as most of them are still struggling to introduce new vaccines like PCV (and even Hib) despite the practitioners and public pressure and the availability of strong evidence of high disease burden related to these new vaccines.

Participants raised as well concerns about bOPV and IPV global production capacity, the best timing for the IPV dose (with DPT1 to provide better protection against VAPP, or with DPT3), IPV and maternal antibodies, OPV birth dose and the new proposed strategy, OPV/IPV sequential versus simultaneous administration, IPV as additional dose or replacing one of the OPV doses, the lack of trained human resources in poor health system countries and the need to reach high coverage with the required additional injectable vaccine (IPV), the expected impact on the cold chain of the additional IPV dose, etc). Participants from some GCC countries reported that their countries are currently considering adding a second IPV dose to their routine immunization schedule, and that this issue is one of the agenda items of the 2nd GCC States Symposium on New trends in Vaccination that will be held in Dubai from 9 to 10 Ocober 2012.

In summary from the plenary session, participants agreed on the importance for each country to start preparing for registering the bOPV as well as mOPV1 & mOP2 as soon as possible. They raised several concerns in particular about the cost of IPV. They requested SAGE to be more explicit about the recommended IPV dose to be an additional one or to replace one OPV dose, as well as the best recommended administration time.

Considering the fact that countries that have already introduced at least one IPV dose into their routine immunization schedule won't have much concerns about the proposed tOPV=bOPV switch except for the bOPV, mOPV1 & mOPV3 registration; the meeting organizers decided to have a special gropu work with the remaining 12 countries that did not introduce yet any IPV into their routine EPI, to discuss their future plans as well as financial and programmatic capacities and expted constraints in relation to proposed switch strategy. The main outcomes from this group work (see detailed information attached) include:

1. Morocco and Tunisia are already planning to introduce at least one dose of IPV by and of 2014 and 2015 respectively. Egypt and Iran raised their national vaccine production as major constraint for both bOPV and IPV use. All remaining countries think that introducing one dose of IPV in the context of a global tOPV-bOPV switch might be possible and pending partners financial support (GAVI ++). Pakistan representatives were the only ones that believe that this won't most probably be possible for their

country mainly because of the expected financial impact, even if supported by GAVI, as well as the expected programmatic implications.

2. All countries, except Tunisia, and in particular the GAVI eligible countries, are more in favor for an IM IPV option, mainly because of the capacity of the field staff to deliver ID injections. Tunisian representatives mentioned that their country will definitely go for the ID IPV option for financial reasons. All participants were concerned about the possible impact of a non-correct ID injection of IPV on the expected immunologic response and requested SAGE to clarify that.

3. The main expected challenges mentioned by the participants relate to financial constraints for both the IPV vaccine price and the introduction cost (training, cold chain, etc), programmatic (another injectable vaccine for some already overloaded and poor delivery systems, increased number of injections during same session (IPV, Penta, etc), capacity of the field staff to deliver ID injections, capacity of the programme to reach as high coverage figures with an injectable vaccine as with OPV, in particular in some remote and difficult areas, etc) and logistic (cold chain issues). Participants highlighted their wish to see a low cost hexavalent vaccine option among WHO and partners priorities.

Scientific evidence in support of:

Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012

Statements under 2.2 (pages 2-3)

2.2 *Use of IPV to manage risks associated with OPV2 cessation.* OPV2 cessation will expose the global population to a new, exceptional era in the history of vaccination, in which there will be a low, but real risk of type 2 polio outbreaks due to circulating vaccine-derived polioviruses, long-term VDPV excretors and reintroduction from containment failures (the last WPV type 2 cases, which occurred in northern India in 2002-2003, were associated with the introduction of a laboratory strain).

The risks of new cVDPV2 emergences extend into the period immediately following OPV2 cessation, because some OPV2 viruses may be circulating silently in populations with relatively low population immunity at the time of cessation. The possibility of sustained transmission of a type 2 virus increases with increasing population susceptibility following cessation of all routine and supplemental use of OPV2. IPV, which is trivalent and includes serotype 2, will be the only poliovirus vaccine available for type 2 protection. At least 1 dose of IPV should be introduced into routine immunization programmes prior to or at the time of OPV2 cessation to yield the following expected benefits:

a) the prevention of paralytic polio in individuals successfully vaccinated with IPV who get exposed to a cVPDV type 2, Sabin type 2 (VAPP) or wild poliovirus type 2;

b) improved immunological response in individuals previously vaccinated with IPV when receiving mOPV2 vaccination given in response to a WPV2 or cVDPV2 outbreak that occurs after OPV2 cessation;

c) reduced transmission of cVDPV2 or WPV2 should they be introduced (i.e. there is evidence to suggest that IPV reduces the titer of fecal virus excretion and duration of shedding and is equivalent to OPV in decreasing oropharyngeal shedding);

d) boosting of immunity to wild polioviruses type 1 and 3 in vaccine recipients, which may further accelerate wild poliovirus eradication.

For countries at particular risk of cVPDV emergence, the suggested minimum 1-dose IPV policy may need to be complemented with additional measures (e.g. pre-OPV2-cessation boosting with tOPV SIAs to maximize population immunity to serotype 2 or introduction of a 2nd IPV dose, potentially with catch-up campaigns).

a) the prevention of paralytic polio in individuals successfully vaccinated with IPV who get exposed to a cVPDV type 2, Sabin type 2 (VAPP) or wild poliovirus type 2;

Supporting evidence:

- *Efficacy against Sabin virus (i.e., surveillance for vaccine-associated paralytic poliomyelitis [VAPP])*:
    - the most convincing evidence emanates from countries that used sequential schedules of one or more doses of IPV followed by OPV to prevent vaccine-associated paralytic poliomyelitis (VAPP) [1].
    - in the United States, after introduction of a sequential schedule of IPV followed by OPV in 1997, no case of VAPP was reported in infants that had received at least a single dose of IPV [2].
    - in Hungary, a country that has traditionally reported the highest rates of VAPP in the world, not a single VAPP case was reported, after introduction of a single dose of IPV in 1992, suggesting that a dose of IPV is highly efficacious in preventing VAPP [3-6, & WHO unpublished data].
    - WHO is aware of only single case of VAPP in a child that had received a dose of IPV in the modern era (with enhanced-potency IPV) [WHO unpublished data].
- *Efficacy against wild poliovirus*:
    - there are data on one-dose efficacy generated in a case-control study in Senegal that reported 36% effectiveness (95% confidence interval 0-67%) in preventing paralysis during an outbreak of poliomyelitis caused by poliovirus type 1 [7].
- *Immunogenicity of a single dose of IPV in naïve infants:wild poliovirus*:
    - a single dose of IPV administered to naïve infant s aged 4 months reported that 63% seroconverted against type 2 (compared to 47% of infants that received fractional-dose IPV [0.1. ml intradermally, 1/5 of a full dose] and that 98.3% of infants that didn't seroconvert did actually respond with a priming immune response (compared to 94.0% in the fractional-dose IPV group). [Data presented to SAGE WG. WHO unpublished data from Cuba, 2012]

Summary:

The data suggest high efficacy (close to 100%) of a single dose of IPV against VAPP and somewhat lower efficacy against wild poliovirus. The biological plausibility seems established with the recent data from Cuba on one-dose IPV seroconversion and priming. Given that indigenous wild poliovirus type 2 has been eliminated since 1999 globally, the challenge to IPV-induced type 2 immunity will be primarily Sabin type 2 poliovirus.

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b) improved immunological response in individuals previously vaccinated with IPV when receiving mOPV2 vaccination given in response to a WPV2 or cVDPV2 outbreak that occurs after OPV2 cessation;

Supporting evidence:

- a single dose of IPV will effectively close the immunity gaps to poliovirus type 2 in previously OPV-vaccinated children. In Cote d'Ivoire and India studies one IPV dose in seronegative infants closed the immunity gaps against type 2 completely [8, 9].
- Data suggest that IPV and OPV are interchangeable. A study from the United States with arms of IPV followed by OPV and OPV followed by IPV reported similar results in terms of seroconversion [10, 11].
- in seropositive individuals, a dramatic boosting of antibody titers is seen (~60-70%) against type 2 after a single IPV dose [12,13].
- a single dose of IPV in immunologically-naïve infants in Cuba aged 4 mos seroconverted 63% against type 2 (compared to 47% after a fractional dose). [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012. Submitted for publication].
- data from Cuba showed that 98.3% (94.0% following a fractional IPV dose) infants who didn't seroconverted after a single dose of IPV responded with a priming response to poliovirus type 2. [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012. Submitted for publication].
- OPV after IPV results in closing of immunity gaps and substantial boosting of antibody titers [10-12, 14-15].
- new data from India demonstrate that a single dose of IPV in infants and children (aged 6-11 mos, 5 and 10 yrs) with a history of multiple doses of OPV boosts intestinal mucosal immunity, and reduces excretion prevalence after a challenge by 51-81%. [Data presented to the SAGE WG. WHO unpublished data from India, 2012. Submitted for publication].

Summary:

- since levels of antibody (after mucosal exposure of live poliovirus) are predictive of likelihood of excretion, a single dose of IPV should substantially decrease prevalence, titer, and length of poliovirus excretion.
- and more importantly could allow rapid (within 3 days) boosting of immune response (both humoral and mucosal).

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c) reduced transmission of cVDPV2 or WPV2 should they be introduced (i.e. there is evidence to suggest that IPV reduces the titer of fecal virus excretion and duration of shedding and is equivalent to OPV in decreasing oropharyngeal shedding);

Supporting evidence:

Intestinal mucosal immunity:

General:

- Introduction of IPV in advance of Sabin type 2 cessation would decrease the proportion of population naïve to poliovirus and boost both humoral and mucosal immunity.
- convincing evidence suggests that mucosal exposure with live poliovirus is necessary to obtain an IgA response after IPV booster vaccination. In subjects that were naturally immune (to wild poliovirus), a single booster dose of IPV resulted in strong increases of IgA levels within a week in 93%, 94% and 83% against poliovirus types 1, 2, and 3, respectively [16,179].

After sequential (OPV and IPV) vaccination:

- in sequential schedule of OPV and IPV, nearly a high proportion of infants formed local neutralizing and IgA antibody responses [18].
- IPV was administered at age 9 months in infants with a history of 5 doses of OPV in Oman [19]. Infants were then challenged with monovalent type 3 poliovirus vaccine (mOPV3) 6 months later. In the IPV group, 12.7% subjects excreted virus compared with 17.0% and 16.4% in the two tOPV groups, respectively.
- new data from India demonstrate that a single dose of IPV administered to infants and children (aged 6-11 mos, 5 and 10 yrs) with a history of multiple OPV doses dramatically boosts intestinal mucosal immunity, and reduces excretion prevalence after a bOPV challenge by 54-72% against type 1, and 51-81% against type 3 The effect is largest in children age 10 yrs and considerably larger than with a supplemental dose of bOPV. [Data presented to the SAGE WG. WHO unpublished data from India, 2012].

After IPV vaccination only:

- after 2 doses of IPV, the excretion prevalence is similar to unvaccinated control groups (>90% excrete after a challenge) by day 7, but virus titer in stool is 0.5 log10 lower by day 7 [12]; a follow-up study suggested that excretion period is shortened by half (median 10-12 days compared with >20 days in unvaccinated controls), and titers are ~0.5-1 $\log_{10}$ (3-10-fold decrease) lower at day 7 [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012].
- After 3 doses, the responses appear to be similar to those after 2 doses of IPV [12, 20].

Oropharyngeal mucosal immunity:

- after 3 doses of IPV, oropharyngeal shedding is rare, and appears to be similar to OPV-induced immunity [21].
- no data are available of oropharyngeal shedding after a single dose of IPV.

Summary:

- in infants whose mucosal surfaces had been exposed to live poliovirus (for example, after OPV vaccination), resistance to excretion following a challenge (e.g., OPV) depends on levels of type-specific antibody (the higher the antibody levels, the less likely to excrete). WHO unpublished data from Cuba, 2012. Netherlands.
- a dose of IPV (after multiple doses of OPV) closes the immunity gaps (both humeral and mucosal) and substantially boosts antibody titer [8-13].
- as shorter excretion duration with lower viral titer likely equates with lower transmission), the addition of a single dose of IPV would be expected to have a substantial effect on population transmission.
- the lower prevalence of excretion, the shorter length of excretion duration, and the lower stool titers of poliovirus among IPV-vaccinated infants should curtail endemic or epidemic spread of poliovirus.

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d) boosting of immunity to wild polioviruses type 1 and 3 in vaccine recipients, which may further accelerate wild poliovirus eradication.

Supporting evidence:

- in the schedule proposed for OPV2 cessation, 3 doses of bOPV (birth, 6, and 10 weeks) would be administered prior to simultaneous bOPV (4^{th} dose)/IPV (single dose) administration (at 14 weeks), so both the humoral and mucosal immunity against type 1 and 3, respectively, should be expected to very robust. These are the viruses that still circulate in the remaining polio-endemic countries.
- solid evidence from multiple studies demonstrates that a single dose of IPV in previously OPV-vaccinated children closes the immunity gaps to all three serotypes (including types 1+3) [examples: 10-11, 12, 14-15].
- similarly the evidence suggest rapid and massive increase in antibody titers [10-11, 12, 14-15].

Summary:

- the combination of these effects (closure of immunity gaps, and boosting antibody titers) after a dose of IPV in infants who had previously received multiple doses of OPV, should decrease excretion prevalence after poliovirus exposure, and therefore, accelerate eradication.

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From: Mr.ACP [mailto:acp@seruminstitute.com]
Sent: 03 October 2012 08:48
To: CHAN FUNG, Margaret F.C.
Cc: BUSTREO, Flavia; AYLWARD, Raymond Bruce J.
Subject: IPV

Dear Dr. Margaret Chan,

In view of our ongoing discussions with the Polio Working Group of WHO SAGE, Dr. Bruce Aylward and also with the Gates Foundation, we are pleased to commit the following with respect to the pricing of Inactivated Polio Vaccine (IPV) from our plant at Bilthoven Biologicals (BBio), the Netherlands.

Although the UNICEF's current latest procurement price of our IPV is Euro 2.50 per dose in a single dose container, we can offer this product at Euro 1.25 per dose in a single dose container for the procurement in 2013. However, if this price needs to be lowered further, we can offer Euro 0.90 per dose in a multi dose container (5 doses / 10 doses per container) provided such packaging is cleared by WHO-QSS. I trust this gesture of reducing price of IPV substantially will help in achieving the Polio eradication and implementing the Polio End Game strategy.

Besides this, we are also working on additional strategies of using Adjuvanted Inactivated Polio Vaccine as well as using alternate route of administration i.e. by intradermal route; and we are confident that we will succeed in both these strategies and after getting necessary regulatory clearances and approvals from both National Regulatory Authority as well as WHO PQ team, we can substantially lower the price to meet everybody's expectations of achieving price of our IPV at around U.S $ 0.50 per dose. Of course, this will take sometime, as it involves lot of formulation work, stabilities studies and all the regulatory clearances. However, we are confident to achieve this goal in the coming years.

With kind regards,

Yours sincerely,

Adar C. Poonawalla
Executive Director
Serum Institute of India Limited

The Monitoring & Evaluation/Accountability Framework for the Global Vaccine Action Plan 1: Overview

Background

The development of a Monitoring and Evaluation/Accountability (M&E/A) Framework is considered to be a critically important element of the Global Vaccine Action Plan (GVAP). Recognizing the importance to closely monitor the GVAP implementation progress, the World Health Assembly (WHA) resolution called for annual reports on progress at each Regional Committee meeting and at the WHA, through the Executive Board (EB).

In defining the scope of the M&E/A Framework, the GVAP refers to the need:

- to finalize a complete set of GVAP indicators with the appropriate methodology and data sources for each indicator defined and baselines established, where required.
- to invest in improving data quality and developing more robust in-country monitoring and evaluation systems (GVAP WHA 2012 report, paragraph 102).
- to secure commitments aligned with the GVAP from different stakeholders, including countries, civil society organizations, multilateral agencies, private foundations, development partners, and vaccine manufacturers.
- to develop a mechanism for coordinating the implementation of these commitments at global, regional and national levels (GVAP WHA report, paragraph 103).
- to ensure annual reporting of progress at each Regional Committee meeting and at the WHA, through the Executive Board (EB).

The Accountability Framework for the U.N. Secretary General's Global Strategy for Women's and Children's Health

The GVAP calls for leveraging the recommendations of the Commission for Information and Accountability for Women's and Children's Health and aligning work, wherever possible, with other accountability efforts (GVAP WHA report, paragraph 31).

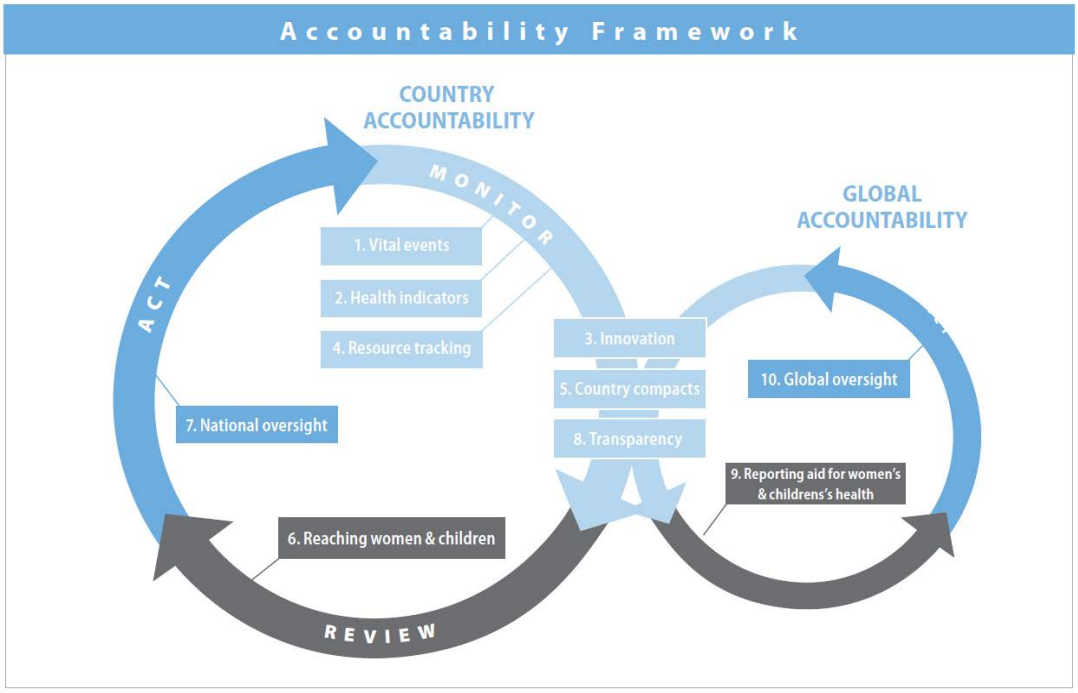
The Accountability Framework of the UN Secretary General's Global Strategy for Women's and Children's Health refers to a cyclical process of monitoring, review and remedy/action to assess progress, document success, identify problems that need to be rectified and take prompt action as and where needed. This process needs to occur at the country, regional and global levels as illustrated in Figure 1.[1]

The Commission on Accountability for Women's and Children's Health report is included in the list of documents on the SAGE meeting website. The framework is structured around the 10 recommendations made by the Commission that are categorized under the following headings: (1) better information for better results; (2) better tracking of

[1] Commission on Information and Accountability for Women's and Children's Health. Keeping Promises, Measuring Results. World Health Organization 2011 (http://www.who.int/woman_child_accountability/en/)

resources for women's and children's health; and (3) better oversight of results and resources.

Figure 1: The Accountability Framework for the UN Secretary General's Global Strategy for Women's and Children's Health



1. Better information for better health results: aims to collect data on progress against the 11 indicators for maternal, neonatal and child health. It also aims to lead to improvements in collection and reporting of data on vital events and on the enhanced use of information and communications technology in national health information systems.

2. Better resource tracking: involves tracking on total health expenditures and expenditures for women's and children's health by source of funds, while also improving capacity in countries to regularly review health spending and relate them to commitments, gender and other equity goals and results.

3. Better oversight of results and resources: at the global level involved the establishment of an independent Expert Review Group (iERG)[2] that reports annually to the UN Secretary General on the results and resources related to the Global Strategy and on progress in implementation of the Commission's recommendations.

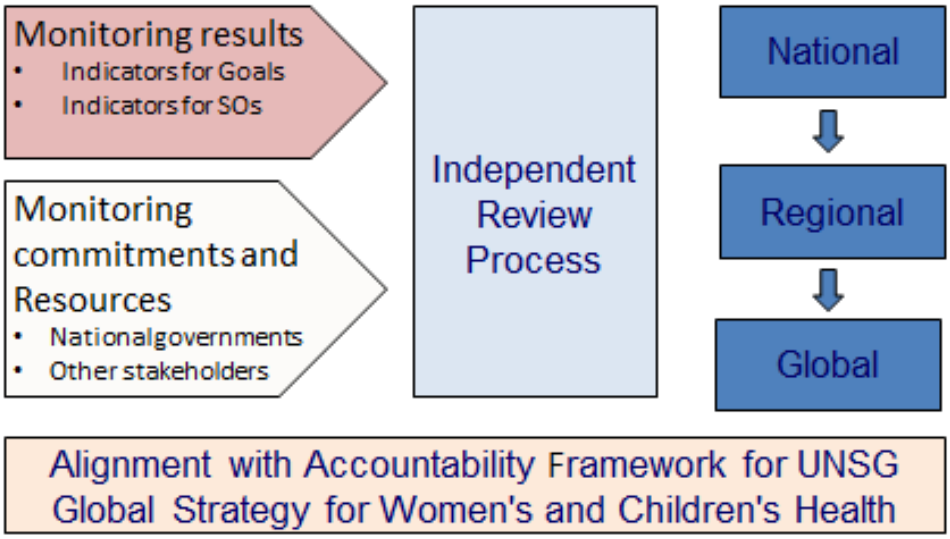
Proposed Process for the GVAP Monitoring & Evaluation / Accountability Framework

[2] iERG members http://www.who.int/woman_child_accountability/ierg/members/en/

A similar cyclical process of monitoring, review, and recommendations for action is proposed for the GVAP M&E/A Framework. In addition to the national and global levels, another level of GVAP M&EA at the regional level is required to accommodate the requirement of reporting annually to the WHO Regional Committees.

Using a similar framework allows for complementarity with the accountability process for the UNSG Global Strategy for Women's and Children's Health and provides opportunities to leverage and/or use these processes for tracking and reporting on some of the aspects of GVAP. This applies in particular to the process to monitor commitments and resources as described in the related documents for this session. Figure 2 illustrates the proposed GVAP M&E/A Framework process. The draft guidelines to make immunization commitments under the UNSG Global Strategy for Women's and Children's Health framework are described in an accompanying document related to this session (Monitoring and Evaluation /Accountability Framework for the Global Vaccine Action Plan – 4: Draft Guidelines for Making Commitments).

Figure 2: Proposed GVAP Monitoring and Evaluation/Accountability Framework



The GVAP M&E/A framework will monitor: (1) results (defined as progress against the GVAP goals and Strategic Objectives indicators); (2) document and monitor stakeholder commitments to GVAP; and (3) track resources invested in vaccines and immunization.

The regional and global level review process will utilize existing WHO processes. At the **global level** the review process will be through SAGE to the EB and WHA. The proposed mechanism for the review and reporting at the global level is through the

constitution of a SAGE Decade of Vaccines (DoV) Working Group and is described in an accompanying document related to this session.

At the **regional level**, the WHO Regional Offices are considering the mechanisms for review and reporting to the Regional Committees. Member States would need to consider the review and reporting modalities at the country level. It is envisaged that countries will develop a national level M&E/A framework to monitor performance of the programme and a review process to document best practices, identify problems and make recommendations for corrective action. At the **country level**, the National Immunization Technical Advisory Groups (NITAGs) and the Interagency Coordination Committees (ICCs) may have important roles to play in this regard.

For the R&D indicators, it is proposed that the Global Vaccine Research Forum (GVRF) be used to review progress and identify priority areas approximately every two years. Accordingly, **progress reports for the R&D indicators will be made every two years**.

Issues for SAGE consideration:

1. *Feedback on the proposed structure of the GVAP M&E/Accountability Framework.*
2. *Comments on the reporting process, taking note of the fact that the reports reviewed by SAGE will contain data on monitoring indicators for the previous year, but the same report presented to the EB and WHA will have data from two years previous (e.g. EB and WHA report of 2015 will have country level data from 2013).*

The Monitoring & Evaluation / Accountability Framework for the Global Vaccine Action Plan 2: The monitoring indicators

Background

The Global Vaccine Action Plan (GVAP) presented to the World Health Assembly (WHA) contained a set of indicators against each Goal and Strategic Objective (SO). Targets were also established for each of the goal indicators. The GVAP indicators were developed initially by the Decade of Vaccines Collaboration (DoVC) working groups and then subjected to a web-based review and prioritization, as well as reviews at a special SAGE meeting and by the DoVC Steering Committee. The indicators were also submitted to consultation by civil society, over 600 people from the DoVC distribution list, and the pharmaceutical industry (represented by International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), BIO and Developing Countries Vaccine Manufacturers Network (DCVMN).

Review and update of monitoring indicators post-WHA

Following the GVAP endorsement at the WHA, an informal consultation was convened to review and refine the existing indicators, develop operational definitions for each indicator, define the source(s) of data if they exist, or how they may be collected, and to establish baselines, milestones and targets, as appropriate. Participants at this consultation included members of the original DoVC M&E working group (WG), with additional participants (see Annex 1) representing the polio eradication and the measles and rubella initiatives, those representing the GVAP Leadership Council (LC) agencies (WHO, UNICEF, Bill & Melinda Gates Foundation, GAVI Alliance secretariat and NIAID), US Centers for Disease Control and Prevention, Measure DHS, and Departments of Health Statistics and Informatics, and Maternal Neonatal Child and Adolescent, respectively, in WHO.

Addition consultations were held by in person, by phone or online with the following groups:

1. Members of the DoV R&D WG, for the R&D related indicators.

2. The SAGE WG on Vaccine Hesitancy, for the indicator for Strategic Objective (SO) 2.

3. Project OPTIMIZE (WHO/PATH), for the indicator on innovations in immunization delivery systems.

4. UNICEF Supply Division and the Quality Standards & Safety (QSS) team in IVB, for the indicator on vaccine supply and access.

The updated indicators with operational definitions were shared with the CSO constituency, the WHO Regional Offices, key development partners, and with IFPMA, BIO, and DCVMN and more than 600 people from the DoVC distribution list for additional feedback and inputs.

The following principles were applied in the process to update the monitoring indicators:

1. The goals and strategic objectives were not subject to change.

2. The indicators for the goals and strategic objectives could be refined or reformulated, though the intent behind the original indicator needed to be retained as far as possible.

3. The operational definitions would provide the required specificity to measure and report on each indicator and would also assist in determining the feasibility of measuring the indicators and additional burden in monitoring them.

4. In reformulating the indicators, due attention would be paid to ensure that an excessive reporting burden would not be imposed on countries and consideration would be given to the resource requirements for monitoring the indicators.

5. For some indicators, a level of judgment would still be required to assess whether the target was met or not, e.g. whether a new vaccine developed addressed the public health needs of all countries, specifically low and middle income countries. This judgment would be left to the review process where progress against the indicators is reviewed (e.g. by the SAGE Decade of Vaccines WG and SAGE at the global level).

6. While milestones to track progress through the decade are relevant for some indicators, for others, tracking trends would be more appropriate.

7. There may be a need for a mid-term review (in 2015) and reset of the indicators and targets.

For the details of the indicators, with operational definitions, sources of data, targets and milestone, please refer to the accompanying spreadsheet.

Issues for SAGE consideration

This section highlights some of the main changes or revisions to the GVAP indicators where feedback is specifically sought from SAGE.

Goal indicators

G 1.1: *Interrupt wild poliovirus transmission globally*
G 1.2: *Certification of poliomyelitis eradication*

The target years for interruption of wild virus transmission and certification of polio eradication were revised to align them with the latest target dates set by the Polio Eradication Initiative. The revised target date for interruption of wild virus transmission is 2014 and for certification of eradication is 2018.

G 3.1: *Reach 90% national coverage and 80% in every district or equivalent administrative unit for diphtheria-tetanus-pertussis-containing vaccines*
G 3.2: *Reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended*

During the last consultation with over a 100 participants in DC on October 9, it was pointed out that the two coverage indicators, for DTP containing vaccines and for all vaccines in national immunization programmes, were actually one indicator with two targets. It was suggested that these two be merged into one indicator with two targets. The indicator would read "Reach 90% national immunization coverage and 80% in every district or equivalent administrative unit". The targets would read: reach 90% national coverage and 80% coverage in all districts/equivalent administrative units with DTP3 containing vaccines by 2015 and for all vaccines that have been in national programme for one or more years by 2020"

There was also a call for an additional indicator on number of countries that have sustained coverage of three doses of DTP containing vaccines of $\geqslant$ 80% for 3 or more years. If the current indicators 3.1 and 3.2 are merged, then this suggested indicator could be used as an additional indicator.

Another discussion item related to the Goal 3 indicators is that currently countries report on proportion of districts that have achieved $\geqslant$ 80% DTP3 coverage. However, for countries where the WHO UNICEF Estimates of National Immunization Coverage (WUENIC) are different from the country reported administrative national coverage estimates, there is no valid source of data for district level coverage. The M&E WG recommends that in such countries, a coverage survey that allows measurement of district level coverage be conducted at baseline and once during the decade to monitor changes in district level coverage. This will entail large and expensive surveys in these countries. A preliminary estimate of the cost is US$800 per district or equivalent administrative unit. Since some large countries may have over 1000 such units, the costs could go up to US$ 1 million per survey. However, it was noted that one of the largest countries, India, does conduct periodic district level surveys. Hence, it was felt that this would be doable in other countries. Also, this may serve as an incentive for countries to improve the quality of their administrative and other data, so that these expensive surveys are not required.

SAGE is asked to consider merging current indicators 3.1 and 3.2 with two targets.

SAGE is asked to consider and make a recommendation on adding the proposed indicator on sustained coverage with 3 doses of DTP containing vaccines of $\geqslant$ 80%.

SAGE is asked to comment on the proposed mechanisms to collect district level coverage data, including conduct of district level surveys is countries where WUENIC does not match national reported coverage.

G 4. 1: *Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases*.

The list of vaccines included in the original indicator was removed since it was felt that the indicator needed to be inclusive, rather than limited to a subset of diseases, as long as the licensure and launch of any new

vaccine was considered to be of significant public health value. The assessment of whether the vaccine is of public health value and whether the indicator is met may be assessed by the proposed SAGE WG that will review the progress reports of the GVAP M&A framework. The list of vaccines originally included in the indicator would be used to actively track progress in their development, though other vaccines developed during the decade would also be considered, should any be licensed for use.

It was also felt that new generation vaccines with improved product characteristics (e.g. a new pneumococcal vaccine with significantly broader coverage, or a rotavirus vaccine with higher efficacy in high child mortality settings) should be included in this indicator, since they would be preventing an additional number of cases of the targeted disease. A similar list of diseases was constructed to proactively monitor progress on a periodic basis, though other products could be considered should a vaccine be developed.

Progress reports would, therefore, provide a summary report on progress with the development of these vaccines.

SAGE is asked to comment on the proposed changes

G 4.2: *Licensure and launch of at least one new platform delivery technology*

The term "new delivery platform technology" was taken to represent technologies for delivering specific vaccines to an individual recipient that made the process of administration easier or more acceptable or resulted in better efficacy, antigen sparing or delivery cost savings. These will include technologies such as micro needles, cutaneous patches, aerosol delivery devices, or new adjuvants. A new indicator to represent innovations in immunization delivery systems (supply chains, ICT etc.), which would cover innovations to facilitate delivery of immunization at the population level, was added to GVAP SO6 on R&D.

Consideration was also given to the inclusion of manufacturing technologies in this category. However, on discussing how this might be monitored and reported publicly, it was felt that this would be near impossible to achieve given the confidentiality around such issues.

The current target is set as licensure and launch of **at least one** such device, with launch being defined as launch in a low or middle-income country.

SAGE is asked to comment on the proposed definition of "platform delivery technology" and the proposed target for this indicator.

G 4.3: *Number of low- and middle-income countries that have introduced one or more new or underutilized vaccines*

This indicator was initially under **Goal 3**, which reads "*Meet vaccination coverage targets in every region, country and community*". After discussion with the M&E WG and with the LC Sherpas, the indicator was moved under Goal 4, which reads "*Develop and introduce new and improved vaccines and technologies*"

The target for this indicator was also revised, from 80 to 90 countries, based on the latest projections of country uptake of new or underutilized vaccines.

A new target for 2020 was established, which is that "all low- and middle- income countries have added one or more vaccines to their national programmes".

SAGE is asked to comment on moving this indicator from G 3 to G 4 and on the proposed revision in targets.

Strategic objective (SO) indicators

SO 1.1: *Domestic expenditures for immunization per immunized person*

The original indicator for this strategic objective was "*Presence of a legal framework or legislation that guarantees immunization financing".* However, at some regional consultations and at the WHA, a few Member States objected to this indicator and felt that legal framework or legislation was not required to guarantee immunization financing in their countries. This indicator was, therefore, replaced with the following indicator: "*Domestic expenditures for immunization per immunized person*."

The original indicator may still be considered relevant and useful in some regions, where it may be used as an indicator in the regional monitoring framework.

SAGE is asked to comment and make recommendations on the change in indicator

SO 2: The SAGE WG on Vaccine Hesitancy was tasked to propose indicators for this strategic objective. The WG proposed that the indicator measure "vaccine confidence" as defined below, using the proposed indicators and sources of data:

Definition of vaccination confidence

Trust in the usefulness and safety of vaccines and in the system that delivers them. Vaccination confidence exists on a continuum and is one of the factors that influences behavior ranging from acceptance to refusal.

Global (Indicator 1):

% of countries that have assessed (or measured) the level of confidence in vaccination at subnational level with implementation of activities to improve it.

This will be collected through introduction of questions in the JRF.
Question 1:
Has there been some assessment (or measurement) the level of confidence in vaccination at subnational level in the past?
Question 2:
If yes, please specify the type and the year the assessment has been done_____
Question 3:
What action has been or will be taken to improve confidence? _____

National (Indicator 2):

% of un- and under-vaccinated in whom lack of confidence was a factor that influenced their decision.

This will be collected through introduction of questions in the JRF.

Question 1:
What is the % of un- and under-vaccinated in whom lack of confidence was a factor that influenced their decision (this applies to all vaccines)?
Question 2:
Was this % measured or estimated?
Question 3:
Any comments or specific issue?

Feedback on this indicator from JRF review meeting

The inclusion on this indicator in the JRF was discussed at the JRF review meeting that included representatives of WHO and UNICEF (from HQ and regional offices), as well as a few country immunization managers.

The group felt that question 1 and 2 for the global indicator (the 1st of the two proposed indicators) could be included. They suggested that the third question needed to be modified to require a simple "yes/no" response. A long narrative would be difficult to collect and analyse through the JRF.

They suggested that the questions for this indicator be included in select regions in 2013 (PAHO volunteered to collect the information) and then included more generally in the 2014 revision of the JRF.

The group had serious concerns about the inclusion of the national level indicator (2nd of the two proposed indicators) questions in the JRF in the absence of clear guidance on how such surveys/studies may be conducted and how the % of population with confidence in immunization would be measured. They suggested that inclusion of this set of questions in the JRF be deferred till such guidance was available.

An earlier suggestion proposed by the SAGE WG was to use the DTP1-MCV1 dropout rate as an indicator for community demand. One suggestion is to revert to this indicator, instead of using surveys, as an indicator for community demand and use DTP1-DTP3 dropout rate for monitoring SO4. However, it may be noted that in 2011, 18 countries reported a negative dropout rate for DTP1-MCV1. The majority of these

countries had high performing systems with close to or over 90% coverage with both DTP1 and MCV1; the two countries with the largest negative dropout rates were, however, those with low immunization coverage, i.e. Nigeria (-18%) and South Sudan (-6%) in 2011. This may be related to stock out of a particular vaccine (in the case of Nigeria). Seventeen countries reported dropout rates > +20%; from available data, it is difficult to determine whether this indicator measures confidence in immunization.

SAGE is asked to provide their recommendations on the proposed options for indicators for community demand for inclusion in the M&E framework.

SO 3.1: *Percentage of districts with 80% or greater coverage with 3 doses of diphtheria-tetanus-pertussis-containing vaccine*

A minor modification was made to the indicator, so it now measures % of districts with ⩾ 80% DTP3 coverage, rather than < 80% coverage.

It was also noted that this overlaps with the coverage indicators under GVAP goals that report on district level coverage and that this indicator could be dropped, if the number of indicators needed to be reduced.

SAGE is asked to comment as to whether this indicator should be retained.

SO 3.2: *Reduction in coverage gaps between wealth quintiles (AND another appropriate equity indicator)*

A minor modification was made to this indicator in that instead of measuring the gap between coverage in the highest and lowest wealth quintiles, it was felt that coverage gaps across the wealth quintiles should be measured since the greatest gaps may not be between the lowest and highest quintile. However, it may be noted that the related indicator monitored as part of the UNSG Global Strategy for Women's and Children's Health reports on differences between the highest and lowest wealth quintiles.

During the consultative process, the GAVI Alliance secretariat requested that all countries be asked to report coverage by wealth quintile as this was also a GAVI target. Of note, all the countdown countries are reporting DTP3 coverage by wealth quintile. CSO organizations requested that other equity indicators be added to the list.

The GAVI secretariat also suggests adding a target to this indicator as follows:

% of countries that have a disparity of <20 percentage points in immunization coverage between the lowest and highest wealth quintile: 60% by 2015 and 75% by 2020

Based on above comments, suggestion is to modify this indicator to read: *Reduction in coverage gaps between wealth quintiles (**AND** another appropriate equity indicator)* with targets as proposed by the GAVI Alliance secretariat.

SAGE is asked to comment and make recommendations on the change in the indicator and the proposed targets.

SO 4.1: *DTP1 to measles first dose dropout rate*

The indicator that is currently included in the GVAP is "*DTP1 to measles first dose dropout rate (DTP1-MCV1)".* The choice between this indicator versus an indicator that measured DTP1-DTP3 dropout rate was discussed at the SAGE special meeting. At that time the DTP1-MCV1 was preferred on the grounds that it measured dropout over a longer time interval between doses. During the post-WHA consultations, several agencies that provided feedback strongly argued for reverting to DTP1-DTP3.

An analysis of the pros and cons of the two indicators with illustrative data from countries was provided by MCHIP and is appended to this report as Annex 2.

The contents of Annex 2 were discussed by the GVAP M&E WG. The consensus of the group was that if only one indicator could be accommodated, then the drop-out rate of DTP1-DTP3 should be used, however, there was value in including both indicators.

SAGE is asked to provide their recommendations on the choice of dropout rates for this indicator or the suggestion to include both dropout rates (see related comment on using DTP1-MCV1 drop out as indicator of community demand for SO 2).

SO 4.2: *Immunization coverage data assessed as high quality by WHO and UNICEF.*

For this indicator, it is proposed that we use the Grade of Confidence (GoC) around WUENIC. This measure does not assess the quality of the administrative data, but rather, on the confidence that WHO and UNICEF have in their estimate for that country and is dependent on consistency between different sources of data that form the basis of WUENIC. The GoC was first published in 2012 and may be subject to slight modifications based on early experience.

A comment was made that, given current status the target of 100% countries with high GoC was too ambitious. Alternative targets suggested were: 50% of countries have high GoC by 2015 and 75% by 2020.

SAGE is asked to consider and make a recommendation on the change of target for this indicator

SO 4.3: There were several requests to include a surveillance indicator to replace the indicator on immunization financing moved to SO 1. The following indicator is proposed:

"Number of countries that have established surveillance, with laboratory confirmation, for invasive bacterial diseases and rotavirus diarrhoea and report data to WHO"

The data required to monitor this indicator is collected through the JRF currently and reports to WHO through the surveillance databases.

SAGE is asked to consider and make recommendations on the inclusion of this indicator as a marker or immunization systems strength.

SO 5.1: *Percentage of doses of vaccine of assured quality, produced, procured and used worldwide*

The indicator "*Percentage of routine immunization costs financed through government budgets*" was deleted. Instead an indicator that monitored total government expenditures was used to frame **SO 1**. It was felt that the % of routine immunization expenditures financed through the government budgets would change as and when countries introduced a new, expensive vaccine with GAVI support and this change may not necessarily reflect a decline in country commitment to immunization. Hence, the decision to just monitor country expenditures per target person and monitor trends in a particular country over time under SO 1.

The second original indicator "*Installed capacity for production of universally recommended vaccines within five years of licensure/potential demand*" was also deleted as further discussions indicated that the process to monitor this indicator would be very labour intensive and expensive.

These two indicators were replaced by the following indicators:

SO 5.1: *Percentage of doses of vaccine of assured quality, produced, procured and used worldwide*

SO 5.2: *Sufficient doses procured to meet stated program requirements*

However, UNICEF SD indicated that the proposed indicator SO 5.2 could not be monitored for self-procuring countries and it would not be possible to track this for all countries. It is proposed that this indicator be dropped. Thus, this SO will have only one indicator, i.e. SO 5.1.

SAGE is asked for their recommendation on the proposed indicator

SO 6: The R&D core group felt that under innovations, indicators should monitor three areas of work, namely vaccine development, innovations in vaccine delivery systems, and research capacity.

SO 6.1: *Progress towards development of HIV, TB, and malaria vaccines*

There was discussion whether the indicator SO 6.2 should be merged with this one, but it was decided to retain these as two independent indicators. For this indicator a vaccine with proof of concept of efficacy > 75% was retained as an aspirational target, though there were comments that this target was unlikely. The proposed SAGE DoV WG would make a decision whether progress was sufficient to determine whether this indicator was met and no specific operational definition was established for what constituted "proof of concept". Biennial progress reports would consist of data on number of clinical trials of these vaccines with a narrative report describing progress.

SO 6.3: *Progress towards institutional and technical capacity to make vaccines and/or carry out related vaccine clinical trials*

The indicator originally read "Progress towards institutional and technical capacity to make vaccines and/or carry out related vaccine clinical trials, operational and organizational research". It was felt that it would be very labour intensive to monitor all these types of research. Instead it was decided to focus on capacity to conduct vaccine clinical trials as a surrogate for research capacity and track this using the international clinical trial registries. Negotiations are on-going to see if criteria to assess quality of the clinical trial may be included in the registries.

SAGE is asked to comment on the reformulated indicator

SO 6.4 & 5: It was felt that innovations in immunization delivery systems should also be added to the strategic objective, instead of limiting it to include only vaccine development. The OPTIMIZE project was asked to propose indicators and have proposed the following two for consideration.

SO 6.4: *Number of vaccines that have either been re-licensed or licensed for use in a controlled temperature chain (CTC) at temperatures above the traditional 2-8 C range*

It is proposed that this indicator be monitored by seeking information through NRAs that are considered as fully functional.

SO 6.5: *Number of vaccine delivery technologies (devices & equipment) that have received WHO pre-qualification compared to the 2010 baseline*

The WHO PQS database will be used to track this indicator. The following devices will be considered:

1. Refrigerators and freezers
2. Cold boxes and vaccine carriers
3. Coolant packs
4. Temperature monitoring devices

Whether or not the pre-qualified device is considered innovative will be determined by the proposed SAGE DoV WG that will review progress reports.

SAGE is asked to provide recommendations on inclusion of one or both of above indicators in the GVAP M&E framework

Specific issues for SAGE consideration:

GVAP Goals

G 3.1 &3.2: *SAGE is asked to consider merging current indicators 3.1 and 3.2 with two targets*
SAGE is asked to consider and make a recommendation on adding the proposed indicator on sustained coverage with DTP containing vaccines of ⩾ 80%

G 3.1: *SAGE is asked to comment on the proposed mechanisms to collect district level coverage data.*

G 4.2: *SAGE is asked to comment on the proposed definition of "platform delivery technology" and the proposed target for this indicator*

G 4.3: *SAGE is asked to comment on moving this indicator from G 3 to G 4 and on the proposed revision in targets*

GVAP Strategic Objectives

SO 1.1: *SAGE is asked to comment and make recommendations on the change in indicator*

SO 2: *SAGE is asked to provide their recommendations on the proposed options for indicators for community demand for inclusion in the M&E framework*

SO 3.1: *SAGE is asked to comment as to whether this indicator should be retained*

SO 3.2*: SAGE is asked to comment and make recommendations on the change in the indicator and the proposed targets*

SO 4.1: *SAGE is asked to provide their recommendations on the choice of dropout rates for this indicator or the suggestion to include both dropout rates (see related comment on using DTP1-MCV1 drop out as indicator of community demand)*

SO 4.2*: SAGE is asked to consider and make a recommendation on the change of target for this indicator*

SO 4.3: *SAGE is asked to consider and make recommendations on the inclusion of this surveillance indicator as a marker or immunization systems strength*

SO 5.2: *SAGE is asked for their recommendation on the proposed indicator*

SO 6.3: *SAGE is asked to comment on the reformulated indicator*

SO 6.4 & 6.5: *SAGE is asked to provide recommendations on inclusion of one or both of above indicators in the GVAP M&E framework*

Annex 1

Informal Consultation of Developing a Monitoring and Accountability Framework for the Global Vaccine Action Plan (GVAP)
June 25-26 June 2012
Geneva

List of Participants

Logan Brenzel (by phone) Consultant **Bill & Melinda Gates Foundation**
David Brown **UNICEF**
Peter Hansen (was unable attend) Head, Monitoring and Evaluation Policy & Performance **GAVI Alliance Secretariat**
Rouslan Karimov Statistics & Monitoring Specialist, Immunization **UNICEF**
Altaf Lal (was unable attend) Consultant Decade of Vaccines Collaboration
Chung-Won Lee Lead, Strengthening the Quality and Use of Immunization Data (SQUID) Team Global Immunization Division **Centers of Disease Control**
Joanna Lowell PhD, MPH Country Manager **MEASURE DHS**
Katherine O'Brien International Vaccine Access Centre **Johns Hopkins Bloomberg School of Public Health**
Magdalena Robert DoVC Secretariat **Barcelona Institute for Global Health**
Laurie Werner Project Coordinator **Program for Appropriate Technology in Health (PATH)**

Lahouari Belgharbi Quality, Safety & Standards (QSS) Department of Immunization, Vaccines and Biologicals **World Health Organization**

Anthony Burton Expanded Programme on Immunization (EPI) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Thomas Cherian Immunization, Vaccines and Biologicals (IVB) **World Health Organization**
Bernadette Daelmans (unable to attend) Policy, Planning and Programmes Maternal, Neonatal, Child and Adolescent Health **World Health Organization**
Nora Dellepiane Quality, Safety & Standards (QSS) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Philippe Duclos Immunization, Vaccines & Biologicals (IVB) **World Health Organization**
Marta Gacic Dobo Expanded Programme on Immunization (EPI) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Joachim Hombach Initiative for Vaccine Research (IVR) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Ivana Knezevic Quality, Safety & Standards (QSS) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Carmen Rodriguez Hernandez Quality, Safety & Standards (QSS) Department of Immunization, Vaccines and Biologicals **World Health Organization**
Jessie Schutt-Aine-Madkaud Policy, Planning and Programmes Maternal, Neonatal, Child and Adolescent Health **World Health Organization**
Rudi Tangermann Global Polio Eradication Initiative **World Health Organization**
Peter Strebel Measles and Rubella Initiative /Expanded Programme on Immunization Immunization, Vaccines and Biologicals (IVB) **World Health Organization**
Ahmadu Yakubu MNTE, Expanded Programme on Immunization **World Health Organization & UNICEF**

Annex 2

GVAP proposed indicator for monitoring drop-out rates: pros and cons of different options
(prepared by MCHIP 30 September 2012)

A set of indicators has been proposed to monitor the implementation of the GVAP. The indicators will be discussed at the November 2012 meeting of the WHO Strategic Advisory Group of Experts (SAGE). As an indicator for the GVAP SO, "Strong immunization systems are an integral part of a well-functioning health system," DTP1 to measles first dose (MCV1) drop-out rate is being considered in the draft M & E plan.

Selecting the most appropriate drop out rate is important, since a focus on drop out at higher levels (global and regional) will continue to validate the importance for national and sub-national levels to actively monitoring their own drop out data to improve their programs. A high drop out rate is generally considered to be a composite indication of multiple failures in the immunization services, reflecting problems in the system, supply, demand, and quality of services.

For over a decade, most countries have been monitoring drop-out rates based on DTP1 to DTP3. The proposal to replace that indicator with DTP1 to MCV1 raises a number of concerns. A comparison of the pros and cons of the two indicators is provided below. A general premise here is that in order to get an estimate of the full magnitude of the problem, underestimating the drop out rate should be avoided.

DTP1 – DTP3 drop out rate ("DTP" refers to vaccine products containing the DTP antigens, for example pentavalent vaccine)

Pros:

1. Measures the ability of the immunization system to reach a child multiple times with the same antigen(s), specifically DTP-containing vaccine.
2. DTP1-DTP3 drop out measures the same delivery system multiple times, thereby giving insight into factors that may hinder caregivers to continue utilizing a delivery system.
3. Drop out between DTP1 and DTP3 is also a better indirect measure of timeliness of coverage during the first year of life than DTP1-measles because many countries currently give MCV1 starting from 12 months. And the number of countries shifting the starting age for MCV1 from 9 to 12 months is expected to increase, as coverage rates at 9 months of age reach high levels.
4. DTP1 and DTP3 are given only through routine immunization and not as supplemental doses. Therefore they describe the routine immunization system.
5. DTP-containing vaccine is a proxy for pentavalent vaccine, which most (but not all) countries use. DTP1-DTP3 drop out rates also provide essential managerial and effectiveness information relevant to pneumococcal conjugate vaccine, which follows the same vaccination schedule as DTP and which an increasing number of countries will be introducing during the GVAP timeframe.
6. The DTP1-DTP3 drop out rate provides information that bridges two broad areas of the GVAP: strengthening routine immunization and introduction of new vaccines.
7. While DTP3 is not the final antigen/dose in the immunization schedule, it has been noted for years that in countries with weaker immunization programs, DTP3 coverage is actually lower than measles coverage. (See Figure 1 and Tables 1 and 2 for data from the African Region.) Thus in countries with weaker systems, the drop out rates for DTP1-DTP3 would, paradoxically, be higher than for DTP1-measles and therefore give a better idea of the magnitude of the drop out rates. More than 60% of surviving infants in AFR live in countries where measles coverage is higher than DTP3 coverage. For AFR and SEAR as a whole, measles coverage is higher than DTP3 (75% vs. 71% in AFR; 79% vs. 75% in SEAR). For other WHO regions, DTP3 is either slightly higher or the same as measles coverage. Globally measles coverage is higher than DTP3 coverage (84% vs. 83%).
8. DTP1-DTP3 drop-out is one of the key indicators in the GAVI monitoring and evaluation plan. As such, its value has already been debated and accepted by the GAVI Board and is part of country reporting to GAVI.
9. The Reaching Every District (RED) strategy and all countries now use coverage with DTP1 and DTP3, as well as the drop out between them, to guide program strategies.
10. Other than for short periods of time or in small geographic areas if service is disrupted, it is impossible to have a true negative drop-out rate with DTP1-DTP3. A negative drop-out rate can only be due to data quality problems.

Cons:

1. DTP3 is not the final antigen or dose in the official infant vaccination schedule when it is optimally implemented.

2. The measurement points for DTP1 and DTP3 fall relatively close together (2-4 months) when the official vaccination schedule is optimally followed, thereby focusing on obstacles in service delivery and uptake over a shorter period.
3. The DTP1-3 indicator does not give any operational information as to the progress of the measles and rubella initiative.

DTP1-measles first dose (MCV1) drop out rate

Pros:

1. Measles is the final antigen/dose in the infant vaccination schedule of most countries. Therefore in places where measles vaccine is given after DTP3, DTP1-measles drop out describes a longer period of time than DTP1-DTP3 drop out.
2. DTP1-measles is thought by some to be a better measure of overall program effectiveness whereas DTP1-DTP3 is considered by some to be a better measure of delivery effectiveness.
3. Adding an indicator on DTP1-measles introduces a measles-related indicator to GVAP monitoring, thus spanning the GVAP goals pertaining to disease elimination and extending immunization benefits to all. In that the global measles and rubella strategic plan calls for attaining high levels of population immunity through both routine immunization and SIAs, it would be useful to have a measles related indicator in the GVAP monitoring plan.

Cons:

1. It is easier to achieve single dose versus triple dose coverage, i.e., measles vs. DTP3; thus the DTP1-measles drop out rate may be artificially low, obscuring the dip in coverage between successive doses of DTP (and other vaccines such as PCV given at the same time) and thus minimizing the magnitude of the challenge facing the routine immunization program.
2. Because measles is easily recognized and feared by communities, demand for measles vaccine may be higher than for DTP, resulting in a lower drop-out rate for DTP1-measles than DTP1-DTP3 that does not capture the challenges of delivering multiple doses of the same vaccine.
3. DTP1-measles compares apples to oranges, since the service delivery systems may differ for the first dose of DTP and the first dose of measles.
4. Measles vaccine is given both through routine immunization and SIAs. There is the possibility that some supplemental doses are inappropriately counted as being given through the routine delivery service. This will become more complicated with plans to start recording measles doses administered during SIAs. Since SIAs are not conducted every year, data interpretation from year to year will become even more difficult.
5. It is possible to have negative drop-out rates for DTP1 and measles because of the different service delivery strategies. (See attached data.)
6. Monitoring DTP1-measles drop out is not included among the global indicators specified in the global measles and rubella strategic plan for 2012-2020, so DTP1-measles drop-out represents a new dimension to measles monitoring.
7. Is not clear what operational information DTP1-measles provides the measles and rubella initiative that would facilitate better programming and strategy development.

Figure 1

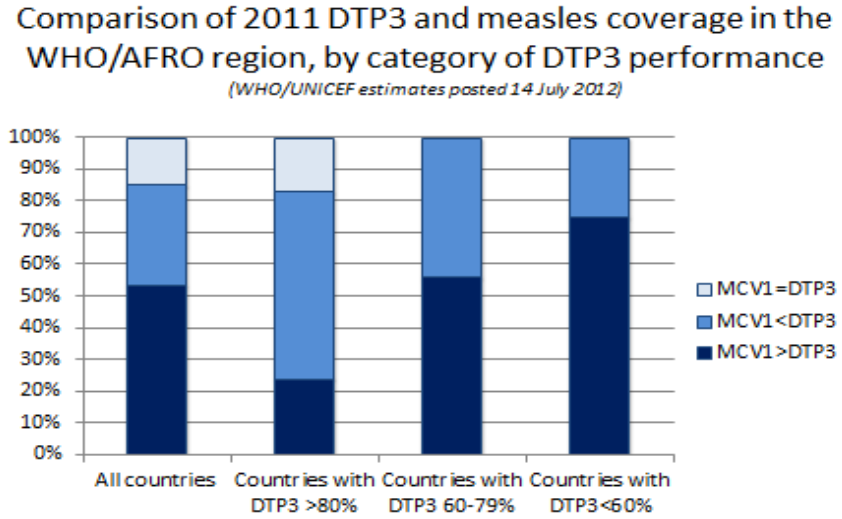


Table 1. Number of AFR Countries by Level of DTP3 Coverage and Drop Out Rates

Category of country, by DTP3 coverage	DTP3 > MCV1		DTP3 < MCV1		DTP3=MCV1
	Number of countries (%)	Mean difference and range in percentage points	Number of countries (%)	Mean difference and range in percentage points	Number of countries (%)
DTP3 ≥80% (N=29)*	17 (59%)	8 (1-28)	7 (24%)	3.3 (1-7)	5 (17%)
DTP3 60-79% (N=9)**	4 (44%)	13 (8-16)	5 (56%)	4.8 (1-10)	0 (0%)
DTP3 <60% (N=8)***	2 (25%)	5 (1-9)	6 (75%)	12 (6-24)	0 (0%)
All countries (N=46)	23 (50%)	8.4 (1-28)	18 (39%)	6.6 (1-24)	5 (11%)

*Algeria, Angola, Benin, Botswana, Burundi, Burkina Faso, Cap Verde, Comoros, Congo, Eritrea, Gambia, Ghana, Kenya, Lesotho, Madagascar, Malawi, Mauritius, Namibia, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe
**Cameroon, Cote d'Ivoire, DRC, Guinea-Bissau, Mali, Mauritania, Mozambique, Niger, South Africa
*** CAR, Chad, Equatorial Guinea, Ethiopia, Gabon, Guinea, Liberia, Nigeria,
Source: WHO Coverage Estimates, accessed September 15, 2012

Table 2. Number of AFR Countries and Percent of Surviving Infants, by Level of DTP3 Coverage and Drop Out Rates

Category of country, by DTP3 coverage	DTP3 > MCV1		DTP3 < MCV1		DTP3 = MCV1	
	Number of Countries (#)	Percent of surviving infants (%)	Number of Countries (#)	Percent of surviving infants (%)	Number of Countries (#)	Percent of surviving infants (%)
DTP3 ≥80% (N=29)	17	24.7%	7	11.2%	5	6.1%
DTP3 60-79% (N=9)	4	5.0%	5	20.0%	0	0%
DTP3 <60% (N=8)	2	1.8%	6	31.2%	0	0%
All countries (N=46)	23	31.5%	18	62.4%	5	6.1%

Source: WHO Coverage Estimates, accessed September 15, 2012

DRAFT

3. Decade of Vaccines commitment guidelines to enable the Global Vaccine Action Plan implementation 18 October 2012

Background

The Decade of Vaccines Collaboration (DoVC) is an effort under the leadership of the World Health Organization (WHO), UNICEF, the GAVI Alliance, the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases (NIAID—part of the National Institutes of Health U.S.) which helped define the Decade of Vaccines vision and develop the Global Vaccine Action Plan (GVAP). The GVAP was developed through the work of over 100 vaccine and immunization experts organized into a Steering Committee and four working groups (Delivery, Global Access, Public and Political Support, and Research & Development).

The DoV Collaboration held approximately 20 consultations on the contents of the GVAP drafts in Asia, Africa, Americas, Europe, Middle East and Western Pacific regions, as well as an online consultation. More than **1,100 people** from **140 countries** and **290 organizations** provided input as part of the consultation process to develop the GVAP. The DoVC process was designed to ensure that meaningful input could be solicited from all key stakeholder groups: governments and elected officials, health professionals, academia, manufacturers, global agencies, development partners, civil society, media and the private sector.

On 25 May 212, the World Health Assembly (WHA) discussed the Global Vaccine Action Plan and its accompanying resolution. Many statements of support were made during the discussion, including statements from more than thirty Member States and organizations like the International Federation of the Red Cross and Red Crescent Societies, Médecins Sans Frontières (MSF/Doctors Without Borders), Save the Children, UNICEF, the GAVI Alliance and the International Federation of Pharmaceutical Manufacturers & Associations. At the end of the discussion, all 194 Member States voted to endorse the GVAP resolution.

Member States committed to apply the GVAP vision and the strategies to develop the vaccines and immunization components of their national health strategy and plans, to allocate adequate human and financial resources to achieve the immunization goals, and to report back every year to the WHO Regional Committees on progress made.

The ultimate success of the GVAP depends on country ownership and the continued engagement of all stakeholders, including academics, civil society, private sector, development partners and implementers, who are committed to the DoV common goal of achieving universal access to the benefits of immunization.

Guiding principles to make commitments towards the Decade of Vaccines

For monitoring commitments for the DoV, it is proposed to use the same framework as that used for documenting towards the UNSG Global Strategy for Women's and Children's Health. However, while the framework and process for documenting commitments may remain the same, the nature of commitments earmarked for immunization need to be fairly explicit to allow tracking of commitments that specifically address immunization. Following the guidelines used for making commitments towards the UNSG Global Strategy for Women's and Children's Health, we provide examples of the type of commitments that could be made towards the Decade of Vaccines.

Ideally commitments should be tangible and concrete, and represent activities or actions that can be reported back on. Preferably they would be connected to items included in existing monitoring mechanisms that can allow for independent tracking of data in relation to the commitment. They should be specific, measurable, achievable, realistic and time specific, in order to easily determine the progress made against them and, if possible, the source of funding should be mentioned for non-financial commitments to avoid double counting. See examples given below as ways to frame your commitment.

Financial Commitments

Financial commitments can include both direct budget allocations on behalf of countries, institutions, or even non-governmental organizations and civil society. There can also be commitments to provide funding to different entities or commit to fundraise on behalf of different immunization efforts. The commitments should focus on supporting key activities and initiatives that are directed towards the strengthening of immunization services and access along the lines of the Strategic Objectives included in the GVAP.

Type of Commitment	**Examples**
Direct financial support to strengthen capacity for delivery of immunization services; e.g., to address identified gaps in the national plans to implement immunization services; to finance immunization delivery and access to all sectors of their society.	XX entity commits $$$ to strengthen immunization delivery systems in five countries in 2013-2015.
Scaling-up programming; e.g., increasing coverage and promoting equity in delivery of routine immunization services; integrated delivery of immunization and other primary health care interventions; introducing new vaccines or expanding services to include new target populations (e.g. elderly, adolescents); or taking innovative pilot programmes to scale, such as pilot introduction of HPV vaccines to scale.	XX entity commits $$ funding to y agency to work with _____ and _____ country to launch the HPV vaccine for adolescent girls in 2013. XX organization makes an "in-kind" contribution of science, technology or data that help to achieve an objective. For example access to epidemiology or clinical data; access to novel technology in national laboratories.
Advocacy & Fundraising; e.g. Advocacy to raise community awareness and demand for immunization; fundraising for specific initiatives and efforts such as World Immunization Week, vaccine introductions, strengthening routine immunization efforts, etc.	XX entity commits $$$ to five local CSOs in Western Africa to promote immunization week activities in 2013.
Research & Development; e.g. allocation of budgets (government agencies, international agencies, foundations, bilateral development partners or private sector) towards new R&D efforts to develop new vaccines, increase access to vaccines and immunization services or to support the development of new technologies to increase access; publish or share data on mechanisms of disease, epidemiology data, new data on relevant science that impacts key issues such as heat stability, broader strain coverage, etc.	XX entity commits $$$ to the development of the HIV vaccine via YY organization.

Policy Commitments

Policy commitments can include overall commitment to the GVAP and its Strategic Objectives, as well as addressing policies and processes that will address specific portions of the actions outlined in the GVAP. Again these commitments will focus on policies to strengthen immunization services and access for all people.

Type of Commitment	**Examples**
Government reform; e.g. establishing advisory, oversight, or management bodies at the national, regional, and/or local levels to facilitate evidence based decision-making on immunization policies and strategies; assuring vaccine quality and safety (through capacity strengthening of national regulatory authorities); formulating and implementing national, regional and/or local immunization plans within the larger healthcare context and planning; improving management of health services – including budgeting, planning and provision of immunization services – at the national and local levels; strengthening budgeting and financial management in connection with overall health care planning and prioritizing.	XX agency commits to develop a programme to strengthen national immunization technical advisory groups in the Sub-Saharan Africa region between 2013-2015.

Education; e.g., create advocacy and education tools and materials to inform the public of the benefits of immunization and their rights associated with such services; training and education for healthcare workers to better address vaccine hesitancy and concerns; etc.	XX agency commits to develop a healthcare worker training programme in ten countries in Southeast Asia, specifically focusing on how to address vaccine hesitancy and concerns by 2015. XX industry organization commits promoting understanding on global heath, immunization and R&D by hosting a biannual global forum for key stakeholders.
Engaging and contributing to campaigns and their outcomes; e.g., partner in existing initiatives to encourage the adoption of immunization legislation or to increase government spending on immunization services; etc.	XX organization will coordinate with GPEI to promote their work in Nigeria in 2013-2014. XX CSO commits to mobilising is grassroots advocates in XX countries for immunization campaigns.
Issue advocacy; e.g., engaging different spokespersons to share key messages related to immunization to educate the public and policy makers; promote awareness raising events and moments (World Immunization Week); advocate for investments to strengthen capacity for R&D efforts globally; etc.	XX agency commits to using their global spokespeople to help promote World Immunization Week in 2013. XX industry association and XX CSOs agree to work together to promote greater research into thermostability of vaccines to determine when they can be used outside of the cold chain.
Mobilizing political support, engaging new constituencies and promoting accountability; e.g., Civil society monitors efforts and events to ensure fulfilment of agreements; advocating locally, nationally, regionally and globally to ensure that all stakeholders remain engaged on immunization services and vaccines and held to account.	XX local CSO commits to hold an event during World Immunization Week in two regions of the Philippines in 2014. XX CSOs commits to producing an annual report on progress towards the DoV. XX industry association commits to producing an annual report on progress toward the DoV.

Service and Delivery Commitments

Service and delivery commitments are key to the implementation of the GVAP and its Strategic Objectives. These include the full spectrum of discovery, development and delivery of critical vaccines and immunization services to those who need them, when they need them.

Type of Commitment	**Examples**
Training; e.g., pledging to strengthen the training of health professionals by supporting pre-service education or continuous professional development (CPD) through the provision of health tutors and teaching materials in harmony with national health plans.	XX university commits to provide health tutors to ten municipalities in Guatemala for healthcare workers in 2015.
Direct provision of products and services; e.g., supporting programmes where health professionals support the delivery of services; donating vaccines and immunization supplies following the WHO donation guidelines, where it is requested and where there is absorptive capacity; donating airtime for public service announcements to educate the populace around immunization; promote the incorporation of global vaccine programmes focusing on eradication and elimination goals into national immunization programmes (and not operated separately).	XX radio station commits to donate public service announcement space prior to and during World Immunization Week in 2014.
Technical assistance; e.g., supporting the provision of health training tutors to expand the training capacity of health training institutions; providing supply chain management advice for hospitals and centres; or secondment of high-level advisors in the ministries of	XX hospital commits to train local healthcare workers in cold chain management in eight regions of y country in 2014-2015.

health, development and social welfare; build and support networks of regulators and suppliers to share best practices and improve quality assurance capabilities.	
Research; e.g., researching and developing new vaccines and vaccine technologies; developing effective health information management systems; researching the impact of different initiatives to improve the health of women and children; conducting social research to improve the delivery of immunization services to better meet the needs of diverse communities.	XX university commits to conduct social research in five countries related to delivery of immunization services in 2015. XX vaccine biotechs, in partnership with XX pharmaceutical companies, XX NGO's and XX governments commit to advancing the R&D agenda for immunization by 2020 and reporting on progress every 2 years.
Driving technological innovation; e.g., utilizing up to date technology to increase local access to care; improve the quality of immunization services; or ensure effective management of the health care system; enhancing innovations for cold chain capacity; use technology to strengthen surveillance mechanisms.	XX company commits to develop y new technology to help with tracking delivery of immunizations in 2015. XX stakeholder commits to enhancing cold-chain capacity and surveillance in country YY by 2015.

What kind of Commitment is encouraged?

The ideal commitments to the Decade of Vaccines will be designed around the six Guiding Principles included in the GVAP: (1) country ownership (so countries have primary ownership and responsibility for providing effective and quality immunization services for all), (2) shared responsibility and partnership (at the individual, community and governmental levels, beyond border and sectors), (3) equity (core component of the right to health), (4) integration (as part of a broader health system), (5) sustainability (informed decisions with appropriate levels of investment and management), and (6) innovation (learning, continuous improvement and innovation in R&D). All commitments should align with the Strategic Objectives of the GVAP, and work to address the different strategies and actions included in the plan.

What should I include in a Commitment?

Following the recommendations of the Commission on Information and Accountability for Women's and Children's Health and the GVAP, commitments should be framed as transparently as possible, and with an emphasis on 'measurability' to support tracking and monitoring to enhance the impact of commitments to the Global Strategy. *Commitments should include the following information*:

- The specific and different types of financial investments, service delivery, policy, or advocacy content of the commitment being made, including timeframe for its achievement.
- Information on the focus of the support being provided (as relevant):
    - Whether support is for service delivery, research and development, for improving access and supply of vaccines and related technologies, or for building public or political support for immunization
    - By geographic scope: region, country, sub-national.
- How the support specifically relates to, and advances the goals of, the GVAP (including which specific Strategic Objective and actions the commitment will address)
- For non-financial commitments:
    - Which GVAP goals, strategic objectives and/or indicators will be impacted by the commitment
    - Expected outcome and funding sources e.g. type of benefit and the population that would benefit (e.g. region/sub-region, population size)
    - Estimated value, either in USD or local currency of services, products and other resources provided
    - Explanation of how this was determined.
- For financial commitments:
    - Which GVAP outcomes and indicators will be impacted by the commitment
    - Total amount, either in USD or local currency
    - If possible, the proportion or element of the commitment that is additional to current disbursements for immunization, including an explanation of how this was determined and how the baseline was identified

- If the commitment is to increase funding for immunization within the context of an overall health funding increase, the amount of the commitment to the *GVAP* may be estimated by applying a percentage representative of the share of overall health spending that benefits through immunization services (a range of 25-40% in the estimation of the value of the financial commitments to the *Global Strategy*, 25% has been used based on data from Countdown to 2015)
- The expected outcome and source of funding to support implementation of the commitment, for example national revenues, bilateral donor government, UN or other multilateral agency, or other institution
- How funds will be channelled (e.g. bilaterally, multilaterally, through CSOs).

How Can I Make a Commitment?

For further information, please email xxxxxxx.

No	Goal	Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
G 1.1	**Achieve a world free of poliomyelitis**	Interrupt wild poliovirus transmission globally	No wild poliovirus isolated globally for at least 1 year, in the presence of certification quality AFP surveillance (annual non-polio AFP rate of at least 1/100,000 population < 15 years at national and sub-national level, with adequate stool specimens collected from at least 80% of AFP cases).	national AFP surveillance systems + supplementary surveillance data where available (environmental surveillance or enterovirus surveillance through national lab networks)	2011: 650 WPV-confirmed cases reported from 16 countries	2014	
G1.2		Certification of poliomyelitis eradication	no wild poliovirus isolated globally for at least 3 years in the presence of certification quality AFP surveillance	final national documentation on polio-free status submitted by NCCs and accepted by RCCs	2011: national documentation on polio-free status accepted by RCCs in 168 out of 194 WHO member states (87%)	2018	Track number of countries with national documentation of polio-free status, accepted by RCCs
G2.1	**Meet global and regional elimination targets**	Neonatal tetanus elimination	< 1 NT case/1,000 live births in each district and maintenance of elimination based on annual WHO/UNICEF District Data Spreadsheet	WHO/UNICEF District Data Spreadsheet, and WHO validation report (based on LQA in worst performing district)	2010 (40 countries still to achieve elimination)	2015	10 countries eliminated NT by 2012; 22 countries eliminated NT by 2013; 36 countries eliminated NT by 2014; 40 countries eliminated NT by 2015
G2.2		Measles elimination	number of regions with 100% of countries having declared interruption of endemic measles virus transmission for a period of > 12 months in the presence of high quality surveillance The surveillance quality criteria published in the WER 2010; 85(49): 490-5 http://www.who.int/entity/wer/2010/wer8549.pdf) will be used to define high quality surveillance as follows: 1. Rate of discarded measles cases*	each region has a verification commission which annually reviews the status of all countries	2010 (0/5 regions - AMRO, WPRO, EMRO, EURO, AFRO)	2015: 4 WHO regions	Monitor # and % of countries in each region that are verified as having eliminated diseases

No	Goal	Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
	Meet global and regional elimination targets		(target: >=2 per 100,000 population per year) 2. Proportion of subnational admin units (province / region) reporting at least 2 discarded measles cases* per 100,000 population (goal: 80%) 3. Proportion of suspected cases where specimens adequate for serology were collected** (goal: 80%) 4. Proportion of laboratory-confirmed outbreaks where specimens adequate for measles virus detection were collected (goal: 80%) 5. Proportion of suspected measles cases with an adequate investigation*** initiated within 48 hours of notification (goal: 80%)			2020: 5 WHO regions	Monitor # and % of countries in each region that are verified as having eliminated diseases
G2.3		Rubella/CRS elimination	number regions with 100% of countries having declared interruption of endemic rubella virus transmission for a period of > 12 months without occurrence of CRS cases associated with endemic transmission in the presence of high quality surveillance	each region has a verification commission which annually reviews the status of all countries	2010 (0/2 regions - AMRO, EURO)	2015: 2 WHO regions	Monitor # and % of countries in each region that are verified as having eliminated diseases
						2020: 5 WHO regions	Monitor # and % of countries in each region that are verified as having eliminated diseases

No	Goal	Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
G3.1	**Meet vaccination coverage targets in every region, country and community**	Reach 90% national coverage and 80% in every district or equivalent administrative unit for diphtheria-tetanus-pertussis-containing vaccines	WUENIC* for national coverage; District data: - accept JRF admin data if WUENIC based on administrative coverage; missing district reports =indicator not met, encourge reporting; –if WUENIC not based on administrative coverage, repeated measure (at least two surveys or special studies to document district coverage); early measure (2009 to 2015) and later measure (2016 to 2020)	WUENIC, JRF, surveys or special studies	2010 or early measure	2015 - all Member states	Monitor trends in coverage
		Number of low- and middle-income countries that have introduced one or more new or underutilized vaccines	low- and middle-income countries= world bank classification 2012; - vaccine added in national immunization schedule and used for a sustained period of at least 12 months (excluding those used only in the private sector and not in national immunization schedule; includes vaccines included in national schedule but for selective use at risk populations, e.g. seasonal influenza); - new and underutilized vaccines = all vaccines that were not previously in national immunization schedule	World Bank, JRF	2010	2015: at least 80	Monitor trends in vaccine introduction

No	Goal	Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
G3.2	**Meet vaccination coverage targets in every region, country and community**	Reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended	WUENIC for national coverage; Coverage refers to coverage with primary series of vaccine. For pneumo and rota vaccines, this will be coverage with primary series by 12 months of age. For other vaccines, the exact measurement of coverage needs to be defined, but will be as reported in the WUENIC. District data: - accept JRF admin data if WUENIC based on administrative coverage; •Missing district reports =indicator not met, encourge reporting; –if WUENIC not based on administrative coverage, repeated measure (survey or special study to document district coverage); •Early measure (2009 to 2015) •Later measure (2016 to 2020) -- applied to all vaccines being used for country-wide, universal immunization (exception of HPV, where country-wide universal immunization of girls would be included)	WUENIC, JRF	2010 or early measure (for district data)	2020: All Member States	Monitor trends in coverage
G4.1	**Develop and introduce new and improved vaccines and technologies**	Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases.	Licensure relates to registration by a functional NRA Launch is defined as addition of the vaccine to the national immunization schedule in one or more low or middle income countries (WB definition) and sustained for a period of at least 12 months. Excludes use only in the private sector. Includes vaccines in national schedule that may be selectively used in "at risk" populations	annual surveys with NRA's; JRF for launch of vaccine; WB for definition of low and middle income countries	0	2020: one or more	Incremental progress (i.e. number of products in phase 1, 2 or 3 clinical trials) on development to be reported and assessed by IRG

No	Goal	Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
G4.2	**Develop and introduce new and improved vaccines and technologies**	Licensure and launch of at least one new platform delivery technology	Licensure relates to registration by a functional NRA; New platform delivery technology is defined as a new mechanism for delivering vaccines to individual recipients that facilitates coverage, improves performance, or reduces cost of vaccine or delivery, e.g. jet injectors, microneedles, aerosol etc.; - launch as defined for new vaccine introduction (see above indicator)	annual surveys with NRA's; JRF for launch; WB for definition of low and middle income countries	0	2020: one or more	Incremental progress on development (i.e. number of products in phase 1, 2 or 3 clinical trials) to be reported and assessed by IRG
G4.3		Number of low- and middle-income countries that have introduced one or more new or underutilized vaccines	low- and middle-income countries= world bank classification 2012;- vaccine added in national immunization schedule and used for a sustained period of at least 12 months (excluding those used only in the private sector and not in national immunization schedule; includes vaccines included in national schedule but for selective use at risk populations, e.g. seasonal influenza); - new and underutilized vaccines = all vaccines that were not previously in national immunization schedule	World Bank, JRF	2010	2015: at least 80 at least 90	Monitor trends in vaccine introduction
G5.1	**Exceed the Millennium Development Goal 4 target for reducing child mortality**	Reduce under five mortality rate	IGME estimates of child mortality			2015: 2/3 reduction compared to 1990 2020: exceed 2015 target	Monitor trends
	*WUENIC= WHO UNICEF Estimates of Nactional Immunization Coverage						

Strategic objective		Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
SO1.1	**All countries commit to immunization as a priority**	~~Presence of a legal framework or legislation that guarantees immunization financing~~					
		~~Domestic resources allocated for immunization~~ Domestic expenditures for immunization per immunized person	Immunization expenditure from national domestic resources, as reported in the JRF Size of target populations as reported in JRF	JRF	reported expenditure for 2010	increasing trend in country allocation to national immunization programmes	Monitor and report trends
SO1.2		Presence of an independent technical advisory group that meets defined criteria	National Immunization Technical Advisory Groups meeting all WHO criteria of functionality Criteria of functionality are as described in the WHO/UNICEF JRF	JRF	2010	Functional National Immunization Technical Advisory Groups in all countries	Increasing trend in number of countries with functional NITAGs
SO 2.1	**Individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility**	% of countries that have assessed (or measured) the level of confidence in vaccination at subnational level with implementation of activities to improve it.	Definition of vaccine confidence: Trust in the usefulness and safety of vaccines and in the system that delivers them. Vaccination confidence exists on a continuum, and is one of the factors that influences behavior ranging from acceptance to refusal.	JRF		Increasing trend	Monitor and report trends
SO 2.2		% of un- and under-vaccinated in whom lack of confidence was a factor that influenced their decision.	Operational definition to determine % with "lack of confidence" is yet to be defined	JRF		Decreasing trend in % with lack of confidence	Monitor and report trends

Strategic objective		Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
SO3.1	**The benefits of immunization are equitably extended to all people**	Percentage of districts with ~~less~~ 80% or greater coverage with 3 doses of diphtheria-tetanus-pertussis-containing vaccine	JRF admin data if WUENIC based on administrative coverage; missing district reports = indicator not met, encourage reporting; –if WUENIC not based on administrative coverage, repeated measure (survey or special study to document district coverage); at least two measures, with early measure (2009 to 2015) and later measure (2016-2020)	JRF annual, or special studies/ surveys for repeated measures;	2010 or early measure	All countries with all districts ≥ 80% DTP3 coverage by 2020	Monitor trends in number of countries meeting the target
SO3.2		Reduction in coverage gaps betweenwealth quintiles (AND another appropriate equity indicator)	All countries to identify and reduce inequity of immunization in at least one domain or demonstrate equity by wealth quintile; If wealth quintile is used should report coverage across all quintiles and not just lowest and highest quintile Data collection by repeated measure (special study or survey), with at least two measurements, early measure (2009-2015) and late measure (2016-2020)	household survey or special study representative of entire population	early measure	Increasing trend in equity in immunization coverage. Proposed target to align with GAVI targets: proportion of countries with < 20% difference in coverage between wealth quintiles 60% by 2015 & 75% by 2020	Increasing trend in equity in immunization coverage

Strategic objective		Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
SO4.1	**Strong immunization systems are an integral part of a well-functioning health system**	DTP1 to measles first dose dropout rate	Difference between % coverage with DTP 1 and % coverage with MCV1	WUENIC	2010	Decreasing trend in drop out rate	Trends in drop-out rates
SO4.2		Immunization coverage data assessed as high quality by WHO and UNICEF	Use qualitative assessment of data quality in WUENIC, based on nationally reported data, consistency in data on estimates of size of target population, and consistency between estimates from administrative and other data sources (surveys and other programmatic information)	WUENIC Grade of Confiden-ce	2010	All countries to have high quality immunization coverage data by 2020	Monitor trends in number of countries meeting the target
SO 4.3		~~Percentage of routine immunization costs financed through government budgets~~ Number of countries that have established surveillance, with laboratory confirmation, for invasive bacterial diseases and rotavirus diarrhoea and report data to WHO	~~As defined in JRF~~ # countries reporting that they have established surveillance in the JRF and whose reports are included in WHO databases	JRF and surveillan-ce reports to WHO		75% of low and middle income countries by 2020	Increasing trend

Strategic objective		Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
		~~Installed capacity for production of universally recommended vaccines within five years of licensure/potential demand~~					
SO5.1	**Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies**	Percentage of doses of vaccine of assured quality, produced, procured and used worldwide	Number of doses of vaccines of assured quality used in a country (licensed by functional NRA)/ total doses of vaccines used in national immunization programme	JRF. Assessment by QSS whether vaccines used in country qualify to be considered of "assured quality"	2010	100% of doses vaccines by 2020	Increasing trend
SO5.2		~~Sufficient doses procured to meet stated program requirements~~	~~# of vaccine doses procured/# of vaccine doses required in low and middle income countries~~				
SO6.1	**Country, regional and global research and development innovations maximize the benefits of immunization**	Progress towards development of HIV, TB, and malaria vaccines	number of HIV, TB, and malaria-vaccine clinical trials assessing clinical efficacy completed and with results reported	WHO; NIH and other clinical trial registries		Proof of concept for a vaccine that shows greater or equal to 75% efficacy for HIV/AIDS, tuberculosis, or malaria vaccines.	Narrative report on progress in development of these vaccines

Strategic objective		Indicator	Operational definition	Data source/ collection	Baseline	Target	Milestones
SO6.2	**Country, regional and global research and development innovations maximize the benefits of immunization**	Progress towards a universal influenza vaccine (protecting against drift and shift variant)	number of influenza clinical trials assessing clinically the breadth of protection completed and reported			at least one vaccine providing broad spectrum protection against influenza A virus licensed	Narrative report on progress in development of these vaccines
SO 6.3		Progress towards institutional and technical capacity to make vaccines and/or carry out related vaccine clinical trials~~, operational and organizational research~~	number of countries per WHO region having reported conduct of a vaccine clinical trials	WHO; NIH and other clinical trial registries		Every Region has a solid base of countries competent in hosting and managing vaccine trials.	
SO 6.4		Number of vaccines that have either been re-licensed or licensed for use in a controlled temperature chain (CTC) at temperatures above the traditional 2-8 C range	As define in indicator	PQS data base	incremen-tal above 2010		Increasing number of vaccines
SO 6.5		Number vaccine delivery technologies (devices & equipment) that have <u>received</u> WHO pre-qualification against the 2010 baseline	Four categories of equipment would be tracked: Refrigerators and freezers Cold boxes and vaccine carriers Coolant packs Temperature monitoring devices	PQS data base	incremen-tal above 2010		Increasing number of technologies

The Monitoring & Evaluation/Accountability Framework for the Global Vaccine Action Plan
5: Resource Tracking

Background

The Global Vaccine Action Plan's (GVAP) Monitoring & Evaluation/Accountability Framework is in need of a resource tracking process to monitor the resources mobilized for immunizations. It would also instruct the assessment of cost projections, funding gaps and other components required for the 2015 review of the financing, costing and impact investments included in the GVAP.

To better understand the state of resource tracking, the costing, financing and impact technical team of experts from the Decade of Vaccines Collaboration (DoVC) Leadership Council (LC) agencies recommended a landscape review of existing resource tracking mechanisms. The Institute for Health Metrics and Evaluation (IHME) is conducting the rapid landscape review and, based on its preliminary findings, suggested a resource tracking framework. On 10-11 October, the technical team met in person and discussed the landscape review, framework and a plan to generate reliable, usable and easily produced information on the resources available for vaccinations. This document outlines the initial thinking of the technical group and different areas currently under consideration.

Summary

The resource tracking exercise will focus on evaluating funding flows from development partners, governments and, to the extent possible, civil society organizations (CSOs) at the global, regional and country level and ultimately to routine immunization programs. This will be reported at the country level for the period 2006-2010 for the 94 countries identified in the DoVC costing and financing analysis. Data sources include information collected from development partner agencies, CSOs involved with immunization, and governments. Funding flows will be evaluated both in the aggregate and be disaggregated, as possible, into funding for vaccines and service delivery, and global and country level funding. Other possible disaggregation will be explored as the quality and breadth of data are explored more fully.

Two components are currently under discussion and consideration: (i) retrospective analyses and (ii) improved quality of financial reporting. The first component would generate retrospective estimates of the resources devoted to routine vaccinations, by country and year, and would be done over the short and mid-term. The second component, which could be implemented in tandem and in collaboration with partners, involves putting a process in motion that fosters the consistent provision of quality data, and would be a longer-term effort. The objective of the improved financial reporting quality component would be to propose and enact modifications to the process by which data are collected from countries, to reduce dependence on statistical inference and improve policymakers' ability to improve the efficiency and sustainability of immunization interventions.

Retrospective Analyses

As discussed and proposed, the retrospective analyses would consist of two activities, over the short and mid-term:

1. First activity (short-term output)

The first activity involved in the retrospective analyses would generate the following metrics: **estimates of the domestic and external funding for immunizations disaggregated by country and year, but would not disaggregate vaccine and service delivery financing flows**. Countries' contributions would be obtained from WHO-UNICEF Joint Reporting Form (JRF) data and potentially other sources. The development assistance for health devoted to vaccines and immunizations would be obtained from the IHME database gathered directly from external sources of financing and additional data collection from development partners, including key immunization CSOs, and supplemented by figures from the baseline year of the Comprehensive Multi-Year Plans (cMYP) if deemed relevant. Based on the availability of JRF data, it is proposed that the initial estimates cover the years 2006-2010. This first activity is estimated would take six-months to be completed.

2. Second activity (mid-term output)

Two challenges associated with the first activity estimates are that funds are not disaggregated by vaccine costs versus service delivery costs, and that source data are subject to measurement error. The second activity would produce these additional metrics: **estimates of vaccines and service delivery financing disaggregated by country and year**. Other distinctions, such as funding flows versus physical stocks, the differences among resources budgeted, allocated and used, and additional disaggregation of service delivery merit further

discussion and consideration by the technical team. In addition, other types of disaggregation of the information will be explored, including assessing funds transfers at the global and country level.

A benchmarking exercise to assess and correct measurement error would also be conducted. Estimates would be validated by comparing financial flows to other data sources, such as the number of doses delivered and coverage rates in a country. There are few areas in health in which this validation is possible, but vaccination is one such area because it has a well-defined supply chain. This analysis would generate a validated estimate by triangulating financing data with supply-chain information and coverage rates. The statistical techniques to accomplish this triangulation have previously been applied to health (most notably to the financing and supply of insecticide-treated bed nets), but not yet to vaccination. Data from immunization costing studies currently underway will also be used, as available, to complete the triangulation exercise. Initially, it appears these estimates could also be made for the period of 2006-2010, depending on the availability of the additional data sources. This second activity could possibly take approximately 10 months to be completed.

Improve the quality of financial reporting activity (long-term output)

Statistical estimation can enhance the utility of problematic data, but statistics is not a substitute for accurate and readily usable information. The LC agencies' technical team has begun to discuss a process to improve the quality of reporting on immunization expenditures and sources of financing which would build off and be pursued in parallel to the retrospective analyses described above. Currently, multiple processes exist to collect similar types of data from countries, and few (if any) feedback and validation mechanisms exist. Our priority would be not to create another data-collection mechanism, but rather to identify strategies to improve existing mechanisms such as the JRFs, GAVI Alliance Annual Progress Reports (APRs), cMYPs and other annual planning exercises and the data collected via these mechanisms. **The objective would be to develop and support a multi-partner process that would strengthen capacities to collect and analyze expenditure data and provide feedback in view of streamlining and enhancing data collection and reporting processes.** It is useful to note that the current GAVI Alliance Business Plan for 2013 includes an activity to strengthen resource tracking.

Improving quality of reporting would require the identification of corrective and enhancement measures and incentives to improve the quality of the data itself. Building off a data quality assessment and stock-taking of data gaps, **a roadmap for improving financing data quality and reporting would be developed.** While the deployment of the road map and its actual contents require further discussion, encouraging the use of annual work plans and budgets at the country level is a proposal to be considered. If data were linked with regular discussions among country level stakeholders on resource planning, allocation and effective use, their relevance and quality would be more important, as would the manner in which they are produced. Based on the recommendations of the road map, **feedback mechanisms and capacity building efforts could be developed and deployed**.

Improving quality of reporting work is ongoing and it should link with the LC work on costing, financing and impact. The improvements proposed are guided by the following principles:

1. The resource tracking process should strive to promote accountability among the different stakeholders involved in immunization.
2. It should encourage the sustainability and country ownership of resource allocation processes.
3. The information provided should be relevant and useable.
4. The tracking process should not be cumbersome to health workers or others involved in producing health service. The system should strengthen, not burden, the operation of the health system and aim for integration of the flows of information.
5. Data should be comparable across time within a country and potentially across space for a subset of countries.
6. The costs to undertake this work should be reasonable, and not detract from the system's provision of service. The trade-off between short-term and long-term costs is a relevant consideration. Significant investment may be required to scale up a tracking system, but the system may still be economical if the costs of maintenance are low.
7. The framework and process put in place needs to be user-friendly and easily replicable on an ongoing basis.

Next Steps

Based on the feedback received from SAGE, the technical team will further develop these concepts and create a concrete proposal that takes into consideration resource needs and timelines for the implementation of the various activities.

6: Updating the Global Vaccine Action Plan cost, financing, and impact projections for 2015

Background

The Global Vaccine Action Plan (GVAP) was endorsed by the WHA in May 2012. As part of the GVAP, globally-aggregated projections for the total cost, impact, and financing available for the period of 2011 – 2020 were developed by multiple groups under the coordination of the Decade of Vaccines Collaboration (DoVC) Secretariat.

In the past weeks, the technical group (composed of representatives of the DoVC Leadership Council agencies) has identified the lessons learned in both process and methodology in order to inform any future update to the projections. Specifically, the need for early alignment on scope, sufficient commitment of enough time and resources, and clear oversight and governance to steer efforts were highlighted as major areas of focus in future update planning.

Summary of limitations of earlier process

Process	• No upfront process created for internal or external validation and review • Lack of clarity on intended audience and use of projections led to one-off exercise and limited flexibility in communicating the output • Additional analyses were brought in late in the process • Sherpas and Leadership Council (LC) were not engaged early and periodically throughout process and there was limited upward communication within the LC agencies
Methodology	• Unable to complete the "return on investments" analysis: delivery costing and health impact misaligned in scope • Analysis relied on extrapolated data (2015-2020) and Comprehensive Multi-Year Plan (cMYP) data with many gaps, resulting in weak projections for the second half of the decade • Poor coordination between technical groups on data sources and assumptions • Agency and CSO costs were not included

Updating the cost, financing, and impact projections in 2015

The LC has requested the development of a specification to update and improve the cost, financing and impact projections provided in the GVAP. The technical group recommends the updated projections be used primarily for global and regional advocacy to highlight the value of immunization and promote resource mobilization. Findings will be reported at the global and regional levels, but not at the country level unless a specific need is identified. The technical group agrees there is value of going beyond the original high level estimated numbers in order to articulate funding priorities for the second half of the decade and even contribute to discussions on the 2014 GAVI Alliance replenishment, the 2015 MDG and beyond 2015 agendas and other future initiatives of relevance.

Resource and timeline implications

The recommended scope of the analysis represents a much broader piece of work than originally undertaken to develop the current GVAP cost, financing, and impact projections. This is to overcome the limitations of the previous exercise and to improve the estimates. As a result, the technical group and DoVC Secretariat are exploring the feasibility of committing the resources required to ensure successful implementation of this proposed scope of work that will continue after the DoVC Secretariat ceases to exist.

In order to be prepared for key advocacy milestones in 2014 and 2015, work would need to begin on this analysis in 2013. Technical resources would need to be committed in 2013 to assess the feasibility of the agreed analysis and a coordinating body would need to be established mid-2013 to convene the technical group necessary to update the projections.

Finally, the group also recognizes that the ultimate output of this work will need to be closely aligned with the scope of the resource tracking system and the monitoring and evaluation process, both detailed in other memos. In addition, recommendations below will need to be reviewed by the team conducting the update prior to reengaging on the 2015 review work.

Recommended ideal scope and assumptions

The past exercise was limited by time and resources available to produce only globally aggregated and total cost, funding, and impact projections. The ideal scope of the future update to meet the resource mobilization and advocacy needs outlined above is as follows:

- **Update the cost, financing, and impact projections at a global and regional level**
  - Leverage new or updated data sources (i.e., more comprehensive funding sources).
  - Expand the scope of vaccines and/or countries for cost and impact analyses as detailed above.
  - Align with cost projections in other vaccine investment cases, i.e. measles elimination/eradication.
- **Expand the analyses to include additional costs and impact**
  - Evaluate both total and incremental costs and impacts. Total and incremental results are recommended in order to give the most flexibility in communicating results in 2015. Given data challenges, the appropriate approach and feasibility of generating incremental costs will be explored through consultation in 2013.
  - Include morbidity and economic impact estimates.
  - Include estimates for agency overhead and civil society costs. The SAGE recommended in February 2012 the technical group to evaluate the inclusion of agency overhead and civil society costs.
  - Conduct funding gap analysis. This analysis would build on the resource tracking work that is being developed and would analyze funds by source and year.
- **Develop a new delivery cost methodology that would enable ROI analysis by vaccine**
- **Output indicators for communication purposes**
  - i.e., total costs and total impact; total cost per child; incremental cost and impact by vaccine and per child; total financing by year; funding gap per child and by cost category.
- **Conduct scenario analysis**
  - Coverage scenarios: Produce projections for cost and impact based on different levels of coverage (for example, scenarios would include: baseline coverage scenario building on the GAVI Strategic Demand Forecast, and aspirational GVAP targets, among others).
  - "What-if" scenarios/ game changers: Scenarios to highlight the impact of new technologies and approaches on the costs and benefits to the immunization community (i.e., lower prices, new devices, new service delivery practices, no cold chain requirement in delivery process, only 1 vaccine to cover all diseases, etc.).
  - Including "what if" scenarios would allow for understanding of major drivers in costs or benefits and inform agenda setting and resource mobilization. In addition, such scenarios are aligned with the GVAP commitment to innovation.
- **Quantify the degree of uncertainty in projections**
- **Validate externally**
  - Technical validation of the methods will be sought throughout the process, through convening a broader group of immunization costing and financing experts from a variety of technical agencies than are involved in the projections (i.e. CDC, World Bank).

Assumptions

The technical group would like to make the following recommendations on assumptions:

- **Vaccines: Include the same scope of vaccines highlighted in the GVAP**
  - At a minimum, updated impact projections will include pertussis, cholera, dengue, and malaria. These vaccines are currently in the costing analysis.
  - In addition, inclusion of typhoid, mumps, hep A, and hep E will be evaluated at the start as well as other vaccines that may be available in the decade.
  - Therapeutic vaccines (i.e., rabies, shingles and anthrax) and flu will not be included in either analysis although they are highlighted in the GVAP.
- **Countries: Continue with the same scope as the initial analysis (94 countries)**
  - Initially, low-middle-income countries and GAVI-eligible countries were selected. This set of 94 countries includes two upper-middle-income countries receiving GAVI support.
  - The technical group recommendation to stay with the initial set of 94 countries is based on the desire for comparability to the past exercise, and the limited feasibility/ ease of expanding to all middle-income countries.
- **Time period** will remain 2011 – 2020
- **R&D costs** will continue to be excluded from the analysis
- This will remain primarily a "desk" exercise, without any major field-based elements. New empirical data will be incorporated as and when they become available.

7. SAGE Working Group on the Decade of Vaccines' Global Vaccine Action Plan

Terms of reference

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

Specifically, the WG will:

1) 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;
2) identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed;
3) identify and document best practices;
4) 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[1].

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

Membership

The group will be composed of 2 SAGE members and an additional 8 experts all serving in their individual capacity. The group will be chaired by a SAGE member. The appointed Chair will remain Chair even after he/she rotates out of SAGE unless he/she becomes ineligible to continue serving on the group (e.g., in view of affiliation and declaration of interests). The selection of the non-SAGE member experts will be made by consensus by the DoV lead agencies (WHO, UNICEF, the GAVI Alliance, the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases (NIAID—part of the National Institutes of Health U.S.) and a representative from the Civil Society Organizations (CSOs) following an open call for nominations. The lead agencies will be asked to nominate one member each who will serve on a WG selection panel together with the appointed WG chair, the Chair of SAGE and the SAGE Executive Secretary.

The WG will aim to have expertise relevant to the GVAP Goals and 6 Strategic Objectives:

1. All countries commit to immunization as a priority.
2. Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility.
3. The benefits of immunization are equitably extended to all people.
4. Strong immunization systems are an integral part of a well-functioning health system.
5. Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies.
6. Country, regional and global research and development innovations maximize the benefits of immunization.

[1] http://www.who.int/woman_child_accountability/ierg/members/en/

In addition, the WG should have broad geographic representation, gender balance, and represent a broad range of stakeholders and constituencies.

Mode of operation and secretarial support

The WG will operate under the rules of functioning for SAGE Working Groups. See: www.who.int/immunization/sage/SAGE_Working_Groups_general_information.pdf.

The WG will meet face to face on an annual basis in September and present its report to the subsequent November SAGE meeting.

Additional teleconferences will be arranged on an ad-hoc basis in order to prepare for the face-to-face meetings.

The Secretariat will facilitate the preparation of the reports to be reviewed by SAGE. Main administrative and secretariat support will be provided by WHO.

The WG proceedings will be informed by:

1. An annual monitoring report of GVAP indicators and achievement of goals and targets.
2. A specific narrative progress report for each of the GVAP 6 Strategic Objectives taking the above mentioned report into consideration.
3. An annual M&E / Accountability report with tracking of resources and commitments.
4. Annual regional reports on the GVAP implementation, themselves generated with input from the Regional Technical Advisory Groups on Immunization (RTAGs).
5. Annual reports from key stakeholders such as civil society and industry

Status Report on Progress Towards Measles and Rubella Elimination

SAGE Working Group on Measles and Rubella

(22 October 2012)

Table of Contents

I. Introduction

This report provides an update on progress, challenges, and opportunities for the global control and eventual elimination of measles and rubella. It has been prepared as a background document for the November 2012 SAGE Meeting and includes eight sections (see Table of Contents). Following the introduction, the second section describes the current global and regional targets. The third section reports on progress towards the global measles immunization coverage, incidence and mortality reduction targets and concludes that progress has plateaued since 2008. The fourth section provides executive summaries of progress, challenges and lessons learnt from each of the 6 WHO Regions and concludes that The American Region has reached its measles and rubella elimination goals, The Western Pacific Region is making good progress towards measles elimination however, the remaining 4 Regions are facing significant challenges that, if not addressed, will result in them not achieving their targets on time. The fifth section provides a synopsis of the major challenges facing each region. The sixth section describes the new opportunities and steps being taken to implement the Global Measles and Rubella Strategic Plan, 2012-2020. The seventh section lists the questions to SAGE and the last section provides draft recommendations for discussion.

SAGE is being asked to review this report, provide guidance on whether the new plans and resources are sufficient to get back on track, and advise on what additional strategies or innovations are needed to reach the global and regional targets.

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. Routine measles vaccination coverage was selected as an indicator of progress towards this goal because of the potential of measles vaccination to reduce mortality among children and consideration of measles vaccination coverage as a marker of access to children's health services.[1]

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:

- exceed 90% coverage with the first dose of measles-containing vaccine nationally and exceed 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.

Regional Targets

All six WHO regions have committed to measles elimination and five regions have set target dates. The WHO Region of the Americas achieved the goal in 2002; the Western Pacific Region aims to eliminate

[1] *The Millennium Development Goals report 2009*. New York, United Nations, 2009 (http://mdgs.un.org/unsd/mdg/Resources/Static/Products/Progress2009/MDG_Report_2009_En.pdf, accessed 18 November 2009

measles by end of 2012; and the European and Eastern Mediterranean Regions are accelerating their measles control activities in order to eliminate measles by 2015. In 2011, countries in the African Region took on the goal to eliminate measles by 2020, and in 2010 the South-East Asia Region adopted a resolution urging countries to mobilize resources to support the elimination of measles, the target date for which is still to be decided.

Three of the six WHO regions have set control or elimination targets for rubella. The Americas has targeted rubella and CRS elimination by 2010 and the European Region, rubella elimination by 2015. The Western Pacific Region aims to have significantly accelerated rubella control and CRS prevention by 2015, and the Eastern Mediterranean Region is currently discussing the establishment of a target date for rubella and CRS elimination. The African and South-East Asia Regions have yet to establish rubella control or elimination goals.

Feasibility of Measles Eradication

The November 2010 meeting of SAGE reviewed results from the programme of work to assess the feasibility of global eradication of measles. The conclusions were that measles can and should be eradicated; that the eradication of measles represents unique disease control and developmental opportunities; and that eradication activities should be carried out in the context of strengthening routine immunization programmes. In addition, the programme efficiencies of using combined measles–rubella vaccine and integrated surveillance for fever and rash provide an opportunity for measles eradication activities to accelerate the control of rubella and the prevention of congenital rubella syndrome. SAGE recommended that demonstration of measurable progress towards existing global and regional targets be made the basis for establishing a target date for achieving measles eradication, and requested frequent updates on progress.

Global Vaccine Action Plan Targets for Measles and Rubella

In April 2012, the core partners of the Measles Initiative (American Red Cross, US Centers for Disease Control and Prevention, United Nations Foundation, UNICEF, and WHO) launched the Global Measles and Rubella Strategic Plan, 2012-2020. The common vision is *a world without measles, rubella and congenital rubella syndrome* with existing global control and regional elimination targets as milestones towards this vision. 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 Regions by 2020. As the targets, strategies and guiding principles in the Global Measles and Rubella Strategic Plan, 2012-2020 are closely aligned with the GVAP it acts as a supporting strategic document that provides more detail on measles and rubella in the wider immunization context provided by the global plan.

In summary, while there is a general consensus that no child should die from measles or be born with congenital rubella syndrome (i.e., eradication of measles, rubella and CRS is the ultimate goal), the target date by which this should be achieved has still to be established.

III. Progress Towards Global Targets

Immunization Activities

During 2000–2010, estimated global MCV1 coverage increased from 72% to 85% then decreased to 84% in 2011; by 2011, 3 of the 6 WHO regions had >90% estimated MCV1 coverage (Table 1). The proportion of all member states with >90% coverage increased from 42% in 2000 to 62% in 2010, then fell to 60% in 2011. Notable progress was seen during this period in the African, Southeast Asian, and Western Pacific Regions, while the American and European Regions sustained a high proportion (i.e., approximately 80%) of Member States meeting this objective. In 2011 the proportion of Member States exceeding 90% MCV1 coverage dropped in 3 of 6 regions, the African, American, and Eastern Mediterranean Regions. In 2011, 21,464 (61%) of 34,200 districts worldwide achieved ≥80% MCV1 coverage; 53 (34%) of the 156 Member States providing this data reached the target in every district. Globally the proportion of Member States meeting this target has not changed significantly since these data were first reported in 2003. Of the estimated 20.2 million children who never received MCV1 in 2011 (i.e., 16% of surviving infants worldwide), 11 million (55%) were in just 5 Member States: India (6.7 million), Nigeria (1.7 million), Ethiopia (1 million), Pakistan (0.9 million) and the Democratic Republic of the Congo (DRC) (0.8 million).

By 2011 all Member States were providing two doses of measles vaccine. The second dose of MCV (MCV2) was offered through routine services in 141 (73%), ranging from 8 (17%) of 46 countries in the African Region to 53 (100%) of the countries in the European Region. In 2011 coverage with MCV2 in target-aged children, based on administrative records, was reported to WHO and UNICEF by 116 (82%) of those Member States having introduced the vaccine with coverage of 45%, up from 13% in 2000. Of Member States reporting coverage, 67 (35%) exceeded 90% national coverage, ranging from 10 (29%) of 25 in the American Region to 28 (53%) of 43 in the European Region. During 2000–2011, over one billion children received a measles vaccination through SIAs. During 2011, based on reports by Member States to WHO, 28 measles SIAs reached >146 million children, including 23 reaching >117 million children among the 47 high-burden countries. Reported coverage was >95% for 11 (39%) of SIAs, including 9 (39%) in high-burden countries.

By 2011, 130 (67%) 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 except Tunisia[2] 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 2011 ranged from 7% in the African Region to 100% of countries in the American and European Regions. During 2000–2011, estimated global coverage with one dose of RCV increased from 21% to 41%; by 2011, the American and European Regions of WHO had >90% estimated RCV coverage.

[2] Based on 2011 Joint Reporting Form information, Tunisia gives single antigen rubella vaccine to adolescent girls

Disease Surveillance

The number of Member States annually reporting measles surveillance data to WHO and UNICEF increased from 169 (88%) in 2000 to 188 (97%) in 2011 and for rubella from 102 (53%) in 2000 to 173 (89%) in 2011. 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 2011, 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 121 (63%) of Member States reported cases of congenital rubella syndrome (CRS) in 2011, up from 75 Member States in 2000, few cases of CRS are reported, as described below.

During 2000–2011, global reported measles cases decreased 57% from 853,480 to 354,820 and measles incidence decreased 64% from 146 to 53 cases per million population, with all WHO regions reporting decreases in case numbers and incidence (Table 1). The greatest decrease in reported measles cases was during 2000–2008, from 853,480 to 277,968.

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 Eastern Mediterranean Region (EMR) from 12,120 to 36,605 balanced by a decrease in the Western Pacific Region (WPR) from 147,987 to 66,609.

From 2009 to 2010, global reported measles cases increased to 329,608. Decreases in WPR to 49,460, in EMR to 10,072, and in the South-East Asia Region (SEAR) from 84,356 to 52,529 were offset by increases in AFR to 186,675 and in the European Region (EUR) from 7,499 to 30,625.

From 2010 to 2011, global reported measles cases increased to 354,820. 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 1).

Globally, the percentage of Member States with reported measles incidence <5 cases per million population increased from 63 (38%) of 167 reporting Member States in 2000 to 121 (67%) in 2008. That number decreased in 2011 to 104 (60%) of 188 reporting Member States (Table 1).

TABLE 1. Estimates of coverage with the first dose of measles-containing vaccine administerd through routine immunization services among children aged 1 year, reported measles cases and incidence by World health Organization region, 2000 and 2011

	2000					2011						2010	
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	% countries with incidence < 5 per million	Estimated Measles Deaths (95% CI) e	% 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	% countries with incidence < 5 per million	Estimated Measles Deaths (95% CI) e	% mortality reduction 2000 to 2010
African	54	520'102	859	5.1	337,000 (216,600-653,000)	75	194'364	63	238	72	46	50,000 (8,900-258,100)	85%
Americas	92	1'755	2.1	89	<100	92	1'249	29	1.4	37	94	<100	-
Eastern Mediterranean	72	38'592	90	17	48,600 (29,400-82,300)	83	35'923	7	63	30	45	10,100 (3,500-39,000)	79%
European	91	37'421	50	45	400 (200-2,300)	94	37'073	1	44	13	44	100 (0-1,300)	87%
South-East Asia	61	78'558	52	0	48,200 (25,700-84,900)	79	65'161	17	37	29	27	10,500 (4,700-38,000)	78%
Western Pacific	85	177'052	107	30	13,100 (4,700-46,100)	96	21'050	88	12	89	62	3,100 (500-32,500)	76%
Total	**72**	**853'480**	**148**	**38**	**535,300 (347,200-976,400)**	**84**	**354'820**	**58**	**53**	**64**	**55**	**139,300 (71,200-447,800)**	**74%**

a Coverage data:WHO/UNICEF estimates of national immunization coverage. Geneva, World Health Organization, 2012 (October 2012 version). (Available at http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html, accessed 6 October 2012)

b Reported case data: Measles reported cases. Geneva, World Health Oranization, 2011 (data as of xx) (http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidencemea.htm, accessed 6 October 2012)
Americas data from Measles/rubella/congenital rubella syndrome surveillance data final classification, 2010. Immunization Newsletter 2011; 33(3):7

c Population data: United Nations, Department of Economic and Social Affairs, Population Division (2011). World Population Prospects: The 2010 Revision, CD-ROM Edition

d Any country not reporting data on measles cases for that year were removed from both the numerator and denominator

e morality estimates from Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, Strebel P. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379(9832):2173-8.

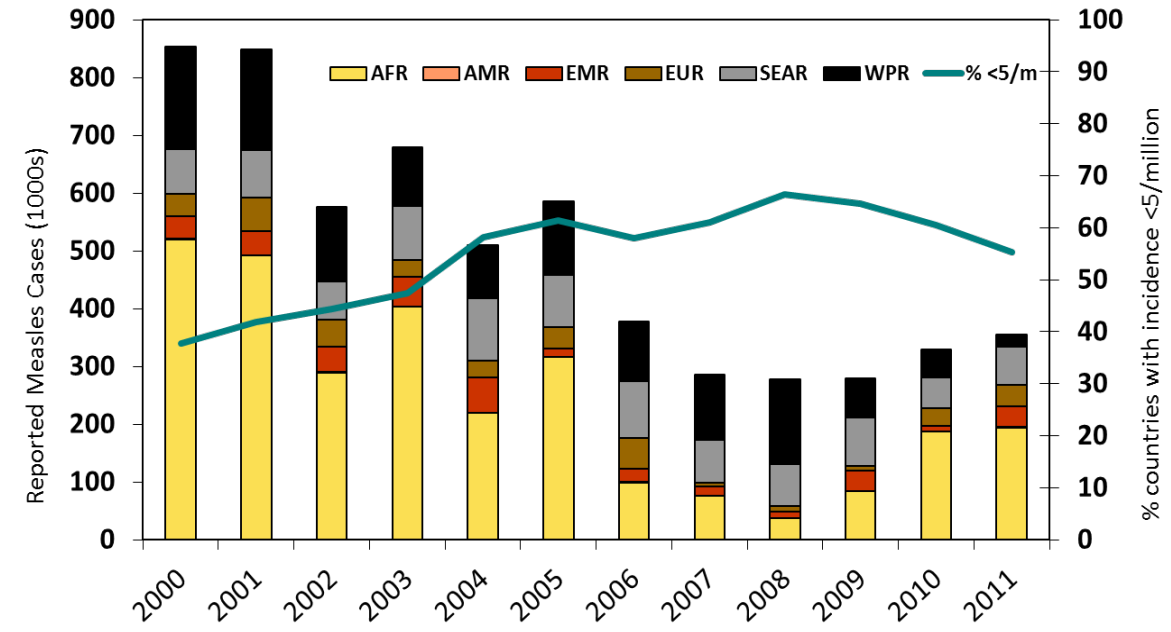


Figure: Reported measles cases by WHO Region and global percentage of countries with estimated incidence <5 per million, 2000-2011

During 2009–2011, a number of Member States experienced large measles outbreaks including DRC (134,042 cases in 2011), Malawi (118,712 cases in 2010), Burkina Faso (54,118 cases in 2009), Iraq (30,328 cases in 2009), Bulgaria (22,004 cases in 2010), South Africa (18,356 cases in 2010), Zambia (15,754 cases in 2010 and 13,324 in 2011), France (14,949 in 2011), Somalia (17,298 cases in 2011), Zimbabwe (9,696 cases), Viet Nam (6,582 cases in 2009 and 2,809 in 2010), Chad (8,650 cases in 2011), Nigeria (8,491 cases in 2010 and 18,843 in 2011), Namibia (7,214 cases in 2009 and 2010), the Philippines (6,368 cases in 2009 and 6,538 in 2010), Italy (5,189 cases in 2011) and Ethiopia (4,235 cases in 2010 and 3,255 in 2011). The outbreaks were primarily due to low MCV1 coverage and, in Burkina Faso, DRC, Ethiopia, Nigeria, and the Philippines, to suboptimal or delayed SIAs. In Viet Nam the outbreak occurred in areas not covered by subnational SIAs in 2007 and 2008. 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. In Bulgaria, Malawi, Zambia and Zimbabwe these gaps were often found in groups with limited access to health services or who were reluctant to vaccinate their children, often for philosophical or religious reasons.

During 2000–2011, global reported rubella cases decreased 83% from 670,894 to 114,449. The greatest decrease in reported rubella cases was a 98% decrease in the European Region, from 804,567 to 9,671, and a 99.9% decrease in the Americas, from 58,755 in 2000 to only 9 cases in 2011. 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 121 (63%) in 2011. Compared to model estimates the number of reported CRS case is very low, with 214 reported CRS cases in 2011 versus an estimated 111,888 CRS cases in 2008.

Disease Burden Estimates

Global measles mortality decreased 74% from 535,300 deaths in 2000 to 139,300 in 2010. Compared with estimated mortality assuming the complete absence of measles vaccination, 9.6 million deaths were averted by measles vaccination during 2000–10. Measles mortality was reduced by more than three-quarters in all regions except the South-East Asia Region. Most measles deaths (79%) were estimated to be in Africa and India during 2000–10. Estimated measles mortality decreased by 85% in Africa, from 337,000 to 50,000, during 2000–10 (Table 1). As a whole, the African Region accounted for 36% of global measles mortality in 2010, down from 63% in 2000. India's small decline in measles mortality (26%) led to an increase in the country's share of global measles mortality from 16% in 2000 to 47% in 2010. Estimated measles mortality decreased by 78% during 2000–10 in the remaining ten countries in the Southeast Asia Region. Planned SIAs in India targeting 134 million children in 11 States and the introduction of a routine second dose in 17 Indian States during 2011–13 should lead to substantially reduced measles mortality by 2015.

The Eastern Mediterranean and Western Pacific Regions accounted for 9–11% of estimated global measles mortality during 2000–10, and estimated measles mortality fell 79% in the Eastern Mediterranean and 76% in the Western Pacific region. Although the European Region continues to have large outbreaks of measles, because of very low case-fatality ratios (CFRs), the region accounted for less than 1% of global measles mortality.

Though surveillance for rubella has greatly improved over the past 11 years, 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.

IV. Progress Towards Regional Targets

African Region

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 60th 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

In the meantime, the Region is working towards measles pre-elimination targets set for the end of 2012. These targets are seen as milestones in the progress towards measles elimination.

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

Between the years 2001 and 2011, countries in the African Region have achieved an increase in MCV1 coverage from 56% to 75% (according to the WHO UNICEF estimates). In 2011, 6 of the 46 member states achieved measles vaccination coverage of 90% or more, while 8 countries[3] had coverage of less than 60%.

As of September 2012, the second dose of measles vaccination (MCV2) is provided as part of the routine immunisation doses in 11 countries.[4] Burundi, Sao Tome and Principe, and Zambia are expected to introduce MCV2 by the end of 2012.

Between 2001 and August 31, 2012, a total of 568.4 million children were vaccinated through Supplemental Immunization Activities (SIAs) in 43 Member States.[5] An additional 24.2 million children will be reached by the end of 2012.

As of September 2012, 43 countries in the Region have established case-based surveillance for measles[6], supported with a network of 44 national measles laboratories, of which three also serve as regional reference laboratories.

Success stories

The majority of countries in the Region continue to have low incidence of measles. In 2012, as of 10th August 2012, the Regional incidence of confirmed measles cases is 15 cases per million population; 26 of the 43 countries have incidence levels of less than 1 confirmed measles case per million.

For instance, Ghana, the Gambia, Eritrea and Rwanda have maintained low incidence of confirmed measles over the past few years, supported by high routine immunization coverage rates, and the

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[3] Chad, Cote d'Ivoire, Equatorial Guinea, Ethiopia, Gabon, Guinea, Liberia, Mali
[4] Algeria, Botswana, Cap Vert, Eritrea, Gambia, Ghana, Lesotho, Mauritius, Seychelles, South Africa and Swaziland.
[5] All countries in the African Region except Algeria, Mauritius and Seychelles.
[6] These 42 countries include all Member States in the African Region except Comoros, Mauritius, Sao Tome & Principe and Seychelles.

conduct of timely, well organized and well-funded follow-up measles SIAs. This is illustrative of the strong national level leadership and commitment to measles elimination in these countries.

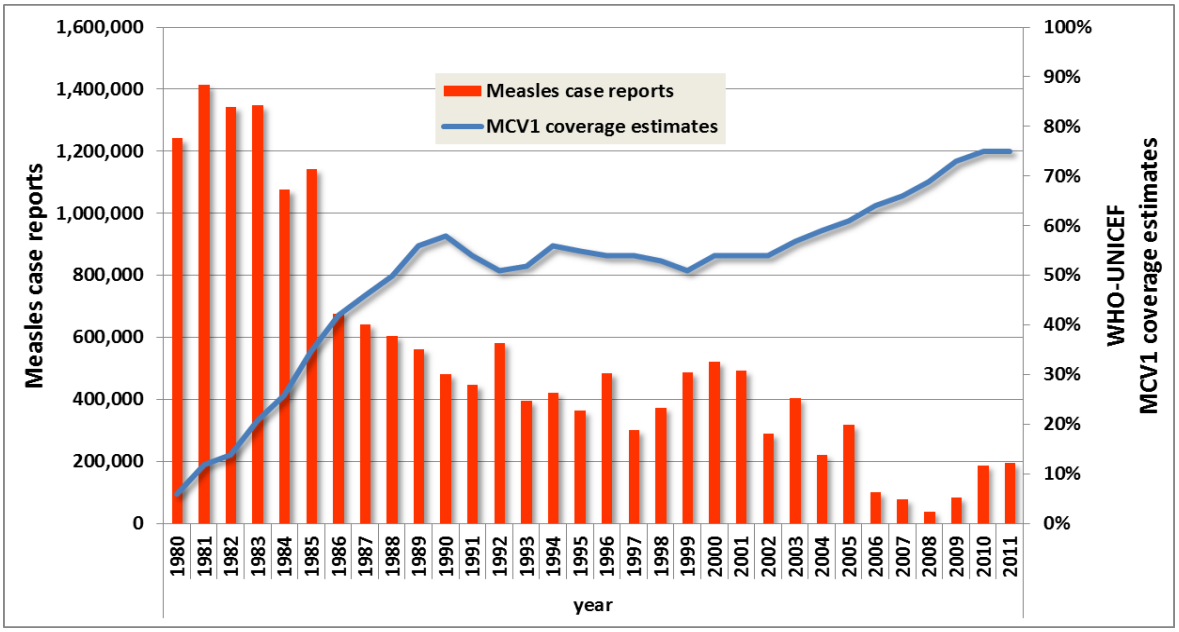


Figure 1. Routine first measles vaccination coverage (WHO-UNICEF estimates) and measles case reports. 1980 - 2011.

Challenges

In 2010, 28 countries experienced measles outbreaks, bringing the overall incidence level to 165 cases per million population at Regional level (as compared to incidence levels of 10 – 40 per million between 2007 – 2009). In 2011, Zambia and the Democratic Republic of the Congo experienced large outbreaks, and a number of districts in DR Congo continue to experience outbreaks as of September 2012.

In DR Congo, the gaps in national and subnational level routine immunisation 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) are the factors behind the large-scale and protracted measles outbreaks which have affected all provinces in the country. 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.

Summary

As of the end of 2011, seven countries (Botswana, Burkina Faso, Ghana, Malawi, Mauritius, Seychelles and Swaziland) are on track to meet the African Regional measles pre-elimination targets for 2012. On the other hand, 25 countries have missed some of the targets set by the pre-elimination goal, and are at risk of failing to reach the 2012 pre-elimination goal.

Strengthening country ownership and leadership of the measles elimination strategies, and ensuring the allocation of adequate resources for the implementation of measles elimination strategies will be of

paramount importance. Countries and partners need to invest in strengthening the immunisation system in order to attain and maintain measles elimination.

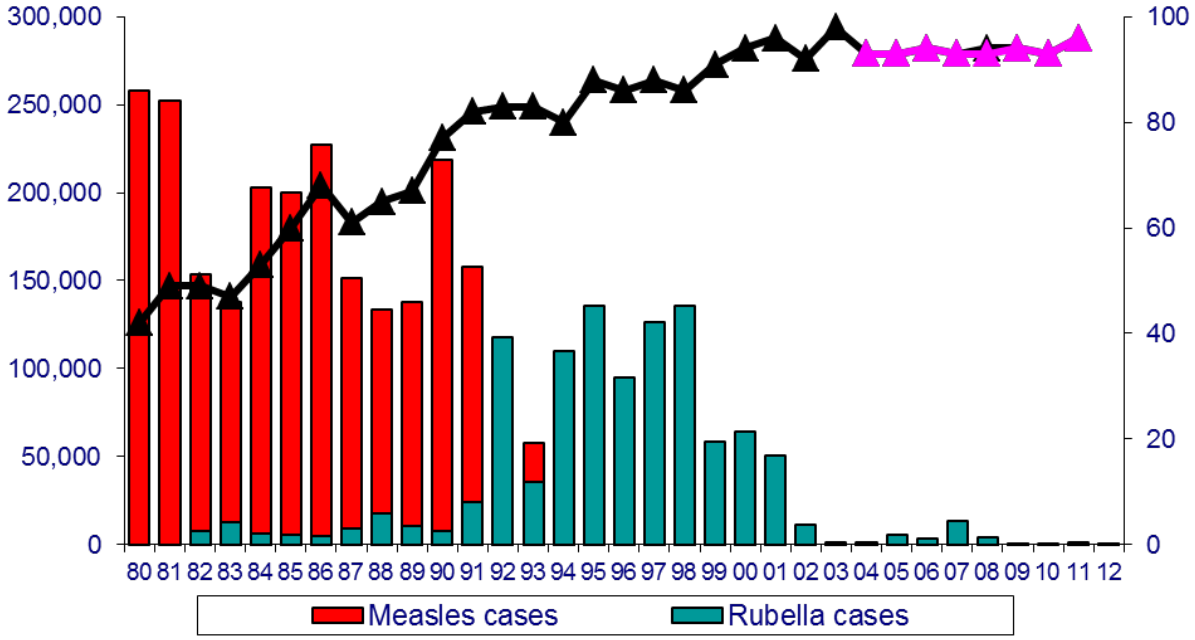
American Region

Regional measles and rubella elimination goals

In 1994, during the 24th Pan American Sanitary Conference, ministers of health adopted Resolution CSP24.R16, setting a **goal to eliminate measles** from the Region of the Americas by 2000. Approval of the resolution was based on the impressive and rapid reduction in measles demonstrated by countries that pioneered the use of immunization strategies for elimination. The Region of the Americas achieved the goal of measles elimination in November 2002.

The strengthening of measles surveillance also revealed that rubella and congenital rubella syndrome had emerged as significant public health problems in the Region. In 1999, the PAHO Technical Advisory Group on Vaccine-Preventable Diseases (TAG) recommended accelerated rubella control and congenital rubella syndrome (CRS) prevention with campaigns targeting a wide age range, including adults. In 2003 the 44th Directing Council adopted Resolution CD44.R1, calling on Member States to **eliminate rubella and congenital rubella syndrome** from their countries by 2010. In addition, the resolution called on the Director to "elaborate a regional plan of action and mobilize resources in support of a rubella/CRS elimination goal for 2010." The last endemic rubella and CRS cases in the Region were reported in 2009.

Figure: Measles vaccination coverage among children <1 year of age and reported measles and rubella cases, the Americas 1970-2012[7]



[7] Source: Country reports to FCH-IM/PAHO.

Progress in verifying elimination

In October 2007, the 27th Pan American Sanitary Conference approved Resolution CSP27.R2 urging Member States to establish National Commissions to document and verify measles, rubella, and CRS elimination in each country. It authorized the formation of an International Expert Committee (IEC) to document and verify the interruption of transmission of endemic measles and rubella viruses in the Region of the Americas. To ensure a standardized approach to documentation, PAHO developed a regional plan of action to guide countries and their National Commissions in compiling and analyzing evidence that endemic measles and rubella transmission has been interrupted.

In accord with Resolution CSP27.R2 of the Pan American Sanitary Conference, an International Expert Committee was formed and 23 National Commissions were established, including a Commission for the French Overseas Departments in the Americas. In addition, a Subregional Commission was established for the English-speaking and Dutch-speaking Caribbean countries and territories, including Suriname. As of September 2012, 20 commissions, including those for the French Departments and the English/Dutch-speaking Caribbean, have submitted their final elimination reports to PAHO for review and comment by the International Expert Committee. The remaining four countries (Colombia, Ecuador, Haiti, and Peru) will submit their reports by the end of November.

After careful analysis of these 20 reports submitted by the National Commissions and the Subregional Commission, it appears that the interruption of endemic measles and rubella virus transmission has been achieved. However, the Region of the Americas continues to be exposed to high risk of virus importations, given the continuing circulation of measles and rubella viruses in other regions of the world. Additionally, some of the countries have reported weaknesses and failures in their national surveillance systems and routine immunization programs, which make them particularly vulnerable to the risk of reintroduction of viruses that, can cause outbreaks. Moreover, some of the National Commissions concluded that the epidemiological surveillance is not sufficiently robust to ensure maintenance of the elimination of rubella and CRS. Nevertheless, the International Expert Committee states that documentation to verify the absence of the endemic diseases in the Region can be achieved if the weaknesses identified are corrected promptly. To that end, countries are urged to take prompt actions to correct challenges identified during the verification process to ensure that the achievements in eliminating endemic diseases will be maintained.

The 28th Pan-American Sanitary Conference (September 17-21, 2012) reviewed the progress made toward the documentation and verification of the elimination of measles, rubella, and congenital rubella syndrome in the Americas, and adopted the resolution (CSP28/R14) to secure regional achievements to eliminate the measles and rubella (i.e. the emergency plan of action to maintain the elimination of endemic measles, rubella and CRS in the Americas). This resolution urges Member States to strengthen active surveillance of these diseases and to maintain high population immunity through vaccination.

Enabling Factors

The countries in the Region have shown strong political commitment by adopting the resolutions to eliminate measles, rubella and CRS and adopting the resolution to document and verify the Regional elimination. In order to achieve the Regional elimination of the endemic diseases the countries have

been improving routine measles-rubella immunization, conducting periodic SIAs and promoting community acceptance of measles and rubella vaccines.

Strengthened capacity and utilization of measles/rubella laboratory testing in the region (there are 21 measles/rubella national laboratories in the network, which are supported by 2 regional referral laboratories, and the CDC global reference laboratory).

The Member Countries have included vaccination and surveillance activities into their national budgets, which increases sustainability of the vaccination programs.

Challenges

Recent Outbreaks

In 2011, there was an eightfold increase of measles cases over the previous annual average of 156 cases between 2003 and 2010. This increase coincided with several large outbreaks in Europe and Africa. Of the 45 countries and territories, 33 (73.3%) reported no measles cases, and 9 (20%) reported 14 confirmed measles cases. Three countries—Canada, Ecuador, and the United States (6.7%)—reported a total of 1,290 cases, 93% of the 1,379 confirmed cases in the Region (unconfirmed data for 2012, as of EW40/2012). The current outbreaks in the Region put measles elimination at risk. The largest outbreak, with duration of seven months (EW14/2011–EW40/2011), occurred in Canada and resulted from an importation of D4 measles virus from Europe. In Canada 803 cases of measles were reported in 2011, 61% of all reported cases in the Region in 2011. The second largest outbreak in Ecuador has caused 329 laboratory confirmed measles cases in 2011 and 2012. The last case has been reported from the week 28/2012. The most commonly identified genotypes in these three countries include D4, which is circulating on the European continent; B3, from Africa; and D8 and D9, from Southeast Asia and the Pacific, respectively.

The recent measles outbreaks (excluding the Canadian outbreak) have similar characteristics. The vast majority of cases have occurred in specific groups of unvaccinated persons (religious groups or other groups that reject vaccination) or in specific geographic areas, such as in indigenous communities, in large cities (especially on the peripheries), and in rural and border areas with limited access to health care. Almost all measles cases are import-associated.

Heterogeneous coverage

Low measles and rubella incidence can lead to a false sense of security. While documenting and verifying the elimination of the viruses in the Region, several PAHO Member States identified challenges in their immunization programs, such as weak surveillance and heterogeneous or low coverage that put at risk the elimination of measles and rubella. These pockets of susceptible populations can sustain future outbreaks.

Sustaining high quality surveillance

Maintaining measles/rubella/CRS surveillance under low incidence requires high specificity and sensitivity. Post-elimination phase requires adoption of high standards molecular biology techniques to facilitate identification of source of infections.

Summary assessment

Based on the final national elimination reports received up to date, the countries in the Region appear to have interrupted endemic transmission of measles and rubella virus. However, the Region of the Americas continues to be exposed to high risk of measles and rubella importations, given the continuing circulation of measles and rubella viruses in other regions of the world. Additionally, some of the countries have reported weaknesses and failures in their national surveillance systems and routine immunization programs, which make them particularly vulnerable to the risk of reintroduction of viruses that can cause outbreaks.

Countries should integrate the activities in the Emergency Plan of Action for maintaining measles, rubella, and CRS elimination in their annual plans of the national immunization programs. The main objective of the plan is to sustain achieved efforts by maintaining very high level of population immunity against measles and rubella and further enhance surveillance systems to detect sporadic imported cases before they spread and cause secondary cases.

The maintenance of the diseases elimination is expensive. Most of the outbreaks in the Region have been sparked by importations from outside the Americas. According to published research from the region and other countries and documented experiences from the region, containing small and medium size outbreaks due to importations costs local and state governments hundreds of thousands, up to millions, of dollars to contain. However, at this stage when the region is maintaining the measles, rubella and CRS elimination, available resources are not enough to keep the program on the track. Fundraising for the maintenance of Regional elimination is challenging.

As a result, strong advocacy combined with financial and technical support will be required by most of the countries in the Region to maintain the countries free of the endemic transmission of measles and rubella. Also advocacy with other WHO Regions and their development cooperation partners to step up their efforts to increase measles and rubella coverage, with a view to achieving elimination worldwide is essential.

Eastern Mediterranean Region

Introduction

In 1997, the 22 countries in the World Health Organization Eastern Mediterranean Region (EMR) had resolved to eliminate measles from their region by 2010 (EM/RC44/R.6). Despite the 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 countries of the EMR are suffering from complex emergency situation, internal conflict and financial constraints which constitute major challenges facing measles elimination. Endemicity of poliovirus in Afghanistan and Pakistan adds 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 with a nationwide measles case-based surveillance, high measles coverage for both MCV1 and MCV2): Bahrain, Jordan, Syria, Palestine

Countries **close to Elimination**: (incidence < 5 cases/1,000,000 with a nationwide measles case-based surveillance, high measles coverage for both MCV1 and MCV2): Egypt, Iran, Oman, Iraq, Tunisia, Lebanon

Countries with **high burden of disease**: Afghanistan, Djibouti, Kuwait, Libya, Morocco, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, South Sudan, United Arab Emirates and Yemen.

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 2011 nine countries (39%) have reported measles incidence of <1 case per million persons in the presence of a sensitive and well-functioning nationwide surveillance system: Bahrain, Egypt, Iran, Iraq, Jordan, Oman, Palestine, Syria, and Tunisia. In spite of this progress, there has been a resurgence of measles cases in several countries from late 2009 which has continued to 2012. The total confirmed measles cases reported in 2011 and January-June 2012 are 9,315 and 7,827 cases respectively, of these 87% and 90% are reported from Afghanistan, Pakistan, Sudan and Yemen. Sudan alone accounts for 50% of cases in 2011 and 62% in 2012, despite implementing 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.

Rubella

Currently, 15 of the 23 countries in EMR are using rubella vaccine in their EPI program with high coverage ≥90% coverage of RCV1 and 14 of them are using a 2 dose schedule. Thirteen countries have established a national target for rubella/CRS elimination. In addition, rubella case-based surveillance is integrated with measles surveillance in all countries in the Region. Ten countries now are implementing CRS surveillance as well. In addition, 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.

Progress Towards the Current Goal

Achieving high population immunity

Based WHO/UNICEF estimates, routine measles-containing vaccine (MCV1) coverage improved during the past decade from 72% in 2000 to 84% in 2010. However, estimates for 2011 indicate 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. In 2011, 12 countries out of those who reported to EMR have achieved 95% or more for MCV1. In addition, the coverage of routine immunization has impressively increased in priority countries. For example, MCV1 coverage estimate was 64% in South Sudan in 2011.

Despite the progress in the Region, countries including Afghanistan, Pakistan, Somalia, Sudan and Yemen have experienced several outbreaks in late 2010 through 2012. These outbreaks occurred due to delay in implementation of the follow-up SIAs, a deteriorating security situation, and/or inadequate funds.

As of 2012, nineteen member states are implementing a 2nd dose of measles vaccine through routine services. Eleven of these countries have reached the 95% coverage with 2 doses of routine measles vaccine at national level based on national reporting in 2011.

Follow-up measles campaigns are being conducted in countries that haven't reached the target 95% coverage with 2 doses of measles vaccine. To date in 2012, around 30 million children have been vaccinated through measles supplementary immunization activities (SIAs). These achievements are due to implementation of measles elimination strategies in most of the member states, thanks to sincere national efforts and support from partners.

Case-based and laboratory surveillance

All EMR countries have moved to measles case-base surveillance with laboratory confirmation, 21 (91%) of these countries are implementing nationwide, and two countries Somalia and S. 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 18,516 serum samples tested in 2011. Countries report to EMRO monthly 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, and this reflected by status of measles surveillance performance indicators in region.

Also much progress has been made towards collecting genotype information from measles cases, 20 (87%) 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 has increasingly being detected accounting 69% of the reported genotype in 2011, 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 reported vaccination coverage improved 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 a big expatriate population. 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

Summary

Most countries in the EMR are likely to achieve the measles elimination goal by 2015. ***However, regional measles elimination will largely depend on progress in countries with high burden of disease*:**
Afghanistan, Djibouti, Morocco, Pakistan, Somalia, Sudan, South Sudan and Yemen. Advocacy, financial and technical support will be required by most of the countries as well as smooth supply of vaccine.

European Region

Regional measles and rubella goals

The European Region of the World Health Organization (WHO) has adopted the goals to eliminate endemic measles and rubella, which will also lead to elimination of congenital rubella syndrome (CRS). In 2002, the WHO Regional Office for Europe developed and implemented a strategic plan for measles and congenital rubella syndrome in the WHO European Region, targeting the interruption of indigenous transmission of measles (measles elimination) and the prevention of congenital rubella syndrome (<1 case of CRS per 100.000 live births) by 2010. Rubella elimination by 2010 was adopted as a regional target at the WHO Regional Committee for Europe in 2005. As the elimination was not achieved by year 2010, the 60th WHO Regional Committee for Europe recommitted to the elimination goals and reset the target date for 2015.

Progress towards the current goals

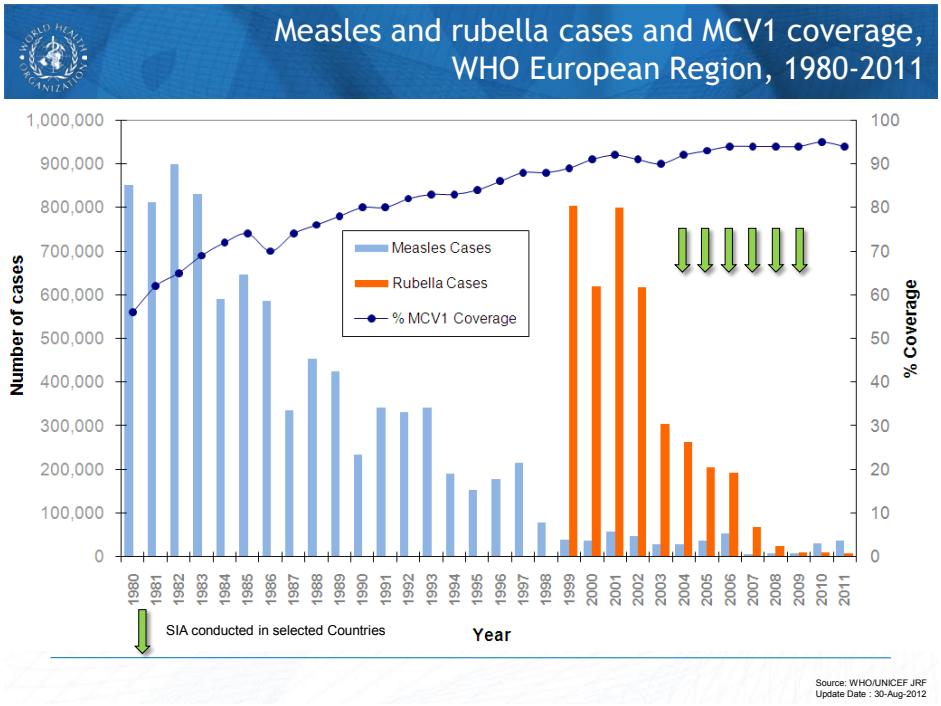
The strategic plan for elimination of measles and rubella and prevention of CRS 2012 – 2015 is under revision. The revised key strategies to achieve measles and rubella elimination in the European Region are to:

- Achieve and sustain very high coverage (≥ 95%), with 2 doses of measles and at least one dose of rubella vaccine, through high-quality routine immunization services;
- Provide measles and rubella vaccination opportunity, including supplementary immunization activities, to all high risk groups and populations susceptible to measles and/or rubella;
- Strengthen surveillance systems by rigorous case investigation and laboratory confirmation of suspected sporadic cases and outbreaks;
- Improve the availability and use of high-quality evidence-based information for health professionals and the public, on the benefits and risks associated with immunization against measles and rubella.

All 53 Member States have routine immunization programmes with scheduled two doses of measles and rubella containing vaccines. Vaccines in use are measles-mumps-rubella (MMR), measles-rubella (MR) and measles-mumps-rubella-varicella (MMRV). In 51 Member States, immunization is performed with MMR for both doses; one country is using MMR for the first dose and MR for the second dose; one country is using MR for both doses. MMRV is used in four countries.

Supplemental immunization activities are organized to target unimmunized and not completely immunized populations.. During the period 2000-2010 about 57 million people were immunized against measles and about 30 million people were immunized against rubella. The Regional Office led activities in many Member States, mostly in countries located in the Central Asian part of the region.

As a result of a strong and sustainable immunization programme in all Member States of the Region, incidences of both diseases decreased (see Figure below). The total number of measles cases in the Region decreased from 597 455 cases in 1983, to 6 936 in 2007. The number of reported rubella cases decreased from 804 567 in 1999, to 9 672 cases in 2011.



The transmission of measles increased after 2007, and 95 027 measles cases were reported in the period 2009-July 2012. The annual reported number of measles cases was 7 419 in 2009, 30 850 in 2010, and 37 893 in 2011. A similar situation is expected for 2012, as 18 856 cases were reported in the first seven months of 2012.

Most of the cases are reported from France, Bulgaria and Ukraine, countries challenged with large outbreaks (Table 1). Outbreaks were also reported from other countries, in part related to susceptible sub populations (minorities, migrants, religious and philosophical groups). In some countries (e.g., United Kingdom, Switzerland and France, measles cases are occurring among the general population.

Table 1. Countries in the WHO European Region with the highest number of reported measles cases, 2009 – 2012

Country	2009	2010	2011	2012	Total
Bulgaria	2249	22006	157	0	**24412**
France	1541	5019	15214	745	**22519**
Ukraine	24	42	1313	11086	**12465**
Romania	8	187	4417	2447	**7059**
Italy	173	861	5179	530	**6743**
Spain	43	285	3507	401	**4236**
United Kingdom	1176	397	1083	1093	**3749**
Germany	572	805	1600	139	**3116**
Russian Federation	101	152	783	1771	**2807**
Switzerland	999	81	644	58	**1782**
Total	**6886**	**29835**	**33897**	**18270**	**88888**
% of all in WHO	92.82	96.71	89.45	96.85	**93.54**
WHO Euroepan Region	**7419**	**30850**	**37893**	**18865**	**95027**

The majority of cases are among unimmunized population, in infants younger than one year, adolescents and young adults. The distribution by age differs by countries. Taking into consideration that MCV has been in use for more than 30 years, these cases could have been prevented.

During the period 2009 – July 2012, Member States reported 36 433 cases of rubella, increasing from 900 in 2009, to 6 757 in 2010 and 8 577 in 2011. However, 20 199 rubella cases were reported in the first seven months of 2012, due to ongoing outbreaks in Romania and Poland (Table 2).

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.

Table 2. Countries in the WHO European Region with the highest number of reported rubella cases, 2009 – 2012

MS	2009	2010	2011	2012	Total
Romania	0	354	3922	13708	17984
Poland	0	4197	4293	4382	12872
Bosnia and Herzegovina	225	1861	23	0	2109
Ukraine	0	0	0	942	942
Russian Federation	0	1	2	890	893
Kazakhstan	306	0	0	10	316
Georgia	67	60	64	52	243
Tajikistan	177	6	0	1	184
Turkey	87	64	0	0	151
Italy	2	41	84	0	127
WHO European Region	900	6757	8577	20199	36433

Different surveillance systems for congenital rubella syndrome, congenital rubella infection and/or rubella in pregnancy, exist in the Member States. The Regional office is receiving annual reports on the case count. The available information is not sufficient and adequate for a detailed analysis. Underreporting is likely, as rubella is still present (endemic or epidemic) in many Member States and only 474 CRS cases were reported in the European Region during 1990 – 2011.

Activities on poliomyelitis eradication in the Region served as a model to initiate similar processes for measles and rubella elimination. Good health system infrastructure and adequate human resources in most of the Member States allowed for major achievements in the measles and rubella elimination. However, some Member States faced insufficient support and political commitment affecting immunization programmes delivery at different points in time.

High routine immunization coverage and supplemental immunization activities, the introduction of rubella vaccine into routine immunization programmes of all MS by 2009 and the improved surveillance for measles and rubella, are critical for elimination activities.

In addition, special approaches were used to increase coverage, like specific strategies to reaching vulnerable and hard-to-reach populations, or creating school entry immunization requirements in some of Member States.

Successes and Challenges

The differences of population immunity between Member States in the European Region, is best presented by the epidemiology of measles and rubella in recent years. Some countries do not face significant increase of incidence after the importation of measles or rubella viruses. While in others, the outbreaks expose weak segments on the national immunization programmes and indicate a need for further activities to increase overall population immunity and strengthening of the surveillance.

Characteristics of well performing countries

Well performing countries (e.g. Finland, Norway, Slovakia and Slovenia) have a fully operational health system, with a consistently high routine immunization coverage of all vaccines, including measles and rubella vaccines introduced in the national programme in the 1970's-80's and early introduction of second dose measles vaccine.

Detailed case-based investigation with laboratory testing is performed for all suspected cases, allowing confirmation that the cases are either imported or import-related, and excluding endemic measles and rubella transmission. Further, due to high population immunity, importations result in outbreaks of limited size and few transmission generations. Most of the outbreaks are among subpopulations (e.g. migrants) with limited spread to the general population. Immunization and vaccines are well accepted by the population, and the national health system and public health authorities are capable of managing anti-vaccination sentiment.

Major challenges in countries with recent outbreaks

Member States affected with outbreaks (e.g. Bulgaria, France, Romania and Ukraine) reported cases in populations with either none or suboptimal immunization coverage. In some of these countries the size susceptible population is significant. All these Member States are facing the following challenges:

- Insufficient political commitment and/or funding for immunization programmes (due to lack of prioritization or in result of an economic crisis)
- Health systems reform, with changed availability and/or accessibility of immunization services. Abolishment of old immunization system with delayed reassignment of the responsibilities for immunization and surveillance.
- Vaccine hesitancy or refusal due to:
    - Lack of confidence in health authorities, public health services, immunization programmes;
    - Vaccine product safety concerns;

- Measles and rubella considered mild diseases with associated misconception “very low risk” of severe or long term complications, while vaccines are considered to impose a “significant health risk” due to adverse events following immunization;
- Anti-vaccination sentiment growth in absence of public health system response;
- Religious or philosophic beliefs;
- Health care workers’ opinions opposing immunisation;
- Lack of understanding and access to reliable information about vaccines and diseases in all segments of the population.

Summary

Comprehensive analysis of the current measles and rubella elimination status in the Region and by Member States is not possible, as much of the critical information is still not routinely collected by countries and submitted to the WHO European Region. Region-wide assessment is planned as of 2013, when countries and their National Verification Committees will be requested to provide annual measles and rubella reports.

According to currently available information, the regional target to eliminate measles and rubella by 2015 is severely challenged. Critical for achieving the target is strong commitment by Member States through: a) improving immunization coverage; b) strengthening/establishing case based surveillance; c) developing new policies to address identified needs of susceptible or unimmunized populations; and d) evidence-based advocacy for immunization targeting decision makers, health care workforce and general population.

South-East Asia Region

Regional Targets

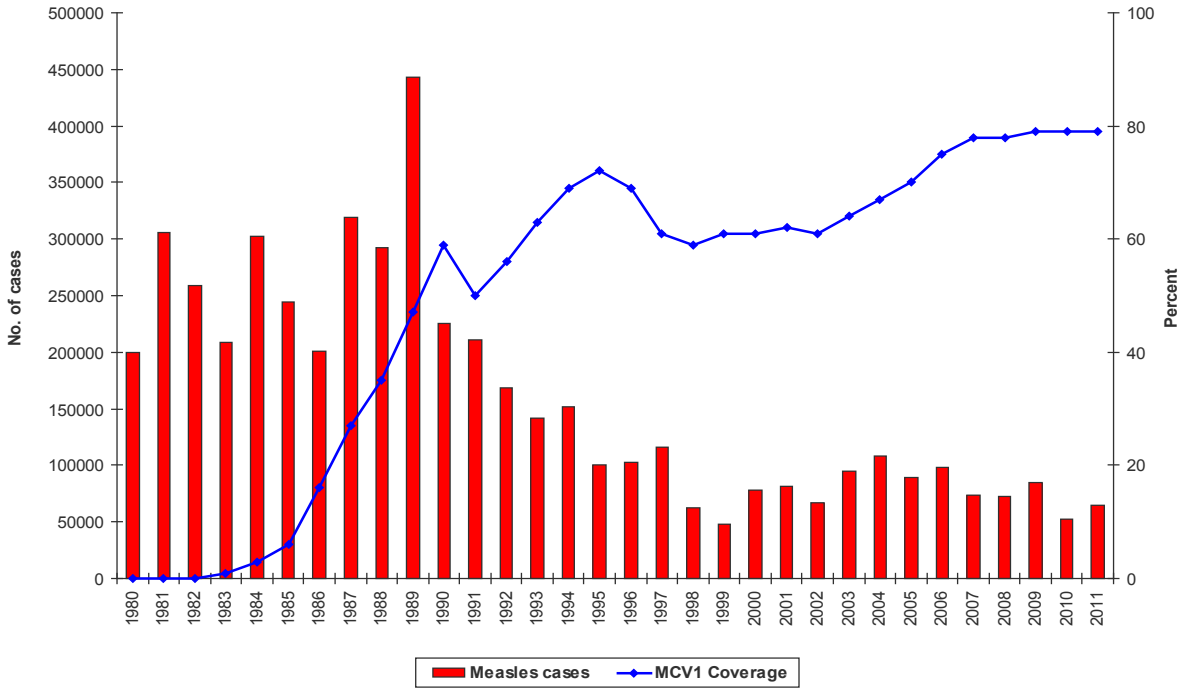
The South East Asian Region is the only WHO Region that has not established a target year for achieving measles elimination. In August 2009, at the regional consultation on measles, there was consensus among all Member States and partners that measles elimination was technically, biologically and programmatically feasible in SEAR by the year 2020 or shortly thereafter for some countries with large populations. In 2010, the High-Level Preparatory Meeting considered the proposal for establishing a measles elimination goal by 2020, but recommended that Member States should initially focus on achieving interim goals of measles mortality reduction by 2015 as approved by the 63rd WHA. The Regional Committee endorsed this recommendation. Hence, the 2015 Regional targets are: (i) at least 90% coverage with the first dose of measles vaccine nationally, and at least 80% coverage in every district or equivalent administrative unit; (ii) reduction in annual measles incidence to less than five cases per million and maintain that level; and (iii) reduction in measles mortality by 95% or more in comparison with 2000 estimates.

Progress

Improving and sustaining routine immunization coverage

Routine MCV1 coverage in the Region increased from 62% in 2000 to 79% in 2011, but it has stagnated at 79% for the last three years. According to WHO/UNICEF estimates (2012), in 2011, seven countries (Bangladesh, Bhutan, DPR Korea, Maldives, Myanmar, Sri Lanka and Thailand) reported national coverage at greater than 90%. Two countries, Indonesia and Nepal reported national coverage at almost 90% (89% and 88%, respectively) and 2 countries lagged behind; India reported national coverage of 74% and Timor-Leste of 62%. Significant progress for MCV1 coverage in India was made from 2000 to 2007 with an increase from 55% to 74%. However, coverage has stagnated over the last 5 years. Only, three countries, DPR Korea, Maldives and Sri Lanka have reported MCV1 coverage greater than 80% in all districts. District level data is not available from Thailand.

Figure: MCV1 coverage and reported measles cases, SE Asian Region, 1980-2011.



Providing MCV2 through SIAs and/or routine services

Between 2000 and 2011, all of the countries in the region except Thailand and Sri Lanka conducted national measles catch-up campaigns. As a whole, the Region achieved 95% coverage during measles SIAs reaching over 290 million children against a target of 305 million children.

Bangladesh, Indonesia, Myanmar, Nepal and Timor-Leste have conducted follow-up campaigns to target the accumulation of children susceptible to measles. In addition to conducting catch-up campaigns, Bhutan, DPR Korea, Maldives, Thailand and Sri Lanka provide a second dose of measles vaccine through routine services.

All Member States are providing MCV1 as measles, MR or MMR vaccine to the children between the age of 9 to 12 months of age. Bangladesh, Nepal and Timor-Leste have provided the second dose of measles vaccine through SIAs. Bhutan has provided measles second dose with measles-rubella vaccine at the age of 24 months. India has provided MCV2 at the age of 16-24 months through the routine immunization programme in 21 districts. India initiated measles SIAs in 14 states with MCV1 coverage <80% with a policy to incorporate MCV2 in the routine immunization programme after six months of completing the campaigns. Indonesia, DPR Korea, Maldives, Myanmar, Sri Lanka and Thailand have provided MCV2 through routine immunization.

Lesson learned from polio eradication show that high immunization coverage is crucial to preventing measles and rubella. Countries in the region have intensified their efforts to increase and sustain high immunization coverage at the national and district levels.

Measles incidence and rubella situation

In the South East Asia Region the number of measles cases declined from 106,419 in 2000 to 65,161 in 2011. The range of reported cases varied from 108,089 in 2004 to 69,301 in 2007 and 52,529 in 2010. The annualized measles incidence of the region was 43.5/million for the year 2007 and 36.01/million in 2011. No case of measles was reported from DPR Korea and Maldives during 2010 and 2011. Sri Lanka had an incidence of 2.91cases per million populations in 2011. Between 2000 and 2010, the region had achieved a 78% reduction in measles mortality (44% if India is included).

Improving measles surveillance

After completion of measles catch-up campaigns, Bangladesh, Bhutan, DPR Korea, Maldives, Myanmar, Nepal and Sri Lanka have started case-based measles surveillance. Indonesia is doing a phased implementation. India and Thailand continued aggregate reporting. All the countries have WHO accredited measles laboratory except Timor-Leste. Samples from Timor-Leste are sent to Indonesia for confirmation.

The rate of laboratory testing has improved over the past few years from 16% in 2009 to 34% in 2011 (see Table-8). Bhutan and DPR Korea have tested 100% of suspected measles cases. Bangladesh and Myanmar have tested >90% of the suspected measles cases. Thailand and Indonesia have tested only small fraction of suspected measles cases.

Challenges

There are five major challenges the region is facing:

- Transitioning from measles mortality reduction to measles elimination and rubella control.
- Achieving and sustaining homogeneous high coverage through routine services and /or SIAs in the two largest countries, India and Indonesia
- Funding: Political commitment and funding both by governments and partners is critical for increasing population immunity.
- Vaccine availability: Possibility of vaccine shortage due to lack of supply plans.
- Case-based surveillance particularly in large countries with autonomous or federalised structures.

Enabling factors

- A regional consultation on setting a target year for measles elimination in SEAR is scheduled for February 2013 and establishing a regional target date is on the Regional Committee agenda in September 2013.
- 2012 is the year of Intensification of Routine Immunization (IRI). Member countries have put efforts to increase the routine immunization coverage targeting high-risk groups and hard to reach areas. This effort is expected to increase measles immunization coverage in member states contributing to achieving the interim goals.
- Ongoing and planned SIAs will further increase population immunity:
    - The measles catch-up campaign in India is targeting 134 million children (9 months to 10 years) in 14 states of 35 States with MCV1 <80%. As of September 2012, the first two phases of the catch-up campaign were completed reaching 53 million children. The 3rd and last phase is scheduled for completion by April 2013. The remaining to 21 states with MCV1 coverage ≥80% are providing the second dose of measles vaccine through routine EPI services.
    - Indonesia completed the third phase measles follow-up SIA in 2011.
    - Myanmar completed nation-wide measles campaign in March 2012.
    - Nepal is conducting the second and third phase MR campaign in 2012-2013.
    - Bangladesh is planning to conduct MR campaign in late 2013.
- Large countries like India and Indonesia are largely self-financing. However, some other countries in the region need further government commitment and funding support from partners in order to achieve interim targets and move towards measles elimination, .
- India is the largest producer of M and MR vaccine. Indonesia produces its own M vaccine and is developing MR production capacity. In addition, at the EPI Managers meeting in Bangkok during 9-12 October 2012, vaccine needs for countries, procurement planning and forecasting was discussed. The EPI managers of all member states agreed to make this a high priority.
- Member states in the region are strengthening measles surveillance. Rubella surveillance is also being integrated with measles control programme. A sensitive measles surveillance in place will help programme monitoring.

Conclusion

Five countries in SEAR (Bhutan, DPR Korea, Maldives, Thailand and Sri Lanka) have surpassed > 90% coverage with measles vaccine and reduced measles mortality by > 90% compared to 2000 estimates. Five countries (Bangladesh, Indonesia, Myanmar, Nepal, and Timor-Leste) have successfully implemented strategies for measles mortality reduction and have achieved or are close to achieving the 90% measles mortality reduction goal. India has already accelerated measles mortality reduction activities by conducting nation-wide measles catch-up campaigns targeting 135 million 9 months to 10 years children of 14 states having MCV1 coverage <80%. By mid-2013, all 35 States in India will be providing a second dose of measles containing vaccine through a combination of routine services and SIAs.

Therefore, the feasibility of achieving measles elimination by all member countries by 2020 is possible. For this, there is a need of country commitment, ownership and support from partners.

Western Pacific Region

In 2003, the Regional Committee for the Western Pacific Region (RC) adopted resolution WPR/RC54.R3, establishing the regional goal of measles elimination. It was followed in 2005 by adoption of resolution WPR/RC56.R8, establishing 2012 as the target for measles elimination. In 2010, the RC adopted resolution WPR/RC61.R7, reaffirming the 2012 measles eliminating goal. Further in September 2012, the RC endorsed a new resolution WPR/RC63.R5, calling for countries and areas to intensify their efforts to interrupt residual transmission as rapidly as possible and sustain the achievements in eliminating measles.

These RC resolutions emphasize accelerating rubella control and CRS prevention by combining them with measles elimination activities. In 2009, the Technical Advisory Group on Immunization and Vaccine Preventable Diseases in the Western Pacific Region recommended that countries and areas should plan to decrease rubella incidence to < 10 cases per million population and congenital rubella syndrome (CRS) to < 10 cases per million live births, by 2015.

Recent progress

In August 2012, based on in-depth review of the regional progress towards measles elimination, the Technical Advisory Group concluded that:

'All countries and areas in the Region have made tremendous efforts to achieve and sustain measles elimination. As a result, the Region is making rapid and remarkable progress and now is on the verge of eliminating measles. Thirty-two countries and areas may have already interrupted endemic measles transmission. The number of measles cases declined by 86% from 145,935 in 2008 down to 21,054 in 2011, and the annual measles incidence reduced from 81.6 per million in 2008 to 11.6 per million population in 2011. In 2012, the number of measles cases has continued to decrease in the Region, with a reduction of 69% from 5,150 measles cases in January-June 2012 compared to 16 431 cases in the same period in 2011. And the number of measles cases is now at historic low in most countries in the Region.'

Rubella incidence varies among countries in the Region, with rubella incidence higher than 10 rubella cases per million population in seven countries and areas. Current reported rubella incidence in WPR countries is impacted by history of rubella vaccination as well as stage of rubella surveillance in individual countries. CRS surveillance presents a challenge because of lack of diagnostic capacity and extensive underreporting in most developing countries. In terms of vaccination, as of July 2012, 31 countries and areas are using MR or MMR in their national routine immunization programmes; and by 2015 rubella containing vaccine will be universally used in the entire region.

Successful practice

Countries and areas have been implementing the key measles elimination strategies recommended by WHO and have tailored them to the country situation.

Cambodia has been innovatively implementing a high-risk community strategy and has taken systematic steps to make it sustainable. The country conducted a focused EPI review in October 2010 to identify

where and why children missed their vaccinations and decided to explore an effective strategy to improve immunization services provided to the underserved populations. High-risk communities were identified and refined during the measles SIAs in 2011 by checking immunization records village by village. These communities were prioritized for actions, including micro-planning, expansion of outreach services, monitoring and supervision.

The last confirmed measles case occurred in November 2011. Success in interrupting endemic transmission in Cambodia has demonstrated that measles elimination is achievable even in the most challenging areas once an effective strategy can be identified and well implemented.

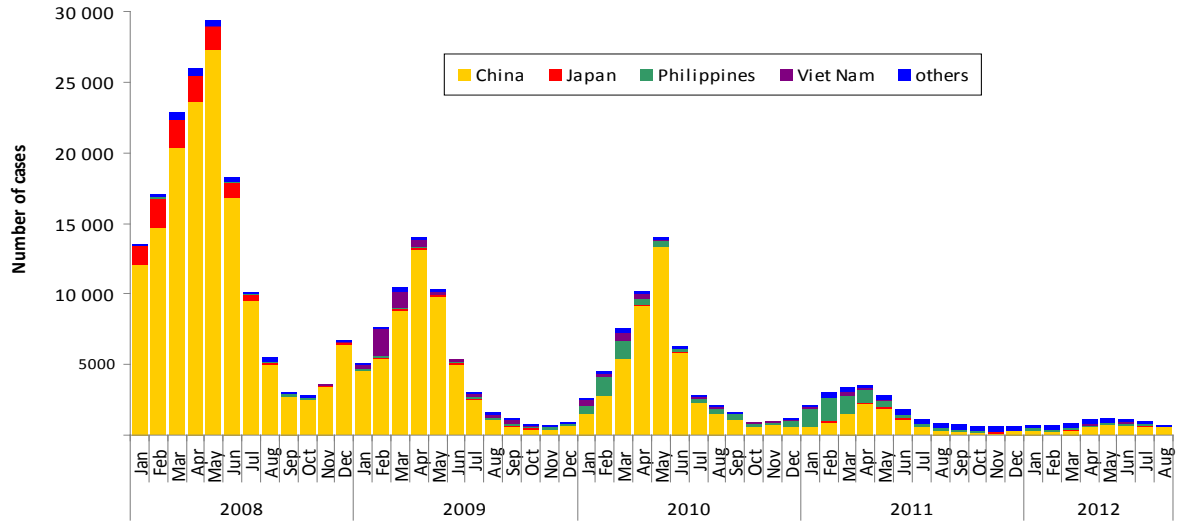


Figure 1 Measles cases by month of onset in Western Pacific Region, 2008–2012* (January-August) (Source: National measles and rubella monthly reports)

Critical Lesson

Some critical challenges remain in the region to interrupt endemic transmission eventually in all countries and areas, requiring greater political commitment and resources and intensified efforts.

In early 2011, measles emerged in Malaysia and mainly affected children under 7 years old. Measles transmission has been prolonged and continues till now, resulting in an incidence of 54 per million population in 2011 and 89 per million population (annualized rate) in 2012 as of 31 September.

Reported national MCV1 coverage is high (95%) in Malaysia while coverage is not universally high within the country, with coverage < 90% in about 36% districts in 2011. Susceptible children built-up rapidly among the pre-school children particularly given MCV2 administered at 7 years old (school entry); while no preventive action was taken to tackle this risk. WHO recommended a national SIA in response to the

recent and widespread measles outbreaks. Subnational SIA targeting high risk areas only has been eventually chosen due to various operational challenges in conducting a nationwide SIA.

The prolonged measles transmission in Malaysia has indicated that, unlike polio, measles is now not only affecting the least developed countries, but also the high-income countries in the region. The region's experiences has also revealed that, not only the constraints in resources and technical capacity (e.g. in most developing countries), but also the public perceptions on measles becoming a mild disease and resistance to vaccination (e.g. in some developed countries), can hamper the measles elimination programme.

Future directions

As highlighted earlier, the Western Pacific Region is on verge of eliminating measles, and all countries and areas remain strongly committed. Countries still with endemic transmission are planning to intensify their strategies and efforts to close the remaining programmatic gaps as soon as possible.

Sustaining the achievement of measles elimination is also challenging while it provides a great opportunity for countries to reach every community with adequate vaccination services and promote for equity in immunization. It is imperative for every country and area to implement proper strategies and activities to close immunity and surveillance gaps using practical means, and rapidly identify risks (areas and population groups), adequately prevent, prepare for and respond to outbreaks caused by either endemic or imported measles virus. Cambodia's high-risk community strategy offers an innovative strategic approach for the region to move on. The Region and countries will continue prioritizing measles elimination and use measles elimination as a means to advocate for synergy with rubella control activities and equity of immunization and other health care services.

V. Synopsis of the major challenges

African Region:

- Large outbreaks in countries with weak underlying immunization systems
- In countries with a stronger programme, a shift in the age distribution of measles cases to older ages requiring SIAs to target a wider age range
- Lack of human and financial resources

American Region:

- Has achieved and maintained measles elimination (since 2002) and rubella/CRS elimination (since 2009)
- Importations are an ongoing threat that result in costly outbreak response activities

Eastern Mediterranean Region:

- Rapid political change in a number of countries is resulting in declines in immunization coverage
- Increased risk of outbreaks in Afghanistan, Pakistan, Somalia, Sudan and Yemen
- Measles epidemiological and molecular surveillance is not up to the standard that supports validating measles elimination

European Region:

- Insufficient political commitment (e.g., in Western Europe) and health system reform (e.g., in Eastern Europe)
- Politicization of immunization and failure of vaccine procurement in Ukraine
- Vaccine hesitancy is a dominant issue in many countries

South East Asian Region:

- Stagnant routine immunization coverage over the past 5 years and the only WHO Region that has not established a target year for achieving measles elimination
- India and Indonesia are particularly challenging because of their large and diverse populations
- Recent eradication of polio from the Region, a renewed focus on the intensifying routine immunization and India embarking on accelerated measles control is providing new momentum

Western Pacific Region:

- All countries in the Region have made tremendous efforts to achieve and sustain measles elimination and the Region is now is on the verge of eliminating measles
- Recent measles outbreaks have involved a high proportion of adult cases and the question remains as to whether these age cohorts will need to be vaccinated to achieve and sustain elimination.
- CRS surveillance presents a challenge because of lack of diagnostic capacity and extensive underreporting in most developing countries.

VI. Opportunities for accelerating Measles and Rubella Elimination

New Policies

The revised position paper on measles vaccine (July 2009) made receipt of 2 doses of measles vaccine the standard for all national immunization programmes. It clarified the criteria for introduction and optimal age of administration of the routine second dose as well as the need to continue SIAs until coverage with both routine doses reaches 90-95% . The revised rubella vaccine position paper (August 2011) encourages countries not yet using rubella vaccine in their national immunization programme to use their delivery system for measles vaccine to introduce rubella vaccine through use of combined measles-rubella (MR) or measles-mumps-rubella vaccines (MMR). These policy breakthroughs were the basis for developing a new strategic plan that fully integrates rubella and CRS prevention with measles control and elimination activities.

New Strategic Plan

In April 2012 realizing the potential of combining rubella with measles, the core partners of the Measles and Rubella Initiative (formerly the Measles Initiative) launched the **Global Measles and Rubella Strategic Plan, 2012-2020**. The development of the plan took over 15 months with extensive consultation with stakeholders and reflects renewed commitment by the core partners. The *Foreword* of the plan is signed by the Heads of Agency of the American Red Cross, US Centers for Disease Control and Prevention, the United Nations Foundation, UNICEF and WHO with the following statement:

> *"With strong partnerships, resources and political will, we can, and must work together to achieve and maintain the elimination of measles, rubella and CRS globally."*

The Plan includes a five-pronged strategy to reach the measles, rubella and CRS national, regional and global targets and goals:

- Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines.
- Monitor disease using effective surveillance, and evaluate programmatic efforts to ensure progress.
- Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases.
- Communicate and engage to build public confidence and demand for immunization.
- Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

The Plan builds on 30 years of experience in implementing immunization programmes and reflects the lessons learned to date by the MR Initiative and other globally coordinated disease-management efforts, including the Global Polio Eradication Initiative. It particularly seeks to extend the experience gained by the WHO Region of the Americas in eliminating measles, rubella and CRS, to all other regions. In addition to these strategies, the Plan outlines the guiding principles of country ownership, strengthening immunization systems, equity and linkages with other programmes that provide the context in which all measles and rubella control activities should be conducted.

Implementing the Strategies

Achieving and maintaining high population immunity

Increasing coverage with the 1st dose is the focus of renewed efforts by countries, regions and partners to strengthen immunization systems and sustainably increase immunization coverage. To address stagnant routine immunization coverage, the SE Asian Region is implementing an initiative in all Member States to make 2012 the year of intensification of routine immunization. In addition in June 2012, the GAVI Board expanded its performance-based awards to include incentives for improving coverage with MCV1 as a means to reduce the DPT3-MCV1 dropout rate and emphasize the value of a fully vaccinated infant by their 1st birthday. The details of this support are still being worked out and funds should be available to GAVI-eligible countries in 2013.

An increasing number of countries are introducing a routine MCV2 dose in their national childhood immunization schedule. In 2011, Bolivia, Botswana, Djibouti, India, Suriname introduced MCV2. Bangladesh, Burundi, Cambodia, Eritrea, Gambia, Ghana, Sao Tome, are introducing routine MCV2 this year and Burkina Faso and Kenya have applied to GAVI to support their introductions in 2013. By end 2012, 149 of 194 WHO Member States will have a routine 2 dose measles schedule in their national childhood immunization schedule. However, coverage with this dose in the 2nd year of life remains low in many countries that have recently introduced MCV2 and increased efforts are needed to realize the full potential of this well child visit in the 2nd year of life.

The most significant boost to population immunity, both against rubella as well as measles, will come from the new GAVI support for introduction of rubella vaccine. Fifty-one of the remaining 60 countries not yet using rubella vaccine in their routine programme are GAVI-eligible. The recommended approach to introduce rubella vaccine through a wide-age range campaign for all children ages 9 months to 14 years 11 months using combined MR vaccine offers the opportunity to rapidly raise population immunity in these age cohorts that typically contribute most to virus transmission. To ensure sufficient MR vaccine supply for the campaigns and allow countries adequate time to prepare for the switch to MR vaccine as part of the routine program, the roll-out is planned over a six-year period (2013-2018). Full implementation of the roll-out will result in nearly 1 billion children receiving MR vaccine in the campaigns and an additional 200 million infants receiving MR vaccine as a routine first dose. High quality campaigns are critical, and best practices campaign guidelines are being updated that include conducting a post-campaign coverage or seroprevalence survey.

Laboratory supported case-based surveillance

Case-based measles surveillance has been established in 183 countries (94%) with 11 countries[8] still to implement it nationwide. The WHO Global Measles and Rubella Laboratory Network includes 690 laboratories organized in a tiered structure that provides diagnostic and virus characterization capacity. The critical role of the laboratory network is under recognized and increasing efforts are being made to showcase its value for money. The laboratory network needs to be scaled up in some large countries

[8] Algeria, Comoros, Guinea-Bissau, Mauritius, Seychelles, Sao Tome and Principe, Somalia, South Sudan, San Marino, India, Thailand

(e.g., India and Indonesia) and expanded to include the remaining countries. There is a shortfall of $1 million in 2013 for enhancing rubella molecular surveillance which is required for monitoring progress towards elimination.

Performance indicators repeatedly show that the field investigation component of measles and rubella surveillance is lagging behind and some countries with elimination goals (e.g., in the European Region) are not reporting measles and rubella case-based data to the WHO Regional Office . Guidelines are being developed for establishing sentinel CRS surveillance and the capacity for technical assistance is being expanded through training both regional and country focal points as well as a pool of consultants in a standard approach for conducting assessments of national surveillance systems. Combining measles/rubella surveillance reviews with AFP surveillance and new vaccine surveillance assessments will allow more frequent focus on this critical component of the programme. There is a need for updated guidance and standard procedures for conducting integrated VPD surveillance reviews. In addition, there is the opportunity and expectation that measles/rubella surveillance will take over some of the costs to maintain the AFP surveillance network (e.g., salaries for surveillance officers who currently do surveillance for measles and other VPDs as well as polio).

Documenting and verifying elimination

Over the past 2 years, PAHO has implemented a process to verify elimination of measles and rubella at country and regional level. The recommendation from the Independent Expert Committee on verification led to adoption of an emergency plan to sustain elimination to be implemented throughout the Region over the next 3 years. Three other Regions with elimination goals (Europe, Eastern Mediterranean, and Western Pacific) are in the process of finalizing their guidelines and establishing both national and regional verification commissions. Because these Regions have not yet achieved elimination, their commissions have the function to monitor and report on progress towards elimination and highlight the need to improve the quality of immunization coverage and surveillance information. At the September meeting of the SAGE working group on measles and rubella, a global framework for monitoring and verification of measles and rubella elimination was reviewed and is near to completion.

Risk assessment, outbreak preparedness and response

Building on the experience from polio eradication, the Regions have developed, or are in the process of developing, a risk assessment tool to identify underperforming districts at risk of measles outbreaks. These tools need to be promoted at EPI Manager Meetings and their usefulness evaluated as a means of outbreak prevention.

Outbreak preparedness and response has been added as a key strategy in the new Plan. Large measles outbreaks affecting predominantly Africa, Europe, and Asia over the past 2 years highlighted long delays in mounting a response, the lack of country preparedness and response plans, and that the 2009 WHO guidelines for outbreak response were difficult to operationalize. In June 2012,the GAVI Board approved $55 million over 6 years (2012-2017) to enable a rapid response to measles outbreaks associated with high mortality. These funds will be administered by the MR Initiative and arrangements for making these funds available to countries are close to being finalized. A workshop is being planned by UNICEF and CDC to develop clear operational guidelines for measles outbreak response. This aspect of the programme

will need to be evaluated and adjusted as more experience is gained in both responding to outbreaks and addressing the underlying causes.

Evidence-based communication strategies

Vaccinating over 95% of the target population against measles and rubella requires well-conceived, professionally implemented communication strategies linked directly to programme goals. A new emphasis is being given to effective communication and public engagement with parents, health professionals, community leaders and the media, to gain their trust, and overcome fears and rumors associated with vaccination. Vaccine hesitancy is an emerging challenge in all Regions and in the European Region it is posing a major challenge to achieving measles and rubella elimination goals. Initiatives in the Region to get ahead of this problem are providing reliable information for parents and providers as well as expanding country capacity to respond to reports of adverse events following immunization. The MR Initiative (www.measlesrubellainitiative.org) has recently benefited from a communications specialist who has developed an e- newsletter, social media sites, and developed its first comprehensive communications plan (StopMeaslesRubella.org; Twitter@MeaslesRubella). There are additional opportunities for immunization programmes to build on the communications experience and expertise established by the polio eradication programme (e.g., in India).

Innovation and strategic oversight

The Global LabNet has maintained an active research agenda developing alternative approaches to specimen collection (e.g., oral fluid and dried blood spots) and more recently a point of care diagnostic test for measles and rubella. However, no ear-marked funding has been made available from the measles and rubella programme budget to fund research and development and foster innovation in the field.

The SAGE working group on measles and rubella was formed to provide strategic oversight to the programme and its' terms of reference include *"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 has formed 3 sub-groups to look at immunization strategies, monitoring/surveillance, and the research agenda.

The **immunization strategies subgroup** is tackling questions on determining the upper age range for M and MR campaigns, how to define the age groups and geographic extent of outbreak response immunization, and developing recommendations for revaccination of children on anti-retroviral therapy.

The **monitoring and surveillance subgroup** with input from the Regions is revising the definitions and framework for monitoring progress towards and achievement of measles and rubella elimination (see document in the Yellow Book entitled "Framework for verifying elimination of measles and rubella").

The **research subgroup** has taken a long list of ideas for applied and operational research and is conducting a prioritization exercise with the aim of identifying a short list of the highest priority areas for immediate investment. Additional products from each of these subgroups as well as results from an economic analysis of the costs and benefits of measles and rubella eradication will be presented to SAGE in 2013.

Applying the Guiding Principles

Country ownership

Country ownership and political commitment at all levels are required for successful control and elimination of measles and rubella. Accelerated measles and rubella control activities are based on a country-driven, bottom-up approach with plans of action submitted through WHO and UNICEF Regional offices to the MR Initiative and GAVI for funding support. Since August 2012, advocacy visits have been conducted to Rwanda, Niger, Cape Verde, and Nigeria aimed at ensuring increased commitment of national-level resources for planned measles or measles/rubella SIAs. The MR Initiative is currently investigating whether it should increase their support for operational costs from $0.32 per child to match the recent GAVI Board decision to provide $0.65 per child. Close coordination between GAVI and the MR Initiative will be needed to avoid duplication of efforts and efficient use of partner resources.

Strengthening routine immunization systems

Measles and rubella elimination activities provide a unique opportunity to strengthen routine immunization systems. Because measles is one of the most transmissible human pathogens, manifests as outbreaks of febrile rash illness, and requires immunization coverage >95% to stop transmission, it can be used to identify underserved communities and highlight gaps in the immunization programme. A recent example of this comes from Cambodia, where during their measles follow-up campaign in 2011, high risk communities were identified by thorough checking of children's immunization cards. This list of missed children was used to plan additional outreach sessions for the high risk communities, use of mobile phones for communication between village volunteers and the health service, and using the newly introduced measles 2nd dose to assess the child's immunization status at 18 months (as well as the mother's TT status) and catch-up missing doses. In 2013, if funds permit, the MR Initiative will provide additional resources for countries to plan and implement specific strategies to be conducted during and after the campaign that will strengthen routine service delivery. A practical example of this is the opportunity SIAs provide for re-training of all vaccinators in safe injection practices. During the measles SIAs in India, health workers were shown to have significantly better knowledge of standard immunization practices after the measles SIA than before.

Equity

Measles and rubella SIAs promote equity by reaching children missed by routine services and continue to be used to deliver additional child health interventions such as vitamin A, deworming medications, OPV and/or insecticide treated nets for malaria prevention. In 2011, of 28 nation-wide SIAs, 21 provided vaccinations against polio (77 million doses) or rubella (23 million doses) or other interventions such as vitamin A (24 million doses), deworming medication (21 million treatments), or long-lasting insecticide-treated nets (LLINs, 8,725 given out).

Linkages with other programmes

Measles and rubella control and elimination activities provide additional opportunities for synergy with other child health programmes. Closer linkages with polio eradication has benefits both for measles and rubella elimination (polio field staff plan and supervise measles/rubella SIAs and do measles and rubella outbreak investigations) and for polio eradication (delivery of additional doses of OPV during measles

SIAs, maintaining AFP surveillance in countries and regions where polio has been eradicated). However, the opportunity for other elimination programmes such as measles and rubella to take over key elements of the polio infrastructure and human resources is at risk of being lost because of lack of transition planning and insufficient funds for measles/rubella surveillance and programme monitoring. As the end-game strategy for polio eradication evolves, new opportunities for linkages between polio and measles may emerge — these may be related to the routine delivery of an inactivated polio vaccine (IPV) dose at nine months, and needle-free injection technologies (patch/jet injectors), among others.

The routine MCV2 contact establishes a "well child visit" in the second year of life that combines vaccination with deworming, growth monitoring and semi-annual vitamin A supplementation. Through participation of the Lions Club in the MR Initiative, the synergy between two proven interventions to reduce blindness, measles vaccination and vitamin A supplementation, will be further expanded, including the mobilization of national Lions Club volunteers.

With respect to the Global Measles and Rubella Laboratory Network, the equipment, training and quality assurance that support the confirmation of measles, rubella, and CRS through an enzyme-linked immunosorbent assay (ELISA) provide an effective platform for confirmation of other vaccine-preventable diseases, such as yellow fever and Japanese encephalitis.

New Partners and Resources

Since the last discussion of measles at SAGE new partners are providing additional financial and human resources in the fight against measles and rubella. GAVI has pledged over $700 million dollars of new support by opening windows to support MR vaccine introduction ($550 million), measles follow-up SIAs in 6 large and challenging countries ($107 million), emergency measles outbreaks response ($55 million) and the yet to be implemented performance based support for MCV1. Lions Club International through a challenge grant from the BMGF have brought both money and Lions volunteers to support measles SIAs in Ethiopia, Nepal, Uganda, and Kenya. Another exciting development is the recent announcement by the International Pediatric Association of their initiative to eradicate measles and rubella and join forces with the MR Initiative.

Developing a measles and rubella eradication investment case

It has been estimated that measles eradication would cost between 6-8 billion USD. Similar costing has not been done for rubella eradication or the incremental costs and benefits of combining rubella eradication with measles eradication. WHO has a contract with Kid Risk Inc.to conduct a comprehensive eradication investment case that compares different options for coordination global control and/or eradication of measles and rubella either together or separately. Results from this work are expected in the first quarter of 2013. This information together with demonstration of further progress towards global and regional targets will be needed before SAGE can advise on establishing a target date for achieving global eradication of measles and/or rubella.

VII. Questions to SAGE

SAGE is being asked to make a realistic assessment of progress towards global and regional targets, identify key challenges, lessons learnt, and new opportunities. The Expanded Programme on Immunization is seeking SAGE guidance and recommendations on the following questions:

- Is the programme on track to achieve global and regional targets?
- Are the new strategies, programme plans, and resources well enough defined, effective and sufficient?
- Have the challenges and areas of uncertainty requiring further investigation been adequately defined?
- What additional strategies, tactics, and innovations are needed?
- Does the workplan and anticipated products from the MR working group adequately address the terms of reference?

VIII. Draft Recommendations

SAGE commends the countries and partners for the tremendous progress made in reducing measles mortality and incidence, contributing significantly to MDG 4, and to the progress made in all regions which would not have been possible without the commitment of the countries and the support of the many partners. In addition, there has been a steady increase in the number of countries using rubella vaccine in their routine childhood immunization programme. However, despite the tremendous progress, a careful assessment of the comprehensive reports presented indicates that based on current trends and programme performance, the 2015 global targets as well as regional elimination targets in the European (2015), E. Mediterranean (2015) and African (2020) Regions will not be achieved on time.

Regaining momentum towards elimination

SAGE noted this lack of progress with concern and the high cost of responding to importations in countries that have achieved elimination and urges country governments, international partner agencies and civil society partners to increase their advocacy, investment and commitment to achieving the existing measles and rubella control and elimination targets as part of the GVAP of the Decade of Vaccines.

Establishing an elimination goal in the SE Asian Region

The eradication of polio from the SE Asian Region and new country-led activities conducted as part of the Regional resolution on Intensification of Routine Immunization has provided new momentum to immunization programmes. SAGE noted the plans for a Regional consultation on measles elimination in February 2013 and encourages Member States in the Region to establish a target date for achieving measles elimination as means to maintain the high political and funding support to immunization and as critical step towards establishing a target date for global eradication of measles.

Equity

Because measles is one of the most transmissible human pathogens, it readily finds susceptible populations and can be used to identify underserved communities and highlight gaps in the immunization programme. Recognizing the potential for measles elimination to promote equity, SAGE encourages immunization and health services to use the occurrence of measles cases as an indicator of inequities in access to preventive health services and use this intelligence for planning more equitable health service delivery.

Strengthening routine immunization systems

Measles and rubella elimination activities provide a unique opportunity to strengthen routine immunization systems. SAGE noted the innovative work done in Cambodia and India where measles SIAs were used to measurably improve routine immunization service delivery. SAGE recommends that countries and partners provide additional resources to plan and implement specific strategies to be conducted before, during and after SIAs the campaign that will strengthen routine service delivery.

Operational planning and financing

The goals of the Measles and Rubella Global Strategic Plan, 2012-2020 are closely aligned with the Global Vaccine Action Plan and the strategies and guiding principles, if fully implemented, should

achieve the regional and global targets. However, the costs of implementing the plan are not yet available. SAGE recommends that a detailed operational plan be developed and its components fully costed so that a realistic assessment can be made of the human and financial resources needed to reach the current regional and global targets.

New partners and resources

Over the past 18 months, new civil society partners (e.g., Lions Clubs International Foundation, The International Pediatric Association, The American Academy of Pediatrics, Sabin Vaccine Institute) have joined the MR Initiative. With the new commitments by GAVI to support measles control and rubella vaccine introduction, low and low-middle income countries have the option to obtain support from both MR Initiative and/or GAVI. SAGE recommends GAVI and the MR Initiative establish effective communication channels at each level of their organizations both with each other and countries to avoid confusion and potential duplication of efforts.

Rubella vaccine introduction

The introduction of rubella vaccine starting with a wide age-range MR SIA with substantial funding support for GAVI-eligible countries is a unique and unprecedented opportunity to rapidly increase population immunity against both rubella and measles and move countries closer to elimination. SAGE recommends that every country introducing rubella vaccine ensure that their planning and implementation is of the highest quality and includes all the strategies recommended by SAGE (Wkly Epid Rec, 28 August 2009, No. 35, 2009, 84, 349–360). Each MR campaign should follow established "best practices" and be independently evaluated to ensure homogeneous vaccination coverage of >95%.

Linkages with other programmes

Closer linkages between measles and rubella programme activities and the Global Polio Eradication Initiative has well recognized benefits both for both programmes. SAGE recommends countries and global immunization partners assess the potential synergies and take active steps, where appropriate, to transition the polio infrastructure and lessons learnt to support achievement of measles and rubella elimination targets.

Laboratory-supported case-based surveillance

While the WHO Global LabNet is providing a high quality diagnostic and virus tracking capacity to nearly all countries, field surveillance is lagging behind in many countries due to lack of human and financial resources. SAGE noted challenges in the integration of rubella with measles surveillance, inadequate quality of case and outbreak investigations, and lack of timely reporting by countries to WHO Regional Offices even in Regions with established elimination goals. SAGE recommends immediate attention to funding shortfalls for both field and laboratory surveillance and stronger advocacy with governments to ensure on-time reporting of measles and rubella surveillance data to WHO Regional Offices. In addition, SAGE requests the MR working group to look in more detail at surveillance and present draft recommendations for strengthening this critical aspect of the programme to SAGE in 2013.

Documenting and verifying elimination

The establishment of Regional and national commissions to document and verify elimination provides much needed attention to improving the quality of vaccination coverage, disease and virus surveillance

information. SAGE stressed the importance of a standardized approach that draws on the experience from countries and Regions involved in verification activities. SAGE reviewed and endorsed the draft Framework for Verification of Measles and Rubella Elimination and encourages Regions and countries, as they approach elimination, to adopt this approach.

Risk assessment, outbreak preparedness and response

SAGE welcomed the new GAVI funds to support more effective response to measles outbreaks. The experience from elimination of measles and rubella in the Americas is that, in addition to timely outbreak response, attention should be given to outbreak prevention. SAGE recommended that Regional and country experience be used as the basis for developing and evaluating a risk assessment tool to identify and intervene in underperforming districts as a means to prevent outbreaks.

Overcoming vaccine hesitancy

SAGE noted the increasing challenge being faced in all Regions, but particularly in the European Region, with regard to vaccine hesitancy and recommended that the measles and rubella working group liaise closely with the new SAGE working group on vaccine hesitancy in this regard.

Innovation and strategic oversight

SAGE reviewed and agreed that the planned products from the MR working group adequately address the terms of reference of the working group. With respect to the research agenda, SAGE noted the short time line to achieve the GVAP goals and requested that the working group present the results of their work on prioritization of research needs at the next SAGE meeting.

Strengthen global coordination

The inclusion of regional measles and rubella elimination in the GVAP goals for 2020 and the addition of new partners and funding to support implementation will require stronger coordination among partners, across regions and with countries. SAGE encourages all partners in the Measles and Rubella Initiative to review their management structure with a view to strengthening their ability to support efficient programme implementation. In addition, WHO as the lead technical agency, should assess its capacity to effectively coordinate programme activities in this expanding area of work.

Framework for Verifying Elimination of Measles and Rubella

SAGE Working Group on Measles and Rubella

(Draft of 18 October 2012)

Preamble

The Global Vaccine Action Plan 2012-2020, established the target of eliminating measles and rubella in at least 5 WHO Regions by 2020. The SAGE Working Group on Measles and Rubella has prepared revised guidance on how to monitor progress towards and verify elimination of measles and rubella to ensure alignment between the activities of different regions. This guidance, or framework, builds on the experience gained so far in regions and countries, and provides an approach to integrating rubella surveillance into measles and rubella elimination activities.

This framework is developed for settings where the aim is to interrupt transmission of both measles and rubella, and the revisions to all the elements are tailored for that context. Modified definitions and indicators may be appropriate in settings where measles and/or rubella are still endemic.

It is also recognized that not all countries will be able to measure all the indicators laid out below, and alternative and complementary lines of evidence may be used to verify elimination of measles and rubella. The aim is to balance standardization against the need for flexibility to accommodate differences in national health systems.

This document does not cover definitions and surveillance indicators for determining the elimination of congenital rubella syndrome (CRS). An approach to verifying the elimination of CRS in the Region of the Americas has been published by Castillo et al (2011)[1] and fieldwork is ongoing to evaluate approaches to CRS surveillance in other regions.

Principles and process

The achievement of measles and/or rubella elimination should be verified for individual countries and areas and eventually for each of the WHO Regions as a whole following a standard process. While each region may adapt the process to its specific situation, the basic principles and process should be common to all regions.

At country level, a national verification committee should be established to conduct an annual review of progress towards elimination. This committee does not have authority to verify elimination; rather it's role is to help countries document progress towards elimination by gathering, analyzing and validating the national data and submitting the necessary documentation to the regional verification commission. The national committees should be multi-disciplinary including laboratory, epidemiological, public

[1] Castillo-Solorzano C, Reef SE, Morice A, et al. Guidelines for the Documentation and Verification of Measles, Rubella, and Congenital Rubella Syndrome elimination in the Region of the Americas. Journal of Infectious Diseases 2011;204:S683–S689.

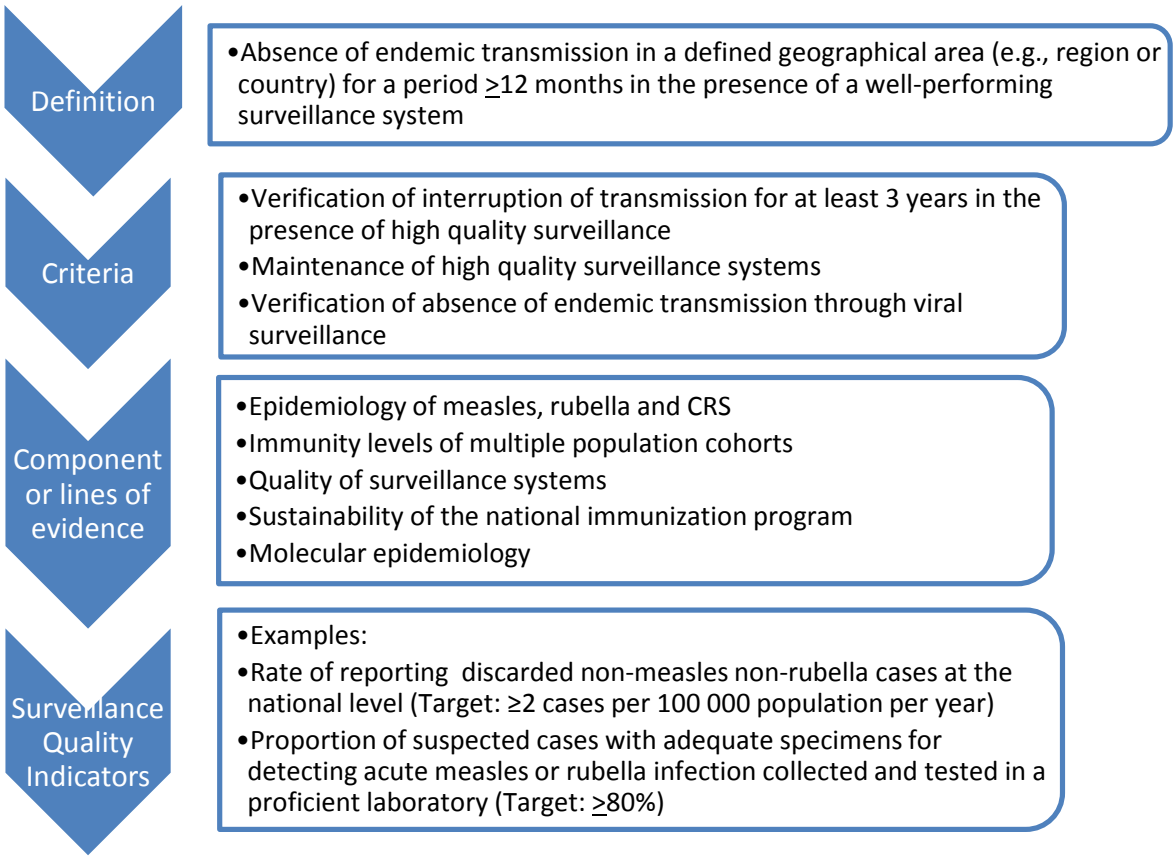
health, and clinical expertise. As far as possible the members should not be involved in the day-to-day management of the national immunization or surveillance activities. In addition to national-level data, disaggregated data should be assessed at the 3rd administrative level (i.e., district, municipality, county, or equivalent administrative unit with a population size of no more than 500,000). Also, information should be analysed on populations served by the private sector and underserved subpopulations (e.g., minorities, migrants, or marginalized communities) who may fall outside the national health and surveillance systems because these groups have been shown to be important for sustaining measles and rubella transmission.

At regional level, a regional verification commission should conduct an annual review to determine progress towards and accomplishment by individual countries of measles and/or rubella elimination. Verification of elimination for the region as a whole is possible when all countries are able to document interruption of endemic virus transmission for a period of 36 months or more. Members of the regional verification commission should be recognized leaders with expertise in the fields of public health, epidemiology, laboratory science, clinical medicine, and social sciences. They should be independent of the day-to-day management of national immunization programmes and conflicts of interest should be sought and declared.

Conceptual Framework

A framework for thinking about the evidence to be assembled to monitor progress towards and eventual elimination of measles and rubella includes explicit definitions, criteria for elimination, lines of evidence, and indicators of the quality of field and laboratory surveillance (Figure 1).

Figure 1. Hierarchy of evidence for verification of elimination



Definitions

Table 1. Definitions for verifying measles and rubella elimination

Word or Phrase	Definition
Measles or rubella eradication	worldwide interruption of measles or rubella virus transmission in the presence of a surveillance system that has been verified to be performing well
Measles elimination	the absence of endemic measles transmission in a defined geographical area (e.g., region or country) for ≥12 months in the presence of a well performing surveillance system Note: verification of measles elimination takes place after 36 months of interrupted measles virus transmission

Rubella elimination	the absence of endemic rubella virus transmission in a defined geographical area (e.g., region or country) for ≥12 months and the absence of CRS cases associated with endemic transmission in the presence of a well performing surveillance system Note: There may be a lag (up to 9 months) in occurrence of CRS cases after interruption of rubella virus transmission has occurred. Evidence of the absence of rubella transmission from CRS cases is needed because CRS cases excrete rubella virus for up to 12 months after birth. Note: verification of rubella elimination takes place after 36 months of interrupted rubella virus transmission.
Endemic measles or rubella virus transmission	the existence of continuous transmission of indigenous or imported measles virus or rubella virus that persists for ≥12 months in any defined geographical area
Endemic measles or rubella case	laboratory or epidemiologically-linked confirmed cases of measles or rubella resulting from endemic transmission of measles or rubella virus.
Re-establishment of endemic transmission	occurs when epidemiological and laboratory evidence indicates the presence of a chain of transmission of a virus strain that continues uninterrupted for ≥12 months in a defined geographical area (region or country) where measles or rubella had been previously eliminated Note: a measles or rubella virus strain is determined by sequencing the WHO standard 450nt region of the N gene for measles and the 739nt of the E1 gene for rubella.
Measles or rubella outbreak in an elimination setting	a single laboratory confirmed case
Suspected case of measles or rubella	a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular (non-vesicular) rash
Laboratory confirmed measles case or rubella case	a clinically-compatible case of measles or rubella that has been confirmed by a proficient laboratory Note: a proficient laboratory is one that is WHO accredited and/or has an established quality assurance programme
Epidemiologically-linked confirmed	a clinically-compatible case of measles that has not been confirmed by a laboratory but that was geographically and temporally related (with dates of rash onset occurring between 7 and 21 days apart) to a laboratory-

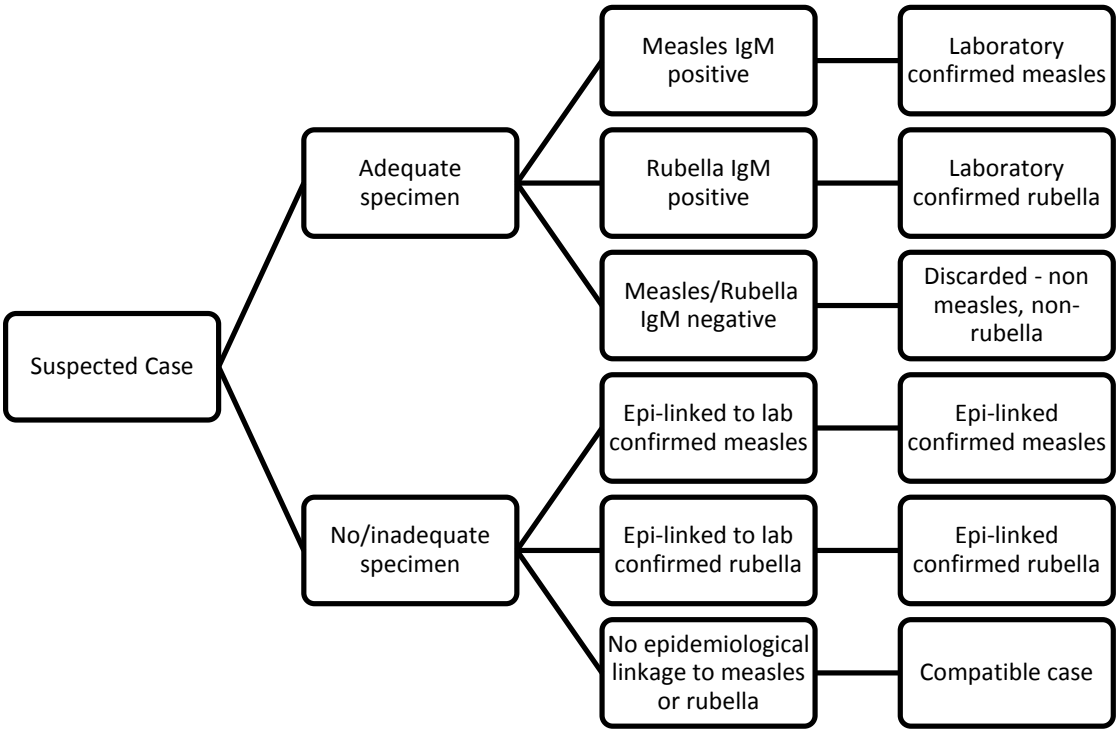
measles case	confirmed case or (in the event of a chain of transmission) to another epidemiologically confirmed measles case
Clinically-compatible measles case	a case with fever and maculopapular (non-vesicular) rash and one of cough, coryza, or conjunctivitis but for which no adequate clinical specimen was taken and which has not been linked epidemiologically to a laboratory confirmed case of measles or another laboratory-confirmed communicable disease
Clinically-compatible rubella case	a case with maculopapular (non-vesicular) rash and fever (if measured) and one of arthritis/arthralgia or lymphadenopathy but for which no adequate clinical specimen was taken and which has not been linked epidemiologically to a laboratory confirmed case of rubella or another laboratory-confirmed communicable disease
Non-measles non-rubella discarded case	a suspected case that has been investigated and discarded as a non-measles and non-rubella case using (a) laboratory testing in a proficient laboratory or (b) epidemiological linkage to a laboratory-confirmed outbreak of another communicable disease that is neither measles nor rubella
Measles vaccine-associated illness	a suspected case that meets all 5 of the following criteria: (i) the patient had a rash illness, with or without fever, but did not have cough or other respiratory symptoms related to the rash; (ii) the rash began 7–14 days after vaccination with a measles-containing vaccine; (iii) the blood specimen, which was positive for measles IgM, was collected 8–56 days after vaccination; (iv) thorough field investigation did not identify any secondary cases; and (v) field and laboratory investigations failed to identify other causes. Alternatively, a suspected case from whom virus was isolated and found on genotyping to be a vaccine strain.
Imported measles or rubella case	a case exposed outside the region or country during the 7–21 days (12-23 days for rubella) prior to rash onset and supported by epidemiological or virological evidence, or both. Note: for cases that were outside the region or country for only a part of the 7-21 day interval (12-23 day interval for rubella) prior to rash onset, additional evidence including a thorough investigation of contacts of the case, is needed to exclude a local source of infection.
Importation-related measles or rubella case	a locally acquired infection occurring as part of a chain of transmission originating from an imported case as supported by epidemiological or virological evidence, or both. Note: if transmission of measles or rubella cases related to importation

	persists for ≥12 months, cases are no longer considered to be import-related, they are endemic.

Case classification

Countries nearing elimination of measles and/or rubella, should immediately investigate all suspected cases and obtain a clinical specimen for laboratory testing. Once the case investigation form has been completed and laboratory test results are available, suspected cases should be classified according to the algorithm below.

Figure 1. Flow chart for classification of suspected cases



Criteria for verifying elimination

Three criteria for verifying elimination are recommended based on experience with assessing measles and rubella elimination in the Region of the Americas. They are:

- documenting the interruption of endemic measles, or rubella, virus transmission for a period of at least 36 months from the last known endemic case
- the presence of a high-quality surveillance system that is sensitive and specific enough to detect imported and import-related cases, and
- genotyping evidence supporting interruption of endemic transmission.

All 3 criteria are necessary to verify elimination at the regional level. As some small countries may not have genotyping information prior to interruption of endemic transmission, this criterion is not an absolute requirement for determining if elimination has been achieved at the country level.

Lines of evidence

Five lines of evidence, or components, should be considered by the regional verification commission when determining whether a country or the region as a whole has achieved elimination:

1. Epidemiology of measles and rubella over at least the past 60 months and description of the epidemiology including programmatic changes. Where available, summary information since the introduction of measles and rubella vaccine should also be reviewed.

Analyses of the epidemiological data from high-quality surveillance systems provide the critical information on whether and when endemic virus transmission has been interrupted. Standard case definitions and case classification systems should be used (see Definitions and Figure 1). The analyses should include the pre-interruption and post-interruption epidemiological periods to support the identification of a time-point at which endemic virus interruption was achieved. Analyses to be conducted should include annual disease incidence rates and case numbers by case classification; temporal and spatial characteristics; seasonality; and demographic characteristics of the cases. For outbreaks, a description of the epidemiology (e.g., by person, time and place) as well as any results from case-control or cohort studies should be included. Countries and regions that have eliminated either measles or rubella will characteristically have low rates of or no disease, absence of seasonality, imported cases with little or no disease spread, and few outbreaks of which most will be of small size.

2. Population immunity presented as a birth cohort analysis with the addition of evidence related to any marginalized and migrant groups per birth cohort

To achieve and maintain elimination of measles and rubella high levels of population immunity are required. Assuming nearly all persons born before vaccine introduction have natural immunity against measles, it is sufficient to document measles immunity for each annual cohort born since the introduction of measles vaccine in the national immunization schedule. For rubella, countries need to assess the epidemiology of rubella stratified by age groups to identify any susceptibility in the older age groups. A seroprevalence study may be needed to document the immunity in the older age groups. To assess coverage, countries should review and analyze data from administrative reports for routine delivery and supplementary immunization activities, as well as coverage surveys where available. This analysis should be available at the district/municipality, department/state, and national levels. This information will allow for the estimation of population immunity (= vaccination coverage x vaccine effectiveness) against measles and rubella. Countries may want to include other sources of immunity data such as well conducted seroprevalence studies.

3. Quality of laboratory and epidemiological surveillance systems for measles and rubella (see indicators)

Interpretation of the epidemiological data is dependent on the quality of the surveillance system for detecting and confirming measles and rubella. The performance of the surveillance system can be assessed by core indicators such as timeliness of reporting, the reporting rate, adequacy of case investigation, laboratory confirmation of sporadic cases and chains of transmission, and viral detection (see table below). Active case finding and use of retrospective case searches provide additional evidence of system performance and are particularly useful in outbreak situations to identify the primary case, secondary cases, and contacts that may occur within the corresponding incubation period. Active searches should also be considered in high-risk areas, which include silent areas or areas that do not achieve weekly reporting standards and areas with low vaccination coverage.

4. Sustainability of the National Immunization Program including resources for mass campaigns, where appropriate, in order to sustain elimination

The elimination of measles and rubella must be sustained, so assessing the sustainability of national immunization programs is necessary to ensure that these programs will be able to maintain the goal. Political commitment at all levels, efficient programme management, and a favorable economic and legal environment are fundamental requirements to ensure that national immunization programs are successful. Components that may be used to assess sustainability of the programme include:

a. A current national plan for the elimination of measles and rubella
b. Standard operating procedures at each level of the programme (e.g., a check list for conducting an immunization session)
c. Evidence of vaccine demand forecasting and vaccine stock management
d. Secured funding for vaccine procurement (e.g., a line item in the national budget for vaccine procurement and programme implementation).

5. Genotyping evidence that measles and rubella virus transmission is interrupted

Molecular epidemiologic data are used to verify that elimination has been achieved by documenting the interruption of transmission of endemic viruses. Prior to elimination, the genetic information obtained provides a baseline of the circulating strains including predominantly endemic strains and some imported strains. After elimination has been achieved, the molecular epidemiological information from the new cases can be compared with the pre-elimination endemic viral strains. The absence of previously endemic strains for $\geq$ 12 months with or without sporadic imported strains is consistent with elimination. For example, the rubella virus genotype 1C was identified as endemic in the Americas because it was frequently found in the region and had not been identified in other regions of the world. The last occurrence of 1C virus transmission was identified in 2005 in Chile and Peru. In 2006, the genotype 2B was isolated during rubella outbreaks reported in Brazil, Chile, and Argentina. However, 2B appears to be no longer present in the Americas with the last endemic case identified in Argentina in February 2009.

The individual lines of evidence should not be considered alone but rather should be evaluated together to establish the case for elimination. The process of correlating and integrating the evidence from the various sources of information will allow countries to determine whether the available data are valid, complete, representative, and consistent. The work of the Regional Verification Commission is to correlate and integrate the information from each line of evidence and make an overall determination as to whether elimination has been achieved and maintained or not.

Surveillance indicators

High quality epidemiological and laboratory data are required to allow a meaningful assessment of progress towards elimination. The routine surveillance system should provide sufficient and timely data based on pre-established performance indicators. Supplementary approaches to determine the quality of surveillance data include active and retrospective case searches and detailed field investigations conducted during outbreaks.

The set of core indicators that should be used to monitor the quality of field and laboratory surveillance are summarized below (Table 2). These include timeliness of reporting to the national level, the reporting rate of suspected cases, proportion of sporadic cases or chains of transmission laboratory confirmed, proportion of chains of transmission with genotyping information, adequacy of case investigations, time for specimens to reach the laboratory, and the turnaround time for laboratory results. For countries without systems in place to collect data on some of the core indicators, alternative analyses or additional indicators may be provided to allow assessment of surveillance system performance. For countries where substantial numbers of measles cases present to the private sector, additional evidence should be submitted to demonstrate that cases identified by the private sector are being adequately reflected in national surveillance data.

Table 2. Indicators of the quality of field and laboratory surveillance

Indicator	Description
Timeliness of reporting	Proportion of surveillance units reporting to the national level on time (Target: ≥80%) Proportion of countries reporting to their WHO Regional Office on time (Target: 100%) Proportion of Regions reporting to WHO Headquarters on time (Target:100%) Note: At each level reports should be received on or before the requested date
Reporting rate of discarded non-measles non-rubella cases	Reporting rate of discarded non-measles non-rubella cases at the national level (Target: ≥2 cases per 100 000 population per year)

Representativeness of reporting	Proportion of subnational administrative units (e.g., at the province level or its administrative equivalent) reporting at least 2 discarded non-measles non-rubella cases per 100,000 population (Target: ≥80%) Note: if the administrative unit has a population <100 000, then the rate should be calculated by combining administrative units to achieve a population of ≥100 000.
Laboratory confirmation	Proportion of suspected cases with adequate specimens for detecting acute measles or rubella infection collected and tested in a proficient laboratory (Target: ≥80%). Any suspected cases of measles that are not tested by a laboratory and are (a) confirmed as measles by epidemiological linkage or (b) discarded as non-measles by epidemiological linkage to another laboratory-confirmed communicable disease case should be excluded from the denominator of suspected cases. Note: Adequate specimens are: blood sample, minimum of 0.5 ml; dried blood sample, at least 3 fully filled circles on filter paper collection device; oral fluid, sponge collection device should be rubbed along the gum until the device is thoroughly wet (this usually takes one minute). Adequate samples for serology are those collected within 28 days after rash onset. Note: a proficient laboratory is one that is WHO accredited and/or has an established quality assurance programme
Viral detection	Proportion of laboratory-confirmed chains of transmission with samples adequate for detecting measles or rubella virus collected and tested in an accredited laboratory (Target:≥80%). The numerator is the number of chains of transmission for which adequate samples have been submitted for viral detection and the denominator is the number of chains of transmission identified. Note: Where possible, samples should be collected from 5–10 cases early in a chain of transmission and every 2-3 months thereafter if transmission continues. For virus isolation, adequate throat or urine samples are those collected within 5 days after rash onset. For virus detection using molecular techniques, adequate throat samples are those collected up to 14 days after rash onset, and adequate oral fluid samples are those collected up to 21 days after rash onset.

Adequacy of investigation	Proportion of all suspected measles and rubella cases that have had an adequate investigation initiated within 48 hours of notification (Target: aim for 80%). The numerator is the number of suspected cases of measles or rubella for which an adequate investigation was initiated within 48 hours of notification and the denominator is the total number of suspected measles and rubella cases. Note: An adequate investigation includes collection of all the following data elements from each suspected measles and rubella case; name or identifiers, place of residence, place of infection (at least to district level), age (or date of birth), sex, date of rash onset, date of specimen collection, measles-rubella vaccination status, date of last MR vaccination, date of notification and date of investigation and travel history. Note: Some variables may not be required for cases that are either confirmed as measles by epidemiologic linkage (e.g., date of specimen collection)
Timeliness of specimen transport	Proportion of specimens received at the laboratory within 5 days (Target: ≥80%)
Timeliness of reporting laboratory results	Proportion of results reported by the laboratory within 4 days of receiving the specimen (Target: ≥80%)

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MEASLES AEROSOL VACCINE PROJECT - REPORT TO SAGE

GOAL OF THE MEASLES AEROSOL VACCINE PROJECT

The goal of the Measles Aerosol Project is to license at least one method (vaccine and delivery device) for respiratory delivery of currently licensed measles vaccines. A measles vaccine that is effective, safe, easier to administer and with a comparable cost to subcutaneous administration.

WHY A MEASLES AEROSOL VACCINE?

The potential to reduce the challenges link to injection safety and waste management

Measles immunization campaigns are effective elements of a comprehensive strategy for preventing measles cases and deaths[i]. However, if immunizations are not properly administered or if immunization waste products are not safely managed, there is the potential to transmit bloodborne pathogens (e.g., human immunodeficiency virus and hepatitis B and hepatitis C). A safe injection can be defined as one that results in no harm to the recipient, the vaccinator, and the surrounding community. Proper

equipment, such as the exclusive use of auto-disable syringes and safety boxes, is necessary, but these alone are not sufficient to ensure injection safety in immunization campaigns. Equally important are careful planning and managerial activities that include policy and strategy development, financing, budgeting, logistics, training, supervision, and monitoring. The key elements that must be in place to ensure injection safety in measles immunization campaigns are outlined.
According to the Safe Injection Global Network (SIGN) 2010 meeting report[ii], the global burden of disease from unsafe medical injections has been estimated for the year 2008 by the World Health Organization from a probabilistic model. In total unsafe medical injections led to 340,000 HIV infections, 15 million HBV infections, 1 million HCV infections, 3 million bacterial infections and 850,000 injection site abscesses in 2008. These infections accounted for 14% of HIV infections, 25% of HBV infections, 8% of HCV infections and 7% of infections with bacteraemia worldwide and accounted for 28 million disability adjusted life years, a metric of the years of life lost to death and disability from AIDS, acute hepatitis, liver cancer, end-stage liver disease and fatal sepsis. After adjustment for a change in methodology in calculating the number of HIV infections resulting from unsafe medical injections, these figures represent a reduction in the burden of disease from unsafe medical injections since the year 2000.

Positive lessons learned from polio campaigns suggest that a vaccine that can be given by volunteers and be provided house to house can reach high coverage in low resource environments

The use of the bifurcated needle was one of the key elements in the achievement of smallpox eradication goal, together with strong political support and the adequate implementation of appropriate strategies. Similarly, experiences with polio eradication suggest that vaccination by volunteers using a house to house strategy had resulted in effective outbreak control and interruption of wild poliovirus transmission. Selected experiences over time are described below.

In 1993, due to persistence of poliomyelitis cases in the Pacific Coast of Mexico and particularly in the state of Sinaloa, a house to house vaccination strategy named "Sinaloa Operation" was carried out in 100% of the territory of this state[iii]. Simultaneously, teams of nurses carried out a population census of children less than five years old and pregnant women and vaccinated the children with Sabin trivalent vaccine in undiscriminating form. In total, 301, 441 Sabin vaccine doses were administered. As a result of this programme Sinaloa has not had any other polio case ever since. In a 1993, during a mass immunization campaign in Egypt, the vaccine coverage rate and per child vaccination costs were compared for house-to-house versus fixed-site oral poliovirus vaccine (OPV) delivery [iv]. House-to-house delivery achieved 100% OPV coverage, compared to about 86% for fixed-site delivery (p 0.01). The cost for house-to-house vaccination was 25% higher than for fixed-site vaccination in urban areas, while they were similar in rural areas. In urban areas, the cost per child vaccinated was similar for both fixed-site and house-to-house vaccinations ($0.11). In rural areas, it was higher for fixed-site delivery than for house-to-house delivery ($0.14 vs. $0.11). OPV wastage for both delivery approaches was the same (around 25%) in urban areas, while it was much higher for fixed-site vaccination than for house-to-house vaccination (41.5% vs. 23.5%). These findings suggested that, in Egypt, house-to-house delivery was the most cost-effective strategy to achieve universal coverage and thus to eradicate polio. A cross-sectional study in Ethiopia aimed at collecting qualitative and quantitative data for the systematic and epidemiological assessment of the extent of a polio outbreak in three regions between December 2004 and February 2006 (24 confirmed wild poliovirus cases), its determinants, and the lessons learned as well as the implications for future control strategies to interrupt wild poliovirus transmission[v]. In

response to the outbreak, Ethiopia implemented detailed outbreak investigations and large-scale, house-to-house vaccination campaigns. As a result, the three regions interrupted the wild poliovirus transmission within the regions within one year of confirmation of the index case. Outbreak response vaccination were successful in interrupting the imported wild poliovirus transmission within a one-year period of time.

IS THE MEASLES AEROSOL VACCINE SAFE?

A systematic review examined the safety of aerosolized measles vaccine one month or more after vaccination[vi]. Fever was the most frequently reported adverse event in six of the eight studies, followed by cough and rhinitis. Adverse events following aerosolized vaccine delivery were generally mild and infrequent. The studies reviewed did not identify severe side effects. The definitions and reporting of adverse events, was however, inconsistent and the authors were not able to synthesize data meaningfully.

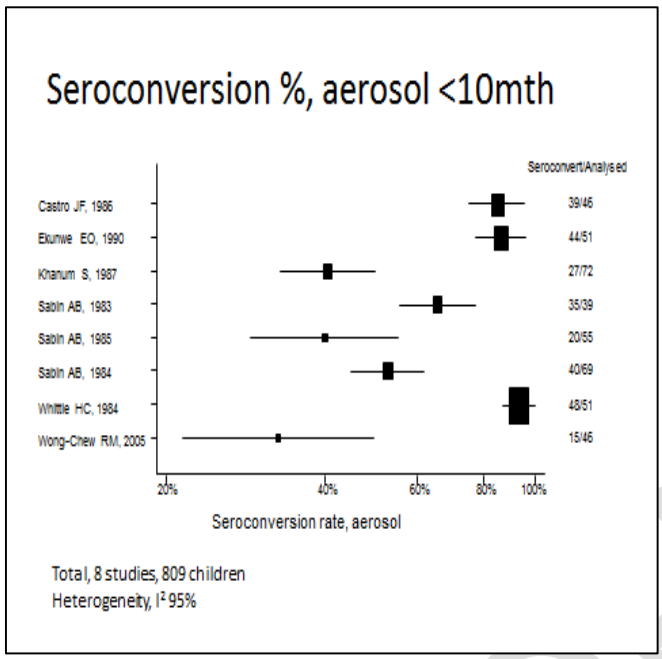
Another systematic review[vii] suggested that clinically, the aerosol route of delivery of vaccines is less reactogenic than the subcutaneous route. According to the authors, a numbers of studies have documented that the administration of vaccine through the injectable route is associated with a comparatively higher rate of adverse events. Measles vaccine administered through the aerosol or the respiratory route is well tolerated; common clinical adverse reactions are fever and mild conjuctival discharge. The aerosol group in each of the studies reviewed showed significantly lower frequency of fever, rhinitis, cough, generalized morbilliform rash, arthalgias and conjuctival hyperemia in infants.

During a Phase I trial in India[viii], the measles aerosol vaccine was administered to healthy measles immune volunteers 1-35 years of age using three different devices with comparable performance characteristics to the Classic Mexican Device (CMD) in three different sites in India. In total 145 volunteers were followed, among them 53 children 5-17 years of age and 32 children 1-4 years of age. The study found that the measles aerosol vaccine was safe, well tolerated and immunogenic in three different sites in India (WHO unpublished data).

A Phase II/III trial in India[ix] assessed the frequency of adverse events following measles aerosol and subcutaneous vaccination. Two thousand children 9 to 11.99 months of age received measles vaccine and were followed-up to 91 days after vaccination. A sub-set of 100 children enrolled were followed-up to 365 days after vaccination to ascertain the frequency of adverse events. The study reported adverse events that were generally mild and not related or unlikely to be related to vaccination. The most commonly reported adverse event was coryza followed by cough, diarrhoea, fever and vomit. One serious adverse event (urticaria with angioedema) that was deemed possibly vaccine related. It was resolved without sequelae. An independent Data Safety Monitoring Board (DSMB) had access to unblinded data for the assessment of serious adverse events. Based on the information presented in the Final Safety Report dated June 2012, the DSMB members concluded that they have no concerns regarding the safety profile of the aerosolized measles vaccine. Furthermore, the DSMB stated that the adverse event profile of the aerosol vaccine was similar to that of the subcutaneous vaccine. However, the DSMB noted the differences in symptoms and behaviour between the two groups during vaccine administration with a lower percentage of children crying, struggling or exhibiting shallow breathing in the aerosol group, suggesting better immediate tolerability. Aerosol administration was, however, associated with coughing in a minority.

IS THE MEASLES AEROSOL VACCINE EFFICACIOUS AND EFFECTIVE?

Evidence on immunogenicity of Measles Aerosol Vaccine in infants below 10 months of age



A systematic review examined the immunogenicity of aerosolized measles vaccine . In children below 10 months, eight studies provided data from a total of 809 infants. Serological responses were heterogeneous. Serological responses in infants < 10 month-old receiving measles aerosol vaccine ranged from 33% amongst 8-10 month-old infants in Mexico to 94% of 4-6 months old in the Gambia and; with subcutaneous measles vaccine from 51% in 4-6 month-old in Bangladesh to 100% in 6-9 months old in Mexico. In four trials that compared subcutaneous and aerosol routes the seroconversion was lower with aerosol than subcutaneous.

Seroconversion rates in children receiving the aerosol vaccine and with measles antibodies at baseline were lower than those for subcutaneous vaccination.

Conversely, a meta-analysis of studies comparing the aerosol route with the subcutaneous route reviewed seven studies involving children less than nine months of age . The summary estimate suggested that the seroresponse was 4% higher amongst vaccinees in the aerosol group than those in the subcutaneous group (M_H pooled RR=1.04, 95% CI = 0.98-1.1). %/). Inclusion criteria may account for some of the differences between these two systematic reviews.

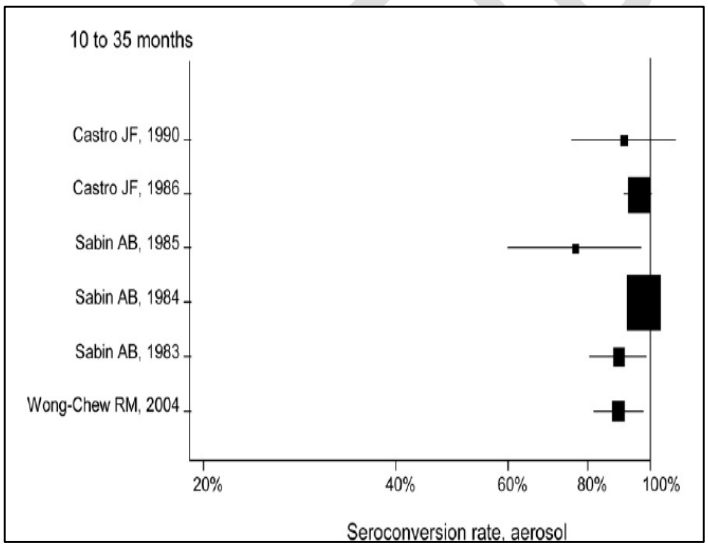
A phase II/III randomized, open-label, active-control, parallel group, non-inferiority trial of measles vaccine in healthy infants from 9-11.9 months of age was initiated in India in 2009[1]. The same dose (NLT 1000 CCID50) was administered by aerosol or by subcutaneous injection to a total of 2000 infants randomized 1:1 to the two arms. A subset of 100 subjects per arm was followed-up for 364 days for any serious or unexpected adverse events. Blood samples were taken at baseline and 91 days post-vaccination. Subjects in the sub-set also had blood samples taken at 28 days and 364 days post vaccination. Preliminary results are summarized below[x]. As per the PP analysis, the sero-positivity at Day 91 in aerosol group was 85.42% (CI: 82.53% to 87.90%) and of subcutaneous group was 94.65% (CI: 92.79% to 96.05%). The difference between aerosol and subcutaneous seropositive rate is -9.23% (CI: -12.22% to -6.30%) (p<0.05). As per the ITT analysis, the sero-positivity at Day 91 in aerosol group was 85.39% (CI: 82.44% to 87.91%) and of subcutaneous group was 94.72% (CI: 92.81% to 96.14%). The difference between aerosol and subcutaneous seropositive rate is -9.33% (CI: -12.30% to -6.42%) (p<0.05). The Product Development Group for this project reviewed the results of this trial and stated[xi]

[1] (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=862).

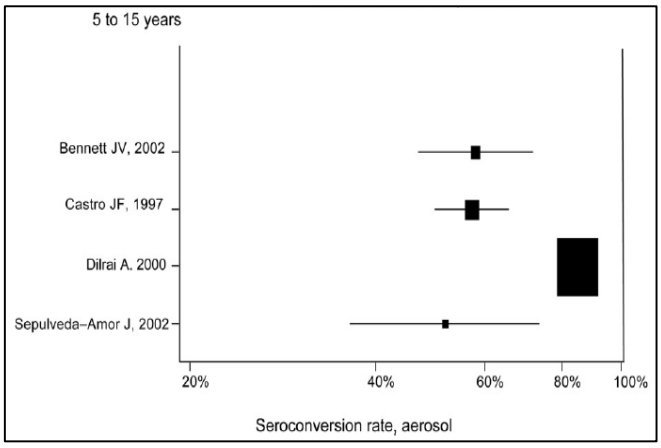
that the primary conclusion of this trial is that although the aerosol arm achieved seropositivity of 85.42% (CI: 82.53% to 87.90%) as per protocol analysis and of 85.39% (CI: 82.44% to 87.91%) as per intention to treat analysis, the non-inferiority criteria was not met. The difference in seropositivity between both study arms in this trial was -9.23% (CI: -12.22% to -6.30%) as per protocol analysis and -9.33% (CI: -12.30% to -6.42%) as per intention to treat analysis. This is greater than the non-inferiority margin of 5% defined in the study protocol. Therefore, the results of this trial suggest that measles aerosol vaccination is inferior to subcutaneous vaccination as a primary means of immunization in 9-11 months old children. The analysis of risk factors did not show any evidence that any of the factors investigated had a significant association to remaining seronegative. Data available suggest that there may be differences in the kinetics of the immune responses between the aerosol and subcutaneous routes. However, the PDG members acknowledged that they lack the data that would allow a clear interpretation that this differences exists and of the potential relevance. The results are applicable to the trial settings and aerosol delivery device used in this trial.

In a recent study in Mexico[xii], 113 healthy 9-month-old infants were enrolled; 58 received aerosol EZ measles vaccine for 2.5 minutes and 55 received the vaccine subcutaneously. Adaptive immunity was induced in 97% after aerosol and 98% after subcutaneous administration. Seroconversion rates and GMCs were 95% and 373 mIU/mL (95% confidence interval [CI], 441-843) following aerosol vaccination and 91% and 306 mIU/mL (95% CI, 367-597) after subcutaneous administration at 3 months. CD8 memory cell frequencies were higher in the aerosol group at 3 months compared with the subcutaneous group. The authors concluded that increasing exposure time to aerosol measles vaccine (i.e. from 30 seconds to 2.5 minutes) elicits immune responses that are comparable to those seen when an equivalent dose is administered by the subcutaneous route in 9-month-old infants.

Evidence on immunogenicity of Measles Aerosol Vaccine in older infants and children



A systematic review examined the immunogenicity of aerosolized measles vaccine .
In children 10-35 months of age, six studies included data on 449 children (five in Mexico and one in Brazil). Two studies included comparisons of seroconversion rates with aerosol and subcutaneous delivery. Four studies assessed only the aerosol route. The summary weighted seroconversion rates in aerosol (93.5%, 95% CI 89.4-97.7%) and subcutaneous (97.1%, 95% CI 92.4-100%) groups were similar and there was no statistical evidence of between study heterogeneity.

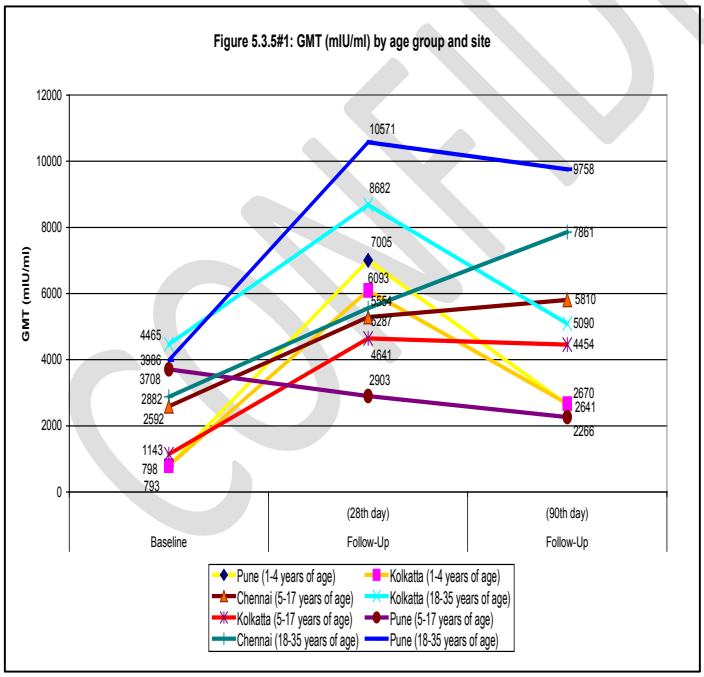


There were five reports (from 4 studies) including data about serological response in children 5-15 years old.

The studies were heterogeneous; therefore no pooled estimate was calculated. In all studies and all settings serological response rates were higher with aerosol than subcutaneous vaccination

A meta-analysis to evaluate the efficacy of measles vaccine administered through the respiratory route compared to the subcutaneous route reported that for vaccinees over 9 months of age, seroresponse was 15% higher in the respiratory group (M-H pooled RR = 1.15; 95% CI = 1.98 to 1.17).

During a Phase I trial in India (2007) , the measles aerosol vaccine was administered to healthy measles immune volunteers 1-35 years of age in three different sites in India. In total the study followed up 145 volunteers (WHO unpublished data). Blood samples were taken at baseline, 28 days and 90 after aerosol immunization.



Because all subjects in the study were measles immune (PRN titer ⩾ 120 mIU/mL), signs of immunogenicity are documented by boosting of baseline antibody titers.

This boosting effect was best documented in subjects with low (⩽ 2000 mIU/mL) and medium (2000 – 6000 mIU/mL) anti-measles antibodies, throughout the study (all groups, all sites).

Subjects with lower baseline anti measles titers showed very good boosting at 28 days and at 90 days, thus indicating that measles aerosol vaccine has good potential immunogenicity.

In summary, the measles aerosol vaccine was immunogenic in healthy volunteers 1-35 years of age in three different sites in India, using three different nebulizers.

Evidence on immunogenicity of measles aerosol vaccine when administered as a second dose.

In a randomized controlled trial of aerosol and subcutaneous measles vaccines in South African schoolchildren[xiii], 4327 schoolchildren (aged 5-14 years), assigned by block randomization of classrooms, received standard titre doses of either Schwarz or Edmonston-Zagreb measles vaccines subcutaneously or by aerosol. Blood samples for antibody assay were collected before vaccination at 1 month, and 1 year after vaccination. Eighty five per cent of all enrolled children had either had measles or been vaccinated. Serological responses were measured in all children who were seronegative and a 9% random sample of seronegatives. Overall, amongst those followed up 85% seroconverted. 14 (3.6%) of 385 children who received Edmonston-Zagreb vaccine by aerosol were seronegative 1 year after vaccination, compared with 28 (8.6%) of 326 children who received Edmonston-Zagreb subcutaneous vaccine and 39 (13.9%) of 281 children who received Schwarz subcutaneous vaccine. At 1 month, 326 (84.7%) children who received aerosol Edmonston-Zagreb vaccine had seroconverted compared with 257 (78.8% who received subcutaneous Edmonston-Zagreb vaccine and 176 (62.6%) who received subcutaneous Schwarz vaccine.

Evidence of long-term persistence of measles antibody titer after measles aerosol vaccine administration

To assess the long-term persistence of measles antibody after vaccination by the aerosol route the children in the South African trial described above were followed up 6 years after their re-vaccination with Edmonston–Zagreb (EZ) and Schwarz (SW) measles vaccine given by aerosol and subcutaneous routes[xiv]. Measles antibody levels and the proportion of children who were seropositive at year 6 remained significantly higher in the Edmonston–Zagreb aerosol group compared to the groups that received Schwarz or Edmonston–Zagreb vaccine subcutaneously. Authors concluded that measles re-vaccination by aerosol evokes a stronger and much longer lasting antibody response than injected vaccine and should thus provide more durable protection against measles.

Proportion seropositive 6 years after re-vaccination among younger and older children receiving aerosol or injected vaccine.

	Aerosol (%; 95%CI)	Injected (%; 95%CI)	*p*-value
Younger (5-9 years at re-vaccination)			
Baseline seropositive	56/65 (86%; 75-94)	68/98 (69%; 59-78)	0.01
Baseline seronegative	38/47 (81%; 67-91)	36/71 (51%; 39-63)	0.001

Seropositivity at 6 by vaccine group and other covariates

	Number seropositive/total (%)	Adjusted odds ratio	95%CI	*p*-value
Vaccine group				
EZae	105/124(84.7)	1.00	-	-
EZsc	72/99(72.7)	0.33	0-16-0-69	0.003
SWsc	59/101(58.4)	0.20	0.10-0.40	0.000
Age when vaccinated				
5-9 years	188/270(69.6)	1.00	-	-
10-14 years	48/54(88.9)	3.90	1.6-10	0.001
Gender				
Female	142/181(78.5)	1.00	-	-
Male	94/143(65.7)	0.60	0.35-1.0	0.06

Adapted from Dilraj et al, 2007.

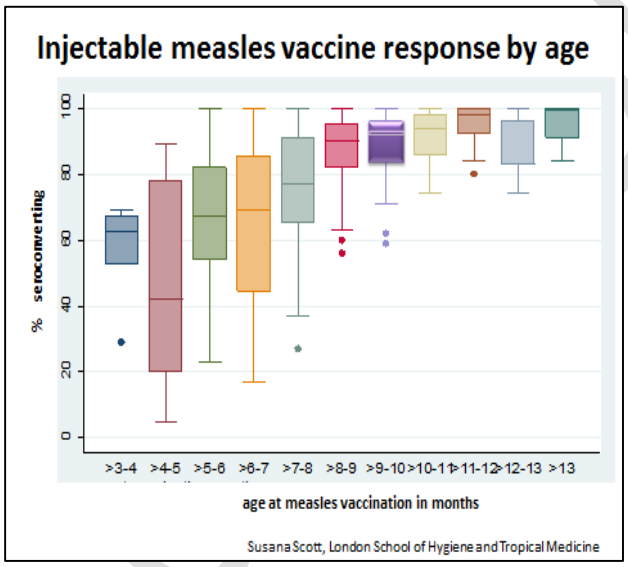
Evidence of impact of measles aerosol vaccine when used during outbreaks

In 1988-90, at the time of a large measles outbreak in Mexico a mass campaign using measles aerosol vaccine was conducted[xv]. A total of 3,760,684 children were vaccinated with measles aerosol vaccine. Of those 10.5% were aged 1-5 years old and 89.5% were 6-12 years old.

The authors acknowledged difficulties with impact evaluation due to different coverage in the various States involved and the fact that the vaccine administration was not simultaneous everywhere and spread over a long time period. However, data from cases 1-4 years of age in the State of Aguas Calientes where the vaccination status could be ascertained yielded a vaccine efficacy of 95.5%. Similarly, in a town in Jalisco State (San Juan Cosala) where 95% of the population from 8 months to 14 years of age were vaccinated with measles aerosol vaccine. The attack rates among the unvaccinated was 0.0035 (58/16167) and among the vaccinated it was 0.00015 (9/58370). The estimated vaccine effectiveness was 95.7%.

Evidence on the efficacy and effectiveness of measles injectable vaccine in infants and older children

Frequently cited figures are that approximately 85% of children develop protective antibody levels when given one dose of measles vaccine at nine months of age, and 90% to 95% respond when vaccinated at 12 months of age[xvi].



Among the 44 studies included in a systematic review[xvii], for children vaccinated between 8 and 9 months of age, the median proportion of children responding was 89.6% (mean 86.7; minimum 56; maximum 100; interquartile range (IQR) 82, 95).
Among the 24 studies included in which children were vaccinated between 9 and 10 months of age, the median proportion of children responding was 92.2% (mean 88.2; minimum 59; maximum 100; IQR 84, 96).
Among the 21 studies included in which children were vaccinated between 11 and 12 months of age, the median proportion of children responding was 99% (mean 95.7; minimum 80; maximum 100; IQR 93, 100).

A review of vaccine effectiveness studies published during 1960–2010 included seventy papers with 135 vaccine effectiveness (VE) point estimates[xviii]. For a single dose of vaccine administered at 9–11 months of age and at 12 months of age, the median VE was 77.0% (interquartile range [IQR], 62%–91%) and 92.0% (IQR, 86%–96%), respectively. When analysis was restricted to include only point estimates for which vaccination history was verified and cases were laboratory confirmed, the median VE was 84.0% (IQR, 72.0%–95.0%) and 92.5% (IQR, 84.8%–97.0%) when vaccine was received at 9–11 and at 12 months, respectively. Published VE vary by World Health Organization region, with generally lower estimates in countries belonging to the African and Southeast Asian Regions. For 2 doses of measles-containing vaccine, compared with no vaccination, the median VE was 94.1% (IQR, 88.3%–98.3%). The VE of the

first dose of measles-containing vaccine administered at 9–11 months was lower than what would be expected from serologic evaluations but was higher than expected when administered at $12 months. The median VE increased in a subset of articles in which classification bias was reduced through verified vaccination history and laboratory confirmation. In general, 2 doses of measles-containing vaccine provided excellent protection against measles.

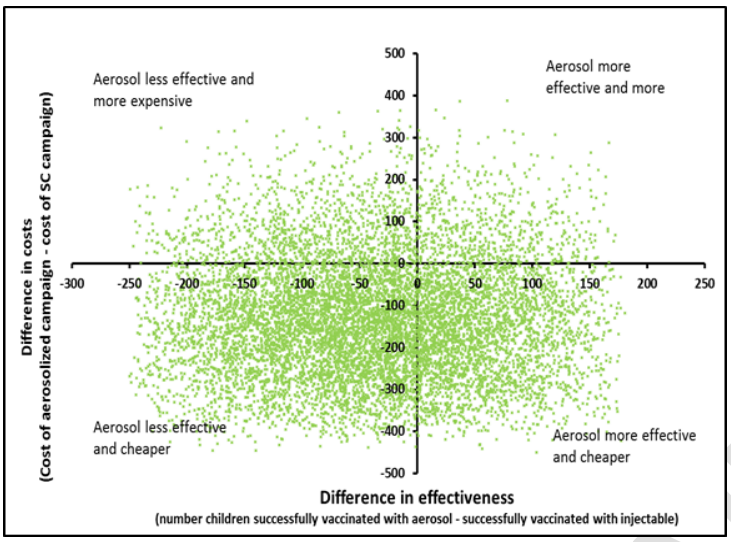
Evidence on the cost and cost-effectiveness of a measles aerosol vaccine

A study evaluated 4 new measles vaccine technologies[xix]: aerosol delivery, needle-free injection, inhalable dry powder, and early administration DNA vaccine included 4 major components: (1) identifying potential innovations, (2) developing transmission models to assess mortality and morbidity impacts, (3) estimating the unit cost impacts, and (4) assessing aggregate cost-effectiveness in United Nations Children's Fund countries through 2049. Results suggested that these technologies are projected to have a small absolute impact in terms of reducing the number of measles cases in most scenarios because of already improving vaccine coverage. Three (all but the DNA vaccine) are projected to reduce unit cost per dose by $0.024 (jet injector), $0.044 (aerosol nebulizer) to $0.170 (inhalable dry powder) and would improve overall cost-effectiveness. Each will require additional investments to reach the market. Over the next 40 years, the aggregate cost savings could be substantial, ranging from $98.4 million (jet injector), $154.1 million (aerosol nebulizer) to $689.4 million (inhalable dry powder). Authors concluded that these three new measles vaccination technologies under development hold promise to be cost-saving from a global perspective over the long-term, even after considering additional investment costs.

Another study used a modified Child Health and Nutrition Research Initiative (CHNRI) methodology for setting priorities in health research investments assessed the strengths and weaknesses of measles aerosol vaccine to decrease the burden of childhood pneumonia[xx]. A panel of experts expressed mixed feelings about an aerosol measles vaccine. The group expressed low levels of optimism regarding the criteria of likelihood of efficacy and low cost of development (scores around 50%); moderate levels of optimism regarding answerability, low cost of production, low cost of implementation and affordability (score around 60%); and high levels of optimism regarding deliverability, impact on equity and acceptability to health workers and end-users (scores over 80%). Finally, the experts felt that this intervention will have a modest but nevertheless important impact on reduction of burden of disease due to childhood pneumonia (median: 5%, interquartile range 1-15%, minimum 0%, maximum 45%). Aerosol measles vaccine is at an advanced stage of development, with evidence of good immunogenicity. This new intervention will be presented as a feasible candidate strategy in the campaign for global elimination of measles. It also presents a unique opportunity to decrease the overall burden of disease due to severe pneumonia in young children.

A study evaluated the incremental cost-effectiveness ratio of delivery of measles vaccine with an aerosol device as compared to delivery with traditional subcutaneous injection. The model used data from a Phase II/III RCT in India.[xxi] A model of the possible impact of reduced personnel costs for the delivery of the aerosolized on the 'Incremental Cost Effectiveness Ratio' of Aerosol vs. Injectable measles vaccine used the same base values as for the RCT of 2000 children. The researchers ran a simulation to estimate the incremental cost-effectiveness ratio (ICER) comparing the aerosolized to the injectable vaccine in the context of a very small vaccination campaign (n=2000, the size of the trial). The difference in the costs of the two approaches included the treatment of adverse events, estimated from the trial data, and salaries of the vaccinators, which depended on the time required to deliver the vaccine and the person who were to give the vaccine (i.e. nurse vs. non-health professionals). The difference in effectiveness

was varied by assuming that the coverage would vary between 70% and 90% for the injectable vaccine and between 70% and 99% for the aerosolized vaccine. The efficacy estimates are from the trial results.



Preliminary results are available Running this scenario resulted in a median ICER of $0.65 (95% CI: -$12.23; $12.61) in favour of the aerosolized vaccine. In summary, 53% of the iterations resulted in the aerosolized vaccine being less effective but cheaper, and in 29% of iterations resulted in a cheaper and more effective aerosol vaccine.
Work is ongoing to refine the assumptions and parameter estimates and to run the model using a larger population size and using even more realistic costs for the treatment of adverse events.

Assessment of the usability and acceptability of a measles aerosol vaccine

Four qualitative assessments of acceptability of the measles aerosol vaccine were conducted (Guyana, Oman, Burkina Faso and Vietnam). Methods included: focus groups (informal, semi-structured and flexible group dynamic), semi-structured interviews (Ministry of Health staff at national, regional and health facility level; community members: parents of children with target age groups, children, community leaders) and immunizations session observations. In general the results from these four studies supported the introduction of measles aerosol vaccine on the grounds that it is pain free, easy to use, less anxiety for parents, no injection safety concerns, easier waste management, potential for less AE and, “modernity". Different groups also raised concerns related to aerosol vaccination including: health workers were concerned about not providing the correct dose, parents/community members raised concerns about potential risk of cross-contamination and potential for measles aerosol vaccine to result in greater number of AE. Managers where reportedly anxious about potential costs of introduction and use of an additional route of administration. Although there are common findings, these are likely to be setting and background-specific and therefore caution should be exercised on the generalizability of these results.

During a Phase II/III trial in India a qualitative evaluation of the acceptability and usability of the measles aerosol vaccine device from the perspective of the vaccinators and the parents/guardians was conducted. In general the majority of vaccinators found that the device was: easy to assemble and operate, easy to place the vial in the dropper, easy to squeeze the dropper to obtain a defined number of drops, easy to store after use and, appeared easy to use and to function. Nearly 65% of the parents interviewed expressed their preference for the aerosol route of administration if both methods (aerosol or subcutaneous) were equally good to protect their child against measles. 38% of the parents whose child received the subcutaneous vaccine and 91% of the parents whose child received the aerosol vaccine expressed their preference for the aerosol.

Evidence on immunogenicity of Aerosol Measles Rubella and measles Rubella Mumps containing vaccines

There are an increasing number of studies where subjects were randomized to receive either MR or MMR vaccines. Below we summarized two studies to illustrate the progress and potential but this information is not comprehensive.

A study compared antibody responses and side-effects of aerosolized and injected measles vaccines after revaccination of children enrolling in elementary schools[xxii]. Vaccines for measles (Edmonston-Zagreb) or measles-rubella (Edmonston-Zagreb with RA27/3) were given by aerosol or injection to four groups of children. An additional group received Schwarz measles vaccine by injection. These five groups received vaccines in usual standard titre doses. A sixth group received only 1000 plaque-forming units of Edmonston-Zagreb vaccine by aerosol. The groups were randomized by school. Blood specimens were taken at baseline and four months after vaccination from randomized subgroups (*n*=28-31) of children in each group. After baseline antibody titres were controlled for the frequencies of fourfold or greater increases in neutralizing antibodies did not differ significantly between the three groups that received vaccine by aerosol (range 52%-64%); but they were significantly higher than those for the three groups that received injected vaccine (range 4%-23%). Mean increases in titres and post-vaccination geometric mean titres paralleled these findings. Fewer side-effects were noted after aerosol than injection administration of vaccine.

A trial to assess the reactogenicity and immunogenicity of combined measles and rubella (MR) booster vaccination, via aerosol and subcutaneous routes in 562 healthy children was conducted[xxiii]. Rates of rubella seroconversion and geometric means titers (GMT) were similar for both routes. Rates of measles PN seroconversion, GMT and measles ELISA post-vaccination seropositivity and seroconversion rate were each higher for aerosol vaccine (54%, 3928 IU/l, 99.6 and 98.8%), than for subcutaneous vaccine (7%, 866 IU/l, 92.2 and 82.4%) ($P<0.01$). Reactogenicity was higher for subcutaneous vaccines ($P<0.05$). This study reported that aerosol vaccine was more immunogenic for measles antibodies, and equally immunogenic for rubella antibodies. Aerosol vaccine was less reactogenic.

Potential additional research

During the 11th Meeting of the Product Development Group, PDG members noted that additional studies should be considered to further evaluate the measles aerosol vaccine, namely: immunogenicity in older children (e.g. >12 months of age) and; evaluation of the immune response using other immunological criteria including the assessment of the kinetics and duration of antibodies, and the differences in T cell responses. They also noted that shall individual countries consider moving forward with the licensure and introduction of the measles aerosol vaccine, other key factors besides the immunogenicity results should be included in the assessment such as: the incremental cost effectiveness analysis ; the evidence on its acceptability and usability; the potential performance of the measles aerosol vaccine in older children and in mass campaigns, its likely use for the administration of the second dose of measles vaccine and, the potential device improvements to facilitate its use in low resource environments. They recommended that the results of this trial should be considered in a context of a change in global measles immunization policies and goals, which encompasses recent recommendations for a widespread introduction of a second dose of a measles vaccine, primary vaccination at 12 months of age in countries with high levels of coverage or in the elimination phase and, recommendations for introduction of rubella vaccine.

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SAGE Working Group on Vaccination in Humanitarian Emergencies

Vaccination in Acute Humanitarian Emergencies: a Framework for Decision-Making

Revised Draft

23 October 2012

(Annexes 1, 2 and part of annex 3 removed. Complete version available on the web site).

Contents

1. Executive summary

1.1 Introduction

Humanitarian emergencies result in mass population movements and resettlement in temporary locations, overcrowding, economic and environmental degradation, impoverishment, scarcity of safe water, poor sanitation and waste management, absence of shelter, poor nutritional status as a result of food shortages, and poor access to health care. These risk factors place populations affected by a humanitarian emergency at risk of high morbidity and mortality from vaccine preventable diseases, and often decision makers must decide on use or non-use of one or more vaccines. The WHO SAGE Working Group on Vaccination in Humanitarian Emergencies reviewed current literature and practice experiences relating to decision making on vaccine use in humanitarian emergencies. There was limited widely accepted or generally used guidance for making decisions regarding vaccination in emergencies.

This decision framework document aims to provide an approach for deciding what vaccines, if properly delivered, would constitute high priority public health interventions in emergencies. They will assist the user to thoughtfully, deliberately, ethically and rationally determine whether or not the delivery of one or more vaccines to specific target populations during the acute phase of an emergency would result in an overall saving of lives, a reduction in the population burden of disease, and in generally more favourable outcomes.

The intended audience for the decision framework includes senior level government and partner agency officials who are expected to work together to reach a decision regarding the need of one or more vaccines in a given humanitarian emergency. It is not intended to be used by community level health workers given the level of detail and complexity included in the document.

1.2 Decision making process and organization of the document

Figure 1 provides a schematic representation of the decision making process that consists of three essential steps: 1) an assessment of the epidemiological risk posed by each potentially important vaccine preventable diseases within a given context; 2) a consideration of the properties of each vaccine to be considered for intervention; 3) prioritization of the importance of vaccination in relation to other urgent public health interventions; and careful consideration of key ethical principles and prevailing contextual factors.

1.2.1 Epidemiological risk assessment

In this section epidemiological risk of a vaccine preventable disease (VPD) is defined and a systematic, desk-based process for conducting a risk assessment for each VPD included within the scope of the framework following an acute emergency is presented. The risk assessment process considers both key cross-cutting risk factors (e.g. overcrowding, acute malnutrition) that have an effect on various VPDs, and other risk factors that have a very specific effect for each VPD (e.g. immunization status, geography, climate and season).

At the end of the assessment, depending on the level of risk attributed to the above factors, a decision is arrived at for each VPD: "Definitely", "Possibly", or "Do Not" consider for vaccination. The first two categories result in application of the next steps in the framework (Chapters 3 and 4) to reach a decision on a vaccination intervention. Furthermore, a characterization of the threat posed by these VPDs should be made (e.g. likelihood and timing of an epidemic, age groups affected).

1.2.2 Vaccine characteristics

Key vaccines characteristics that should be considered to reach a decision whether a vaccination intervention should be implemented include determination of vaccine efficacy using the recommended full schedule and efficacy using less than the full schedule; course of vaccine administration; contraindication and vaccine safety considerations; WHO prequalification status; formulation of the vaccine (e.g. most freeze-dried vaccine should never be kept longer than 6hrs after reconstitution and optimal use may require more staff training); vaccine presentation (e.g. multi-dose presentation); storage and cold chain requirements; cost of the vaccine; and whether sufficient quantities can be purchased locally or in the global market.

Other characteristics that assist in delivering successful high quality mass vaccination campaigns include a reasonably accurate estimation of target population, including age range, and prioritization of high risk groups or geographical areas. Other key considerations for optimal implementation include planning, logistics, social mobilization, informed consent and monitoring.

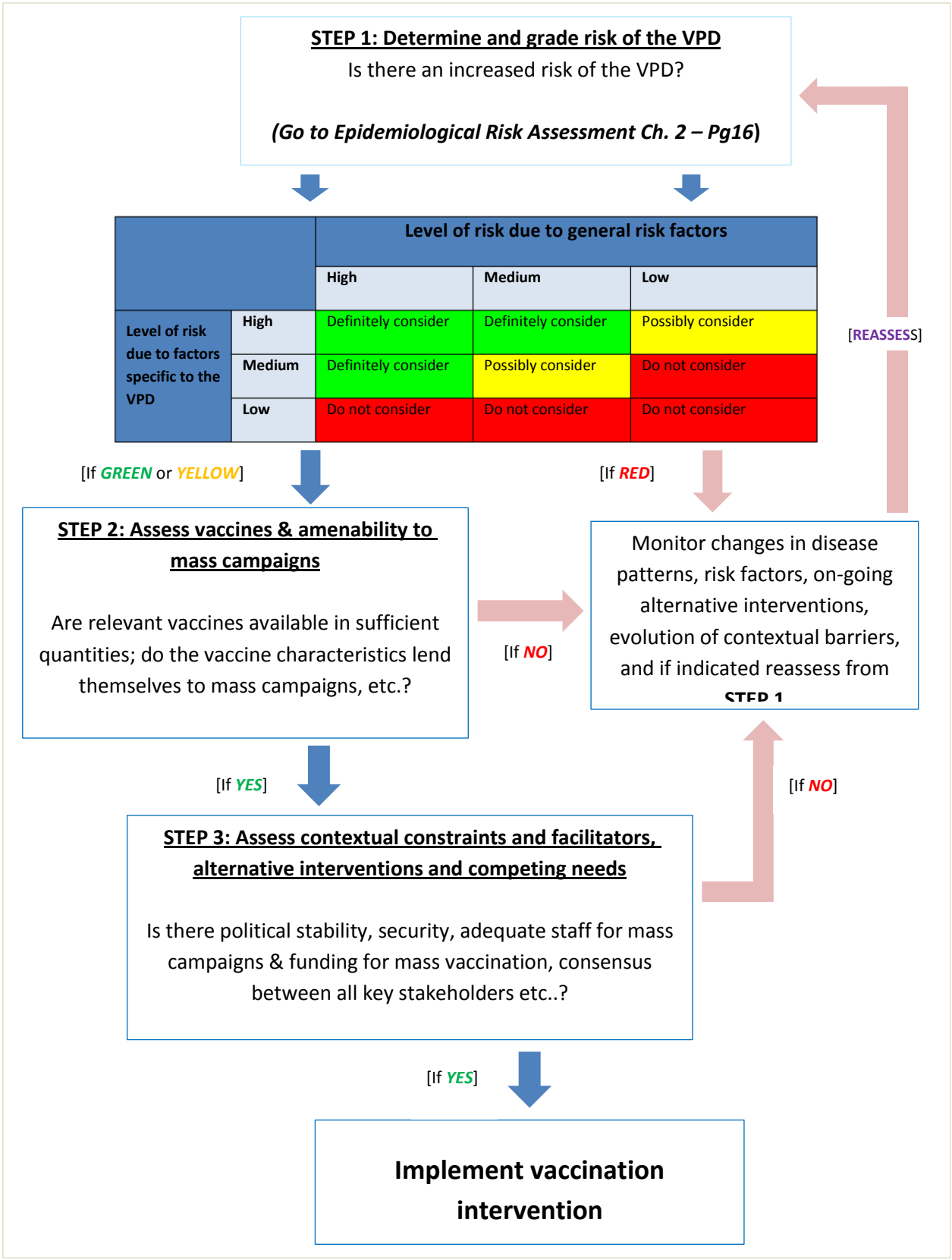
1.2.3 Contextual factors

Even if it is determined that a disease poses a substantial risk to the affected population and that the vaccine that protects against it has physical and biological characteristics that would be amenable to its use in a mass campaign, a challenging political context and competing priorities for limited resources, which are both common factors encountered in acute humanitarian emergency settings, influence the final decision to use a vaccine. However, if a decision to vaccinate is ultimately made additional issues may exist that require careful consideration including the desirability of add-on interventions to the vaccination campaigns; inclusion of host communities in the vaccination campaigns; and whether research should be conducted during the vaccination intervention.

1.3 Conclusion

This document provides key decision makers in the national ministries of health and international partner agencies with a systematic and comprehensive approach to decision making on use of vaccines in acute humanitarian emergencies, it also provides guidance on ethical concerns such as prioritization of interventions, targeting of high risk groups, equity, and informed consent. It is hoped that this document will make a useful contribution to optimal management of vaccine preventable diseases in acute humanitarian emergences, and ultimately to reduction in preventable morbidity and mortality commonly associated with acute humanitarian emergencies.

Figure 1: Decision making steps on vaccine use in acute humanitarian emergencies



2. Introduction

2.1 Background

Humanitarian emergencies, regardless of type or cause, have a number of common risk factors for communicable diseases including mass population movement and resettlement in temporary locations, overcrowding, economic and environmental degradation, impoverishment, scarcity of safe water, poor sanitation and waste management, absence of shelter, poor nutritional status as a result of food shortages, and poor access to health care. These risk factors are inextricably linked to excess risk of morbidity and mortality from vaccine preventable diseases, the reduction of which is the aim of public health interventions during crises.

2.2 Evidence review

In 2011, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) formed the SAGE Working Group on Vaccination in Humanitarian Emergencies to review evidence on vaccination decision making processes and considerations in order to identify current gaps and make recommendations to the SAGE.

The working group carried out a comprehensive review of literature to collate existing guidelines, ethical considerations, and documented experiences of use of vaccines in humanitarian emergencies in order to analyse key factors and methods involved in the consideration of vaccination during emergencies. The review was complemented by 6 case studies with the aim of capturing the multifaceted and often complex contextual and political considerations involved in such decisions, through the recounting of experiences by organizations who participated in such decision in the affected countries; this information was not well captured in the available literature.

Key lessons learnt:

- Formal decision making tools, guidelines or processes were not detailed. Guidelines were rarely consulted; in only four experiences out of 23 experience reviewed were actual guideline or tool cited as justification for implementation of vaccination campaign or not
- Only two decision making tools were identified among the 38 guidance documents reviewed. However, these were not sufficiently detailed to optimally support decision making process
- The phase of emergency in which vaccination was considered was vague and inconsistently defined, only measles, polio, and tetanus vaccines were reliably and consistently recommended for introduction “immediately” in humanitarian emergencies
- Epidemiological factors were considered important, but were not always reflected in the choice of antigens implemented. The most prominent considerations towards a decision to vaccinate were vaccine availability and available funding
- Political and contextual/security issues came through as strongly affecting the actual decisions or the ability to make decisions regarding use of vaccines in humanitarian

emergencies; where there was no central government such as Somalia as the lead decision maker, NGO's failed to reach a consensus regarding choice of vaccines and in some case implemented different vaccines for the same affected population

- Ethical considerations were least considered. Little guidance or experience was identified on how organizations manage decisions when needing to resolve prioritization of interventions, targeting high risk groups, equity, and informed consent

2.3 Aim

This decision making framework attempts to fill this void in the literature, by providing decision-makers with a more transparent and rigorous method for deciding on vaccination options in acute humanitarian emergencies. It provides a clear and consistent approach to assessing the local epidemiological risk of vaccine preventable diseases among a population affected by a humanitarian emergency; vaccine selection and characteristics to consider; and local contextual constraints that could further assist in effective and timely decisions regarding use of vaccines in emergencies.

This document is intended to provide a framework for thinking through the process of deciding what vaccines, if delivered pre-emptively at the outset of and emergency would constitute high priority public health interventions. Even though the principles and general approach may apply in cases when reactive vaccination should be considered during an outbreak in an acute emergency scenario, where detailed guidance already exist, these should be relied upon to guide outbreak response.

The decision making process is predicated on three essential steps: 1) an assessment of the epidemiological risk posed by each VPD within the scope of the Framework, within a given context; 2) a consideration of the properties of each vaccine to be considered for intervention; 3) prioritization of the importance of vaccination as a public health intervention in the context of the urgency of other public health interventions and intervention carried out in other sectors. Careful consideration of key ethical principles and contextual issues are key overarching considerations influencing the decision-making process.

The ultimate aim of this document is to assist the user to thoughtfully, deliberately, ethically and rationally determine whether or not the delivery of one or more vaccines to specific target populations during the acute phase of an emergency would result in an overall saving of lives, a reduction in the population burden of disease, and in generally more favourable outcomes than might otherwise be the case.

2.4 Guiding principles

Certain general principles have been borne in mind while developing the Framework:

- The Framework is not intended to supersede or contradict existing WHO guidance on vaccination and WHO guidance has been taken into account at all times
- The Framework recognizes that acute emergencies pose specific challenges to which guidelines developed for use in non-emergency settings may not apply. For example, acute emergencies may result in sudden changes in the burden of vaccine-preventable diseases, either in their incidence or their case-fatality ratio, or both, as well as in an increased risk of epidemics and changes in the usual geo-distribution patterns.
- Acute emergencies also tend to cause major disruptions in the delivery of all routine health services, including routine vaccination programmes and many of these services need to be addressed on an emergency basis and re-established as quickly as possible.
- Security issues as well as logistic challenges are likely to be much more important during an acute emergency, with important implications for population access to health services and for health provider to the population. This may affect the ability to deliver a recommended full series of vaccinations and forces a consideration of viable alternatives.

- In general, the objective of vaccination in an acute emergency is not to ensure the progressive increase of population immunity that would result in long- term protection against a given disease, but rather the rapid reduction of risk from a disease in order to protect a population during a relative short period of extreme vulnerability. In no circumstances should an acute emergency be seen as an opportunity to rapidly achieve the goals of a routine vaccination program. To the contrary, those goals should be set aside in order to use vaccines for one clear and present objective: to limit the number of excess preventable deaths for which the emergency might be responsible. For these reasons, strategies such as mass vaccination campaigns, expanded target age groups, and reduced courses for certain vaccines warrant greater consideration in acute emergencies than they might in other circumstances, whether or not routine vaccination services remain functional.
- The Framework covers only that period of time between the onset of emergency and when routine vaccination programs can be re-established.

2.5 Intended audience

The decision framework should be used by senior level government and partner agency officials who are expected to discuss in a small group over a period of days in order to reach a decision regarding the need to use one or more vaccines in a given humanitarian emergency. It is not intended to be used by community level health workers. Even though the final decisions should lie with appropriately designated officials of the Member State in which the emergency is occurring, it has frequently been the case in the recent past that emergencies either unfold in countries with non- or poorly- functioning governments or ones that are recognized as not acting in the best interests of the populations affected by the emergency. In those cases, a designated UN agency has frequently been recognized as having policy-making authority and may lead the decision making process. In general, vaccination interventions should be decided upon by consensus and this framework is meant to guide the discussions that result in that consensus.

2.6 Obligation to apply legitimate guidelines

National legal systems should guide the implementation of vaccination programmes in individual nation states; however they do not frequently accommodate humanitarian emergencies. In instances where national legislative frameworks are absent or dysfunctional, international human rights law dictates a duty of care to protect those in need of assistance. In these settings implementation should ideally be guided by legitimate international health guidelines.

WHO vaccination guidelines, including this framework, which are developed with consideration of a broad range of factors including the: epidemiologic features of the disease, clinical characteristics of the disease, vaccine characteristics, economic considerations, health system infrastructure, social impacts, legal and ethical considerations, are a legitimate tool for WHO member states, focusing both on the strength of evidence and the context in which the guidelines will be applied. Guidelines are of particular value in situations where: large numbers of people receive treatment or a preventive therapy (for example through mass vaccination campaigns); emergency situations where delays or sub-optimal approaches could result in severe detrimental outcomes; and health conditions, if poorly managed, have a high mortality rate or cause large-scale epidemics in vulnerable populations.

Although guidelines do not have mandatory status i.e. they are not legislated policy, if they are evidence-based and contextually appropriate they should be considered normative practice against which behaviours of authorities and health practitioners are judged.

2.7 Core ethical considerations

Decision-making on vaccine deployment should include ethical deliberations, as they are pertinent to multiple issues including vaccine availability, target groups, delivery strategies, surveillance and research during acute humanitarian emergencies. Ethical considerations central to these public health activities often arise from conflict between individual good and the common good and include beneficence (duty of care and the rule of rescue), non-maleficence, as well as distributive and procedural justice.

Beneficence (doing good): As the risk of communicable diseases during humanitarian emergencies is often extreme, the duty of care based on the principle of beneficence demands that effective vaccinations against these disease threats should be available to those at risk. A special obligation in addition to the duty of care is the rule of rescue; "the imperative that people feel to rescue identifiable individuals facing avoidable death". The obligation of beneficence is specifically determined by the urgency of the situation, severity of consequences if nothing is done, the ability to prevent such severe consequences and any sacrifice required by the responding individual or agency.

Non-maleficence (avoiding or minimizing harm): Vaccines that are likely to be considered in the acute phase of a crisis usually have established efficacy and safety track records, and thus harm is extremely unlikely. In addition to the benefits they offer to individuals who are directly protected against specific diseases, many vaccines confer additional community benefit through herd immunity that decreases the likelihood of outbreaks where vaccination coverage is high.

Distributive justice (fair allocation): This principle requires the fair allocation of limited resources, including vaccines if in limited supply. One arguably equitable way of distributing a limited supply of vaccine would be a lottery, but this does not take into account groups who are most vulnerable to illness or those who contribute most to transmission. The "best possible" way to distribute resources is often not perfect, as humanitarians can only do the "best they can" in the context of imperfect information, exceptional and unique circumstances. There should be explicit consideration of targeting distribution to high risk or high transmission groups or groups where other interventions, for example water and sanitation, cannot be rapidly deployed.

Allocation decisions require striking a balance between promotion of utility (maximizing the good to the community, smooth economic and societal functioning) and the achievement of equality and fairness. This is essential to promote public trust in vaccination programmes during crises. Egalitarian considerations require that allocation decisions should not be discriminatory and everyone should have a fair chance of receiving vaccination.

Procedural justice (transparent and accountable decision-making): This ethical principle requires transparent decision-making and participation of communities that are affected by the decisions. Sphere, the Humanitarian Accountability Partnership and the Active Learning Network for Accountability and Performance in Humanitarian Action encourage involving beneficiaries in the planning and implementation of aid programmes, codes of conduct for responding agencies, technical standards and the use of performance indicators and impact assessments.

2.8 Definition of acute emergency

The scope of the Framework is comprehensive – it applies to all age groups affected by an acute emergency and to all vaccine-preventable diseases. Because so many different kinds of emergency, including both natural disasters and man-made crises occur in so many places and have so many different characteristics, we have tried to define the situation(s) to which this Framework can be applied. All subsequent mentions of the term "acute emergency" should be understood to signify a situation meeting the criteria specified in the definition below:

This framework is designed to cover populations affected by acute emergencies. Although it may be applied at any point during the period over which acute conditions persist in a given population, its intended use is to guide decision-making on vaccination interventions immediately after the onset of an acute emergency, or during planning in anticipation of a possible or likely acute emergency.

Several definitions of what constitutes an acute (sometimes referred to as humanitarian) emergency have been proposed in the past, and different agencies employ varying classification and gravity benchmarking system. For the purposes of this framework, a single definition is used in order to maintain global equity and consistency. Furthermore, the definition aims to capture any circumstances that are known to result in an increased risk of vaccine-preventable diseases potentially warranting vaccination interventions different from or additional to those recommended for routine practice. Accordingly, an acute emergency is defined in this framework as the occurrence of one or more of the following conditions due to any reason (natural, man-made or a combination thereof):

1) **Sudden unplanned displacement** of a large proportion of the population away from the community of habitual residence and into any settlement (refugee or internally displaced persons' camps; host community; urban areas; other uninhabited areas), within the same country or across international borders;

2) Direct exposure of the civilian, non-combatant population to **new or exacerbated and sustained episodes of armed conflict** resulting in risk factors including reduced access to health care, disrupted water and sanitation, food insecurity, etc.;

3) Consistent and reliable evidence from food security and/or nutritional indicators (see note g) suggesting that **a sudden deterioration of nutritional status is impending or has already occurred,** above and beyond known seasonal fluctuations or situations of chronic poor nutritional status and/or food insecurity;

4) **Natural or industrial (including nuclear) disaster** resulting in temporary homelessness, disruption to critical public services (e.g. health care, water and sanitation, food deliveries, etc.), increased risk of injury and/or exposure to the elements for a large proportion of the population;

5) **Sudden breakdown of critical administrative and management functions,** within the public and/or private sector, due to any reason, resulting in large scale disruption of public health and related services (e.g. water and sanitation, housing).

The following notes accompany the above definition:

a) The conditions included in the definition merely aim to establish the need for potential application of this framework: this need is determined by the occurrence of exceptional risk due to vaccine-preventable diseases. The size of the affected population is not per se a criterion for defining an acute emergency, and relatively small populations should receive appropriate consideration to ensure global equity and maximise the potential impact of vaccination in all emergency-affected populations. However, the framework recognises that scenarios in which a large population assembles within a given site (e.g. a large camp) usually carry a higher risk of vaccine-preventable disease epidemics, warranting more intense interventions. By contrast, it is expected that emergencies featuring very small populations (e.g. communities affected by a localised event such as a landslide) result in limited epidemiological risk and can usually be addressed by available services.

b) Many acute emergencies occur in populations that are already affected by long-duration crises due to protracted armed conflict or displacement, and/or other factors such as food insecurity, frequent natural disasters, environmental decay etc. Whether an emergency does or does not occur against a background of chronic crisis is irrelevant for the purposes of the above definitions. However, this circumstance is explicitly taken account of in the framework, as different vaccination interventions may be warranted (e.g. in long-duration crises, pre-emergency vaccination coverage is usually low).

c) Emergencies are frequently defined and their gravity benchmarked in health terms by estimates of excess population mortality. Accordingly, credible evidence may arise showing that, over a recent period (e.g. within the last 6 months), the crude death rate (CDR: deaths per person-time, e.g. per 10 000 people per day) and/or under 5 years death rate (U5DR: deaths per person-time among children aged less than 5 years) have been greatly in excess of the non-emergency baseline (at least a doubling from the baseline is typically considered evidence of acute conditions). Typically, scenarios featuring such elevations in mortality will also be classifiable as acute emergencies based on one or more of conditions 1 to 5 above. If the cause of the observed elevation is not immediately clear, urgent investigation should be carried out to decide whether the scenario does indeed meet one or more of the definition conditions. Note that plausible baseline figures should be extracted from a recent census or reputable health surveys performed either within the population itself, or, if unavailable, from neighbouring populations or countries with a similar demographic profile. In scenarios where the emergency is occurring against a backdrop of long-duration crisis, mortality may already be elevated from the counterfactual baseline level that would be expected in the absence of a crisis. In such instances, the objective gravity of an emergency should

be benchmarked by comparing observed death rates to a reference baseline that reflects a period before the crisis began, or, if the crisis has lasted many years or decades, that is based on death rates in neighbouring non-crisis affected populations with a similar demographic profile. However, comparison with the recent mortality levels observed in periods of chronic crisis is also necessary in order to decide whether a sudden deterioration consistent with acute conditions has indeed occurred.

d) If any observed elevation in death rate is mostly attributable to a confirmed infectious disease epidemic, the epidemic should be accompanied by one or more of conditions 1 to 5 specified above (displacement, armed conflict, nutritional emergency, natural disaster or breakdown of the state) in order for the scenario to be classifiable as an acute emergency. An epidemic alone is not sufficient to consider that an acute emergency is occurring.

e) Pandemics of influenza and HIV/AIDS or possible future pandemics due to other diseases are not within the scope of this framework, unless they worsen underlying socio-economic and health conditions to such an extent that the population begins to experience one or more of the above conditions 1, 2, 3 or 5.

f) Terrorist attacks, defined as per UN Security Council resolution 1566 (2004) as "criminal acts, including against civilians, committed with the intent to cause death or serious bodily injury, or taking of hostages, with the purpose to provoke a state of terror in the general public or in a group of persons or particular persons, intimidate a population or compel a government or an international organization to do or to abstain from doing any act", are likewise outside the scope of this framework, unless they lead to one or more of conditions 1, 2, 3, 4 or 5 above.

g) A rapid deterioration in nutritional status (often referred to as a nutritional emergency) may be detected on the basis of food security indicators (e.g. staple prices, harvest sizes, household food consumption patterns), nutritional indicators (global [GAM] or severe [SAM] acute malnutrition prevalence) or a combination of both. Food security indicators provide early warning of deteriorations, while elevated SAM and GAM prevalences are typically seen only once a nutritional emergency is underway. Currently, prevalence estimates are typically computed among children 6-59 months old based on the 2006 WHO Child Growth Standards and weight-for-height indices, but the use of middle upper arm circumference, which may be less sensitive to regional body shape confounding, is increasingly advocated. For SAM and GAM specifically, various alert and emergency thresholds have been proposed. The WHO [*http://whqlibdoc.who.int/publications/2000/9241545208.pdf*] considers SAM and GAM prevalences of $\geq$ 5% and $\geq$ 15% respectively as indicative of a "critical" situation. In general, however, a context- specific classification of gravity that also considers underlying trends and concomitant disease risk factors is recommended. In several regions of the world (e.g. South Asia), alarming levels of malnutrition prevalence are noted on a yearly basis. These chronic situations require mostly long-term, developmental solutions, and do not fall within the scope of this framework. For the purposes of this definition, a rapid deterioration that occurs over a timeframe of weeks or a few months, above and beyond secular trends, should be considered indicative of acute conditions.

h) The definition is believed to encompass the large majority of potential scenarios, but there may be cases in which data and available information are imprecise, incomplete or controversial; in such instances, application of the definition should err on the side of caution, i.e. it is preferable to assume that an emergency is taking place. Furthermore, the rationale for the decision should be documented carefully.

i) While it may be relatively straightforward to decide when an acute emergency has begun, it is often difficult to determine when it has ended. For the purposes of this framework, an acute emergency may be considered to have ended or to be moving into a chronic phase if conditions that resulted in a suddenly increased risk of vaccine-preventable diseases have attenuated. Typically, this will occur when routine basic preventive and curative health services and other essential public services that impact public health, particularly water and sanitation provision, have been restored; food security has returned to pre-emergency levels; and shelter conditions are acceptable. Typically, the transition from the acute to the chronic or recovery phase is gradual and subtle. Deciding whether acute conditions have indeed ended therefore requires constant, careful reassessment of epidemiological risk as the emergency evolves. Furthermore, chronic, long-duration crises may relapse into acute emergency conditions: this eventuality should also be monitored vigilantly. In general, the framework is intended to address risk arising from acute conditions, rather than from long-duration crises: therefore, vaccine interventions arising from application of the framework should strive to reduce this risk to a level no higher than before the acute emergency began. However, it is expected that many vaccine interventions implemented during an acute emergency will have beneficial effects that result in improvements in health status even beyond pre- emergency levels

2.9 Beneficiary populations

In many large emergencies there are a number of different groups that require assistance. Some of those affected by the emergency may be living in urban areas, others in rural areas; some may be displaced, while others remain in situ; some may be sheltered in camps, others may be living in unorganized settings. The epidemiological risks, the vaccine-specific characteristics such as cold chain availability, and the contextual setting may be different for each emergency-affected population. Accordingly, many emergencies the Framework may need to be applied a number of times and the decision to proceed with a specific vaccination program may be different, and the details of any vaccination program that is implemented may vary.

In addition, the question of how to deal with populations that are not affected by an emergency but that live in close proximity to those that have been has often raised issues. Whether it refers to populations that are hosting refugees or to people exposed to a higher risk of vaccine-preventable disease because the circumstances around them have changed, it has become generally accepted policy to provide neighbouring populations with the benefits of any public health interventions that are designed for and implemented in emergency-affected populations. Accordingly, the benefits of vaccination programs designed to save lives and to reduce the risk of disease in emergency-affected populations should be extended to surrounding populations as well, to the extent that this is possible financially, logistically, and operationally. The guiding principle should always be: equitable access to vaccination for equal risk.

2.10 Vaccine-preventable diseases

Diseases are considered to fall within the scope of the Framework if the following conditions are met: 1) a WHO pre-qualified vaccine exists that can provide at least some protection; and 2) their burden may be increased as a result of an acute emergency. These diseases include those with vaccines in national routine immunization programmes; those that require seasonal vaccination interventions such as avian influenza and meningococcal meningitis mainly in the meningitis belt of Africa in countries where conjugate meningococcal vaccine has not been introduced; and those with new vaccines that may not be fully integrated in national routine immunization programmes. For this reason diseases such as Anthrax, Hepatitis E and rabies have not been included in the list.

There are also other diseases for which vaccines are in various stages of development and are anticipated to become available in the next decade (malaria, dengue, etc.). These have been omitted from the Framework as there is currently insufficient information regarding their characteristics and, of course; they do not meet the pre-qualification criterion mentioned above. In any event, the Framework, while providing specific guidance for existing vaccines, also provides a general approach that will be applicable to the use of any vaccine in an emergency, including new ones as they emerge.

Relative significance of the vaccine preventable diseases in acute humanitarian emergencies is also considered, and this may vary according to pathogen specific characteristics of respective microorganism; some may cause acute severe disease characterized by high morbidity with or without high mortality, while those at the other extreme may be associated with self-limiting diseases with limited complications (Table 1).

2.11 Cost of vaccines, stockpiles and vaccine donations

Depending on the agency, government or organization funding the intervention, the price of the vaccine itself may play a role in the decision-making process. Vaccine may be purchased directly from the manufacturer (in addition to supplies need for delivery) or through UNICEF Supply Division. UNICEF Supply Division is responsible for buying all vaccines and related items for global campaigns to eradicate polio, eliminate neonatal and maternal tetanus, and control measles. In addition, the Division procures vaccines for UNICEF-supported programs, and for GAVI. Procuring vaccines is complex. In recent years, the market has changed, owing to a growing divergence between the types of vaccines used in industrialized and developing countries. The unpredictability of funding is another difficulty.

Humanitarian emergencies occur frequently enough to warrant timely access to an assured vaccine supply for VDPs with severe outcomes including increased mortality. An obligation falls on global and local communities, including governments and non-government organizations, to facilitate this access.

The international donor community has established stockpiles for meningococcal disease and yellow fever with plans to put in place a similar stockpile for oral cholera vaccine. The stockpiles make use of revolving vaccine doses managed by the four partners, UNICEF, MSF, IFRC, and WHO, through an international coordinating group (ICG). When a country requests vaccines, ICG reviews the request and comes to a decision within 48 hours to deliver the vaccine within a maximum of seven days. The decision whether or not to approve a request is based on predetermined criteria namely epidemiological evidence for an outbreak, which includes laboratory confirmation, availability of an action plan for mass vaccination as well as adequate storage conditions.

Although stockpiles for certain vaccines exist, these stockpiles are not the only recourse for vaccine and there existence does not guarantee vaccine availability for intervention planning. The application process and procedures for procurement of vaccines through existing international stockpiles should be considered as a separate process and the specific guidelines consulted.

Donations of vaccines may form part of the strategy for timely access to vaccines in emergencies. Although WHO and UNICEF have noted five requirements to achieve "Good Donations Practice", including suitability, sustainability, informed key persons, supply and licensing, their joint statement recognizes that in exceptional circumstances, including emergency situations, these minimum requirements may not all be possible or even justified. The most important consideration is that the vaccine is responsive to the needs of the population from a public health perspective as determined by the senior level government and partner agency officials tasked to work together to decide on appropriate vaccine use.

Table 1: Vaccine preventable disease[1]

I.	**Vaccine in routine immunization programmes**
	1. Tuberculosis
	2. Mumps
	3. Rubella
	4. Pneumococcal disease
	5. Haemophilus influenzae type b
	6. Diphtheria
	7. Pertussis
	8. Rotavirus
	9. Yellow fever
	10. Tetanus
	11. Japanese encephalitis
II.	**Seasonal use vaccines**
	12. Avian Influenza
	13. Meningococcal disease (Polysaccharide vaccine)
III.	**New or under utilized vaccines**
	12. Hepatitis A
	13. Typhoid fever
	14. Hepatitis B
	15. Meningococcal disease (conjugate vaccine)
	16. Cholera
	17. HPV
	18. Varicella
IV.	**Special prevention and control initiatives**
	19. Poliomyelitis
	20. Measles

[1] Additional vaccine preventable diseases maybe considered as new vaccines become available

3. Epidemiological risk assessment

3.1 Chapter summary

This chapter outlines a systematic process for assessing the epidemiological risk of each VPD falling within the scope of the Framework, so as to come up with a short-list of VPDs for consideration in subsequent steps of the Framework. Epidemiological risk is defined here primarily in terms of excess mortality, but a high incidence of hospitalisations and disruptions to eradication programmes should also be considered. Risk may be due to epidemics but also to an exacerbated endemic pattern of disease, and may occur in the short as well as the long term, depending on the VPD. Furthermore, risk to host populations should also be assessed. All VPDs should be subjected to the risk assessment, but the process should require only a few days and not be delayed by missing information.

For each VPD, the risk assessment process consists of the following logical sequence of tasks:

1) **Grade the level of risk of the VPD resulting from the occurrence of one or more general risk factors** (high prevalence of acute malnutrition; young population and/or high birth rate; high HIV/AIDS burden; low access to curative health services; overcrowding; insufficient water, sanitation and hygiene) that have a cross-cutting effect on several infectious diseases:

    a) Determine which of the above general risk factors are occurring ("yes" or "no") in the given acute emergency scenario, based on available information; to aid this task, a worksheet containing key questions and suggested criteria for each risk factor is provided (Table 3). Sources of information to complete the worksheet are suggested in Annex 1. The yes-no classification obviously limits nuanced appraisal, but avoids complexity.

    b) Come up with an overall grading of risk due to general factors of "high", "medium" or "low". Risk should be graded as "high" if one or more of the general risk factors that are found to be present is highly relevant to the VPD; "medium" if none of the risk factors present is highly relevant to the VPD but at least one is moderately relevant; and "low" in all other situations. A priori knowledge about the global relevance of each factor to the VPD in question, irrespective of the specifics of the acute emergency in question, should be used here: for each VPD-general risk factor combination, a prescriptive classification of relevance into high, moderate, low and unknown is provided in Table 3.

2) **Grade the level of risk of the VPD due to additional factors that have a specific effect on the given VPD.** Though not all relevant to each VPD, these factors may include population immunity; local burden of disease; geography, climate and season; levels of sexual violence; and incidence of injuries (Table 5). VPD-specific worksheets are provided in Annex 2, containing suggested criteria and questions to consider for each relevant factor. A qualitative approach is recommended to synthesize the information in each worksheet into an overall level of specific risk, again graded as "high", "medium" or "low". A rough algorithm to help with the grading is proposed (Annex 2), and sources of information for each factor are suggested (Annex 1).

3) **Come up with an overall decision for each VPD:**

   a) Combine the "high", "medium" or "low" grading of general and specific risk (tasks 1 and 2) in a suggested matrix (Table 2) so as to classify the VPD into the mutually exclusive categories of "definitely", "possibly" or "do not consider" for vaccination: only VPDs to "definitely" or "possibly" consider are short-listed and carried over to the next step of the Framework.

   b) For each VPD short-listed, characterize the type of threat (e.g. epidemic vs. exacerbated endemic), timing (e.g. how soon excess deaths could occur) and likely age profile. This characterization should be used later in the Framework to define when and whom to vaccinate. Guidance for each disease is provided in the VPD-specific worksheets (Annex 2).

The chapter describes the above tasks in detail. However, the suggested grading procedures are not inflexible, and best judgment as well as specific information from the emergency in question should always be used as a guide. In all cases, risk assessment decisions need to be thoroughly documented.

3.2 General considerations

3.2.1 Purpose of the risk assessment

Before appraising different options for vaccination interventions, it is crucial to carry out a systematic epidemiological risk assessment of the acute emergency so as to identify VPDs for which specific vaccination interventions should indeed be considered. The step by step risk assessment process outlined in this chapter should result in a short-list of VPDs to be carried over into the subsequent step of the Framework (Chapter 3). If this risk assessment has been carried out accurately and equitably, short-listed VPDs should be those that carry the greatest epidemiological risk in the specific emergency scenario being evaluated. A final determination of whether to implement a vaccination intervention against these VPDs, however, is only made after full consideration of all three steps in the Framework process.

Risk assessment must be carried out systematically for every VPD within the scope of the Framework, lest the short-list be unduly influenced by personal bias or a priori considerations about which diseases are likely to be important and which vaccines appropriate. The suggested risk assessment process may result in short-listing VPDs for which vaccination has never or very rarely been attempted in emergencies (e.g. pneumococcal disease), or for which vaccination is unlikely to be an appropriate choice of intervention (e.g. tuberculosis). However, it is important at this stage to let the classification of risk be guided solely by need (i.e. how much excess mortality

could occur), and not by consideration of prior experiences in emergencies or of the feasibility, effectiveness, cost and opportunity of providing a specific vaccine. All of these parameters are considered systematically in further steps of the Framework.

3.2.2 The meaning of risk in the context of this document

As discussed in the Introduction, the overriding metric by which disease risk should be assessed is preventable deaths, since mortality reduction is the primary aim of emergency public health interventions. For some diseases, diminished pressure on curative health services (particularly inpatient facilities) as a result of a decreased incidence of severe disease cases is also a desirable, albeit secondary outcome of vaccination.

Furthermore, in certain emergency situations excess risk due to VPDs that are the focus of ongoing eradication programmes (e.g. polio and measles) may also be thought of in terms of potential regional or global setbacks in the eradication effort that could occur as a result of the emergency, unless vaccination interventions are implemented. This risk should be considered secondary to that of excess mortality, but where appropriate the risk assessment suggests instances in which it could warrant prioritizing a given VPD. Note that WHO regional offices routinely carry out polio importation and outbreak risk assessments: these should be consulted in the event of an emergency.

For specific VPDs (cervical cancer due to HPV, hepatitis B, tuberculosis) most excess risk will manifest well after the end of an acute emergency. For example, an armed conflict may result in a large number of female victims of sexual violence acquiring HPV, but the latency period of HPV-associated cancer means that these women will only experience excess disease and mortality later in life. For hepatitis B a similar dynamic would occur, and in addition women victims could also go on to transmit the virus during childbirth, resulting in further, future, deaths among their children. The Framework does value these lag effects of acute emergencies on health. Balancing the value of preventing a death in the immediate period after the emergency's onset (e.g. by vaccinating against cholera) against the value of preventing a death later in life or among a second generation of affected persons (e.g. by vaccinating against hepatitis B) is extremely difficult, has epidemiological, economic and ethical dimensions, and would generally require much more time and information than will be available for this risk assessment. So as to circumvent this complexity, the Framework assigns an equal value to deaths in the here and now and deaths that will occur later in time, as long as both can be attributed to excess risk due to the emergency.

Lastly, it is important to note that the above risks may arise due to explosive epidemics, but also as a result of exacerbation in the baseline endemic pattern of disease resulting from increased incidence, increased probability of developing disease once infected, and/or higher case-fatality (CFR). The Framework process only distinguishes between these mechanisms insofar as the threat of epidemics may require a particularly urgent vaccination response.

3.2.3 Timing of the risk assessment

Just as the Framework as a whole, risk assessment within the context of this document is intended to be a rapid, desk-based exercise to be completed within a few days as part of emergency preparedness or during the very first few days after the emergency begins (see Introduction).

While assessing each VPD falling within the scope of the Framework may appear time-consuming within the context of a rapid, high work-rate relief operation, it is expected that a small team of experienced assessors having access to the country's disease surveillance and vaccination programme information should be able to complete the risk assessment in a few days, thereby not appreciably slowing down emergency response planning. As suggested in Annex 1, in nearly all scenarios some information will be unavailable or questionable; this should not delay the Framework process, and, if desk-based avenues to rapidly obtain this information are exhausted, best judgment assumptions should be used to fill information gaps. Nevertheless, a balance needs to be struck between the urgency to move forward with vaccination interventions as soon as possible, and the minimal time required to complete a well-reasoned, informed and documented risk assessment which will ultimately be more beneficial than hurried, uninformed decisions.

Due to the dynamics inherent in any emergency, risk due to any VPD may intensify or lessen as the emergency evolves, or information may become available that warrants a revision of the risk assessment. Risk assessment should thus be an ongoing process: an update of the risk assessment for each disease should be performed at least every three months, or as soon as possible if important new information arises on any VPD or the general situation radically shifts, warranting immediate action (e.g. if disease surveillance systems indicate the onset of an epidemic, or if the nutritional situation suddenly deteriorates). In practice, this update will be quicker than the original risk assessment, as the answers to only a few questions are likely to change from one update to the next.

3.2.4 Risk assessment for host populations

While risk assessment will generally be carried out only for the actual emergency- affected population, in cases where a forcibly displaced population finds refuge within a host community (e.g. in a city or in a rural district), or where the two are living in proximity to each other, it is important to also assess risk for the latter, and consider vaccination interventions accordingly.

Risk assessment for host populations should be done separately from that for the displaced population, and can be somewhat streamlined so as to consider the main potential threat, namely introduction or re-introduction of a VPD that is not circulating in the host population, but that may be carried by the displaced population: this is particularly relevant for diseases that are subject to an elimination or eradication programme, such as measles and polio, or that are known to cause explosive outbreaks, such as cholera or meningococcal meningitis. A major factor to consider when assessing this threat is the immunity level of the host population (see below), and whether this is likely to be high enough to prevent an epidemic (i.e. afford herd immunity), even after considering changes in population density due to the influx of the displaced (note that crowding increases the immunization coverage requirement for herd immunity) and the degree of mixing between the host and displaced populations.

3.3 The risk assessment process

This section provides an overview of the risk assessment process for each VPD. Detail on each task in the process is provided in subsequent sections. The risk assessment process should result in a classification of each VPD within one of the following three categories:

- Definitely consider: the VPD has the potential to be one of the leading causes of mortality, and/or to cause a major epidemic (thousands of cases, hundreds of deaths); thus, a specific vaccination intervention against this VPD should definitely be appraised in the next step of the Framework.
- Possibly consider: the VPD will probably not be a leading cause of mortality, but nonetheless could cause a considerable number of excess deaths and/or a large outbreak (hundreds of cases, dozens of deaths); thus, a vaccination intervention against this VPD could be considered in specific circumstances, based on an assessment of competing priorities and other opportunities for control. In particular, vaccination against this VPD could be opportunistically coupled with that against VPDs falling in the above category, e.g. if dosage schedules and target age groups are compatible. Vaccination interventions against this VPD should thus also be appraised in the next step of the Framework.
- Do not consider: the VPD is very unlikely to cause considerable excess mortality or an outbreak consisting of more than a handful of cases; a vaccination intervention against this VPD should thus not be considered further in the Framework, unless an update to the risk assessment results in a change to this classification.

The above classification is reached by running each VPD through a two-dimensional matrix (Table 2). The two dimensions of the matrix are:

1) How high the risk of the VPD is assessed to be as a result of key general risk factors (high prevalence of acute malnutrition, young population and/or high birth rate, high HIV/AIDS burden, low access to curative health services, overcrowding, insufficient water, sanitation and hygiene) that may or may not be present, and, if present, have cross-cutting effects on various infectious diseases;

2) How high the risk of the VPD is assessed to be as a result of additional risk factors that are very specific to the VPD in question, including levels of population immunity to the disease, local burden of disease, geography, climate, season and other factors.

For both dimensions, a simple “high” / “medium” / “low” grading system is adopted. For example, in a given acute emergency scenario the presence of several general risk factors (e.g. overcrowding and insufficient water, sanitation and hygiene) could result in the risk of cholera being graded “high”, the risk of Japanese encephalitis being graded “low” and the risk of diphtheria being graded “medium”. Consideration of specific risk factors for each (e.g. levels of vaccination coverage and the location of the emergency) might result in a grading of “medium” for cholera, “high” for Japanese encephalitis and “low” for diphtheria. The resulting classifications would therefore be “definitely consider” for cholera, “possibly consider” for Japanese encephalitis and “do not consider” for diphtheria.

Table 2: Epidemiological risk assessment classification for any VPD.

		Level of risk due to general factors		
		High	**Medium**	**Low**
Level of risk due to factors specific to the VPD	High	Definitely consider	Definitely consider	Possibly consider
	Medium	Definitely consider	Possibly consider	Do not consider
	Low	Do not consider	Do not consider	Do not consider

Furthermore, for each VPD that is carried over into the next step of the Framework, the overall classification should be accompanied by a qualitative characterization of the VPD's expected manifestation (timing, epidemic potential, age groups most affected), so as to aid in determining the priority level of each vaccination intervention, the time window of opportunity for vaccinating pre-emptively, and which population groups to target.

Accordingly, for each VPD the risk assessment process consists of the following tasks:

1) Grade the level of risk due to general risk factors as "high", "medium" or "low", based on their occurrence and relevance to the given VPD:
   a) Determine whether one or more of the general risk factors is occurring in the given acute emergency situation, based on available information and by completing a suggested worksheet featuring key questions;
   b) Use a priori knowledge about the expected effect of these risk factors on the VPD, and a suggested decision rule, to come up with a grading.
2) Grade the level of risk due to factors specific to the given VPD as "high", "medium" or "low", based on available information: to guide this task, "worksheets" specific to each disease are provided.
3) Come up with an overall classification for each VPD:
   a) Based on the "high", "medium" or "low" grading of general and specific risk (tasks 1 and 2), use Table 2 and the suggested classification system to determine whether the VPD should be considered in the next step of the Framework;
   b) For each VPD short-listed (i.e. to "definitely" or "possibly" consider), characterise the risk in terms of type of threat, timing and age groups affected. This characterisation should be used later in the Framework to help prioritise vaccination interventions and define their key parameters.

The remainder of this chapter provides guidance on how to carry out the above tasks.

3.4 Task 1: Grade the level of risk due to general risk factors

3.4.1 Task 1.a: Determine the occurrence of general risk factors

In acute emergencies, much of the excess burden due to VPDs is attributable to a few key general risk factors that have a biological, behavioural or environmental basis; have a proximate causal relationship with disease; may already be influential before the emergency or may become exacerbated as a result of the emergency; and can affect the risk of transmission, progression to disease or CFR for a variety of VPDs. While in reality the intensity and effects of these risk factors fall along a continuum from negligible to very high, for simplicity this Framework only classifies them as present or not, based on the answer to several questions listed in a general risk factor worksheet that assessors should systematically go through (Table 3).

While a few quantitative decision rules based on relevant indicators are suggested in the worksheet (where possible, based on existing guidelines such as the Sphere Project), *these are meant for guidance only*. Robust data may not always be available within the timeframe of the risk assessment to determine whether each risk factor is occurring, and the risk assessment should not be delayed whilst data are obtained. Therefore, the classification of each should primarily be qualitative, guided by judgment, consideration of available evidence and understanding of the context. For example, in some regions (e.g. South Asia), malnutrition exhibits a predictably seasonal pattern; therefore, the period in which the emergency occurs should thus also be considered (e.g. a flood occurring at the outset of the seasonal "hunger gap"); and a high prevalence of malnutrition should be classified as occurring if there is evidence of a deterioration above and beyond expected seasonal trends.

Annex 1 suggests possible sources of pre-existing data to assess each general risk factor. Given that this Framework can apply to diverse types of emergencies, not all general factors will be immediately relevant to all situations.

Table 3: Worksheet for determining the occurrence of key general risk factors

Risk factor	Main effects on VPDs	Key questions to ask	Possible indicators to consider
High prevalence of malnutrition	Increased risk of infection, disease progression and case-fatality.	Is there evidence of a nutritional crisis, either already established or unfolding? Is there an unusually high prevalence of acute and/or chronic malnutrition, among young children or the general population?	• Prevalence of acute malnutrition among children 6-59m old ≥ 15% (global) or ≥ 3% (severe) measured within the last 3 months, above and beyond seasonal levels • Average nutritional intake or food ration < 2100 kcal per person per day • Deteriorating food security indicators (e.g. price of staple foods or livestock; yield of last harvest)
Young population and/or high birth rate	Greater pool of susceptibles for VPDs mainly affecting children. Higher herd immunity threshold.	Is there a high number of children? Are births rapidly accumulating?	• Proportion of children aged under 5y ≥ 15% • Crude birth rate ≥ 30 per 1000 people per year
High HIV/AIDS Burden	As for acute malnutrition.	Do persons living with HIV/AIDS make up a high proportion of the population? Is there low access to highly active antiretroviral therapy (HAART), or have HAART programmes been disrupted by the emergency?	• HIV sero-prevalence ≥ 15% and • HAART coverage < 50% or probably falling due to the emergency
Low access to curative health services	Increased case-fatality for all VPDs. Increased risk of some vertically transmitted VPDs (neonatal tetanus, hepatitis B).	Has the emergency resulted in reduced access to quality outpatient and inpatient curative health services, and if so to what extent?	• <1 basic health unit per 10 000 people or <1 hospital per 250 000 people • High proportion of non- functional or inaccessible health facilities
Overcrowding	Increased transmissibility of airborne droplet and faecal-oral VPDs.	Is the population living in a large camp or a high-density urban community? How close together are residential structures?	• Size of camp > 10,000 people • < 3.5 m2 covered floor area per person
Insufficient water, sanitation and hygiene	Increased transmissibility of faecal-oral diseases (mostly) and airborne droplet diseases.	Does the population have inadequate access to water, sanitation and hygiene (e.g. soap, health promotion)?	• < 15 L water available per person per day • > 20 persons per latrine • <250g of soap per person per month

3.4.2 Task 1.b: Come up with a grading of risk due to general factors

43 summarizes very approximately what is known about the relevance of each general risk factor considered in the above worksheet to specific VPDs, irrespective of context and region of the world (i.e. all else being equal). The classification of relevance in Table 4 should be interpreted as follows:

- ***High relevance:*** globally, a large proportion of the total disease burden due to the VPD is attributable (whether proximately or distally) to this risk factor: removing the risk factor would result in a substantial decrease in the burden of this VPD. Obvious examples falling within this category are insufficient water, sanitation and hygiene and cholera; high HIV/AIDS burden and tuberculosis; overcrowding and measles.
- ***Moderate relevance:*** globally, a moderate proportion of the total disease burden is attributable to this risk factor: addressing the risk factor is not among the top priorities to control the VPD, but nonetheless its removal would probably bring about some decrease in burden (for example, insufficient water, sanitation and hygiene and influenza).
- ***Low relevance:*** there is evidence that, globally, this risk factor has a small or no effect on the burden of the VPD: removing the risk factor would make a negligible difference to attributable burden. For example, a high birth rate does not influence the burden of typhoid fever.
- ***Unknown relevance:*** there is insufficient evidence on the role that this risk factor plays in the global epidemiology of the VPD.

While Table 4 broadly reflects existing evidence, links between some risk factors and disease are tenuous or not yet investigated. In some cases, an attempt was made to grade the relevance using plausibility reasoning: for example, VPDs that are very similar in their interaction with the host and share the same route of transmission were assumed to have a similar link to certain risk factors. Low access to curative health services is almost always a risk factor for higher CFR, but its relevance was graded here according to the relative impact of treatment: for example, in most settings the absence of treatment would not greatly increase mortality from a yellow fever outbreak, given that there is no effective cure.

It is obvious that contextual factors can heavily modulate these general associations: for example, the relevance of a young population to measles would indeed be high in a setting with insufficient vaccination coverage (VC), but less so where VC is adequate. These factors are considered later when assessing specific risk for each VPD. The risk assessment is designed to ultimately output a classification decision for each VPD that balances both general and specific risk factors.

Having classified the relevance of each risk factor to the VPD being analyzed, one may come up with an overall grading of risk attributable to general factors, for that VPD. To do this, simple categories of "high", "medium" and "low" risk are proposed, as follows:

- High if one or more of the general risk factors that are found to be present according to the worksheet in Table 3 is highly relevant to the VPD in question, according to Table 4;
- Medium if none of the risk factors that are present is highly relevant to the VPD but at least one is moderately relevant;
- Low in all other situations.

In the example of measles, if the emergency features any of the general factors considered to be highly relevant to its epidemiology (high prevalence of malnutrition, high birth rate, low access to curative services, overcrowding), the general risk grade would be "high". If the features only factors considered to be moderately relevant (high HIV/ AIDS burden or insufficient water, sanitation and hygiene), the general risk grade would be "medium". If none of the general risk factors are present, the grade would be "low".

Table 4: Relevance of each general risk factor to each VPD

	High prevalence of malnutrition	Young population and/or high birth rate	High HIV/ AIDS burden	Low access to curative health services	Overcrowding	Insufficient water, sanitation and hygiene
Airborne-droplet						
Diphtheria	Moderate	Low	Unknown	Moderate	High	Low
Hib disease	Moderate	High	Moderate	High	Moderate	Moderate
Influenza	Unknown	High	Moderate	Moderate	High	Unknown
Measles	High	High	Moderate	High	High	Moderate
Meningococcal meningitis	Low	Low	Moderate	High	High	Low
Mumps	Low	High	Low	Moderate	Moderate	Low
Pertussis	Moderate	High	Low	Moderate	High	Low
Pneumococcal disease	High	High	High	High	High	Low
Rubella	Low	Moderate	Low	Moderate	Moderate	Low
Tuberculosis (meningitis and disseminated disease)	Moderate	Low	High	High	High	Moderate
Varicella	Moderate	Moderate	High	Low	High	Moderate
Faecal-oral						
Cholera	Moderate	Low	Unknown	High	High	High
Hepatitis A	Unknown	Low‡	Low	Low	Low	High
Polio	Low	Low	Low	Low	High	High
Rotavirus	Moderate	High	Low	High	Moderate	Low
Typhoid fever	High	Low	Moderate	Moderate	Moderate	High
Vector-borne						
Japanese encephalitis	Unknown	Moderate	Unknown	Moderate	Low	Moderate
Yellow fever	Moderate	Low	Unknown	Low	Low	Moderate
Other or mixed						
Hepatitis B	Unknown	High	High	Low	Moderate	Low
HPV (Cervical cancer)	Low	Low	High	Low	Low	Low
Tetanus†	Low	High	Low	High	Low	High

† A high birth rate and low access to health services are relevant because they can result in a higher incidence of perinatally transmitted cases.

‡ In fact, a young population and/or birth rate actually reduces disease burden, as infection tends to occur earlier in life, when it is mostly asymptomatic or results in mild disease.

3.5 Task 2: Grade the level of risk due to factors specific to each VPD

Next, risk factors that are specific to each VPD are considered in detail. These risk factors are listed separately as they are very contextual and only apply to the individual VPD: for example, risk assessment for Japanese encephalitis should consider whether the emergency is occurring in an area with known transmission of this virus; for typhoid fever, local evidence of previous outbreaks is an indication of higher risk.

The range of specific factors that may be assessed is shown in Table 5, along with key questions to ask. However, not all factors are relevant to each VPD (e.g. climate and season are not known to influence the risk of HPV transmission or disease progression), and the importance of each varies disease by disease. For this reason, **VPD-specific worksheets** are provided in Annex 2: these contain guidance on how to grade risk arising from each specific risk factor relevant for the VPD, based on information available.

Table 5: Specific factors to be assessed for different VPDs

Factor	Relevance	Key questions to ask	Possible data to consider
Population immunity	Major determinant of individual and community risk of transmission.	• Is a significant proportion of the population at risk currently not immune, either through vaccination or natural exposure? • Is the current VC likely to afford herd immunity or a high level of individual protection? • Is there a risk of introduction or re-introduction of the VPD in a naïve or partly naïve population?	• Latest VC data (both routine and campaigns) • Occurrence, size and mortality of past outbreaks in the population
Burden of disease	Indicates the importance of the VPD in the given setting either before or since the emergency, all else being equal.	• Is the region within the known transmission boundaries of the VPD? • What is the mortality attributable to the disease in the country? • Have epidemics previously occurred? • Has an outbreak been confirmed since the emergency began?	• Occurrence, size and mortality of past outbreaks in the region • Burden of disease estimates • Ongoing disease surveillance • Global disease risk maps
Geography, climate and Season	Certain VPDs only occur in given settlement zones (e.g. Japanese encephalitis mostly affects rural areas) or seasons (e.g. meningococcal disease); some carry a higher burden where people are exposed to cold (e.g. Hib disease).	• Does the setting where people are living favour transmission? • Is the population exposed to cold temperatures? • Is the population exposed to indoor air pollution? • Will the acute emergency unfold during the high transmission season?	• Climate data • Cooking fuel source
Levels of sexual violence	High incidence of sexual violence can result in increased transmission of HPV and hepatitis B.	• Has the emergency resulted in high incidence of sexual violence?	• Security reports • Hospital data
Incidence of injuries	A large number of untreated injuries entails a high risk of tetanus, particularly among males and if VC is low.	• Has the emergency resulted in a large number of people with injuries? • Is treatment available and prompt for these injuries?	• Field reports • Evidence from similar emergencies • Hospital data

In the example of measles (see Annex 2, measles worksheet), three factors (population immunity, burden of disease, and geography/climate/season) are considered to be relevant for consideration. Criteria are provided for each based on assumed vaccination coverage, recent outbreaks, and seasonality.

Each VPD-specific worksheet should be completed as accurately as possible given available information. An overall grading of risk arising from specific factors should then be made for the VPD on the basis of this worksheet, according to "high", "medium" and "low" categories. Unlike for general risk, no clear-cut decision rule is suggested, recognizing that the various combinations of the different specific factors constitute too many scenarios to realistically capture in simple classification rules. Instead, a **qualitative** approach informed by all available evidence and sound, objective judgment is recommended. An algorithm to aid this qualitative decision is suggested in Annex 2.

3.6 Task 3: Assess the overall risk of each VPD

3.6.1 Task 3.a: Decide whether the VPD should be considered further

Based on the result of tasks 1 (general risk grading) and 2 (specific risk grading using the disease-specific worksheets), a classification for each VPD should be reached using Table 2. The classification system is not meant to be inflexible, and careful judgment, illuminated by all available evidence, should be exercised to occasionally deviate from it, while erring on the side of caution when uncertainty precludes a clear decision. Written documentation of the rationale for each classification decision is essential to ensure transparency and buy-in from stakeholders, or learn from mistakes if the risk assessment turns out to be faulty.

3.6.2 Task 3.b: Characterize the expected risk for VPDs to be considered further

For VPDs that are carried over into the next step of the Framework, a brief, qualitative description of the expected risk should be made in terms of the following parameters:

- **Type of threat:** Would excess mortality be mainly due to the endemic pattern of the VPD or to an epidemic, or could a mixture of the two occur? For some diseases, this will be clear-cut: for example, in most parts of the world meningococcal meningitis presents mainly an as epidemic threat, while hepatitis A follows a very endemic (i.e. stable) pattern. For many diseases, however, a mix of endemic and epidemic patterns may occur depending on the setting: for example, typhoid fever cases presenting as part of the normal endemic pattern of the disease could experience excess mortality due to malnutrition or reduced access to health care, but a bona fide epidemic of typhoid fever could also occur due to water and sanitation problems.

- **Timeframe:** For each VPD, one should indicate how quickly excess mortality could manifest itself, and/or the window of opportunity for intervening through preventive vaccination. Some general guidance follows:
  - Diseases that manifest in an endemic pattern may cause excess mortality from the very start of an emergency: for example, pneumococcal pneumonia mortality, already high in many countries before an emergency, will immediately increase if the emergency severely curtails access to health care or if nutritional status suddenly deteriorates;
  - An epidemic of faecal-oral and airborne-droplet/direct-contact spread diseases can occur as soon as the first couple of weeks following the onset of an acute emergency, particularly if immune status is low from the very onset.
  - Provided the vector and pathogen are already present, an epidemic of vector-borne VPDs will usually take a few weeks longer to manifest (about one and a half months at least after the emergency), because of the time taken for vectors to breed and the latency periods of the pathogen in both vectors and humans to reach completion.
  - In protracted emergencies, epidemics of VPDs may become increasingly likely as existing vaccination programmes deteriorate and the pool of susceptible individuals increases.
- **Age-specific burden:** Which age groups would be at highest risk of infection and/or disease? Would the age range experiencing excess mortality due to the VPD be the same as the typical target age group for vaccination, or would additional age groups probably also experience excess mortality?

The disease-specific worksheets provide additional guidance on how to characterize the above parameters.

4. Considerations for Vaccines

4.1 Chapter summary

In this chapter, key terminologies are defined at the beginning of the chapter, vaccine characteristics are examined in order to determine suitability for mass vaccination in a humanitarian emergency setting, and the chapter also examines important determinants of quality mass vaccination campaigns.

4.1.1 Vaccine characteristics

Key vaccines characteristics that should be considered to reach a decision whether a vaccination intervention should be implemented or not include determination of:

- Vaccine efficacy at full schedule and efficacy at less than full schedule
- Administration course of the vaccines
- Vaccine presentation (e.g. multi-dose presentation)
- Contraindication and vaccine safety considerations
- WHO prequalification status
- Formulation of the vaccine, for examples, most freeze-dried vaccine should never be kept longer than 6hrs after reconstitution and optimal use may require more staff training
- Storage and cold chain requirements
- Cost of the vaccine, and whether sufficient quantities can be purchased

4.1.2 Mass vaccination campaigns considerations

Characteristics that would ensure successful and high quality mass vaccination campaigns include:

- Estimation of target population including age range
- Determination and prioritization of high risk groups or geographical areas
- Effective execution of the key implementation components including planning, logistics, social mobilization, monitoring and informed consent

4.2 Chapter introduction

The output of the risk assessment step is a list of VPDs that should be **definitely** or **possibly** considered in this next appraisal. Within our defined context, vaccination for the VPDs identified has the potential to save lives and limit disease but the use of these vaccines is not straightforward. An essential component of vaccination interventions in emergencies has to do with the actual implementation of the vaccination intervention: the characteristics of the vaccines themselves and how they are delivered. Before establishing a set of criteria to consider in this next step, it is important to define some common terminology.

Mass vaccination refers to the process of setting up vaccine clinic sites in traditional or non-traditional health care locations in order to administer vaccines to an unusually large number of people in a short period. There are several approaches to the implementation of mass vaccination campaigns but they can be grouped into two main categories: strategies where individuals come to sites to be vaccinated and the other where the vaccine is brought to the individual. Examples of the first type of strategy include vaccination at sites where individuals work, reside, or gather, to receive the vaccine. These may also be specifically set up sites for vaccination when an appropriate facility does not exist. Examples of this approach include vaccination sites in hospitals, health facilities, schools, markets and religious establishments. The second approach involves bringing the vaccine directly to individuals using mobile vaccination teams or door-to-door strategies where individuals may be vaccinated within their homes.

Despite the temptation to simply implement a vaccination campaign, with the assumption that any vaccine delivered does more benefit that harm, appropriate planning is needed to ensure that the campaign achieves its aims of reducing mortality. Mass vaccinations pose specific challenges, due to their objective of reaching a large number of people over a short period, and as a result necessitate extensive forethought. A key component of this decision is which antigens to include in the intervention and definition of the target population.

4.3 Classification of Vaccines

Vaccines are made using several different processes. They may contain live viruses or bacteria that have been attenuated (weakened or altered so as not to cause illness); inactivated or killed bacteria or viruses; inactivated toxins (for bacterial diseases where toxins generated by the bacteria, and not the bacteria themselves, cause illness); or merely segments of the pathogen (this includes both subunit and conjugate vaccines). Although there are differences between types of vaccines, the key difference is whether the vaccine is a live attenuated vaccine or inactivated. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.

Live attenuated vaccines are produced by modifying a disease-producing (“wild”) virus or bacterium in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. The majority of live attenuated vaccines contain live viruses. Live attenuated vaccines produce immunity in most recipients with one dose, except those administered orally. However, a small percentage of recipients do not respond to the first dose of an injected live vaccine or rarely immunity waned (such as measles, or MMR) and a second dose is recommended to provide a high enough level of immunity in the population.

Inactivated vaccines can be composed of either whole viruses or bacteria, or fractions of either. These vaccines cannot cause disease from infection, even in an immunodeficient person. Inactivated antigens are less affected by circulating antibody than are live agents, so they may be given when antibody is present in the blood (e.g., in infancy). Fractional vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include toxoids (inactivated bacterial toxin) and subunit or subvirion products. Most polysaccharide-based vaccines are composed of pure cell wall polysaccharide from bacteria. Conjugate polysaccharide vaccines contain polysaccharide that is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine. Protection from a live, attenuated vaccine typically outlasts that provided by a killed or inactivated vaccine. However, there are overall advantages and disadvantages to live and non-live vaccines (Table 6). These factors will need to be considered in the decision-making process.

Table 6: Key advantages and disadvantages of live and inactivated vaccines

Type of Vaccine	Advantages	Disadvantages
Live attenuated	• Contain a version of the living microbe that has been weakened so that it does not cause infection • Elicit strong cellular and antibody responses and often confer long-lasting immunity with only one or two doses.	• People who have damaged or weakened immune systems—because they have undergone chemotherapy, have HIV, or are pregnant for example—cannot be given live vaccines. • Antibody from any source (e.g., trans-placental) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure) • Live attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be handled and stored carefully. • Need to be refrigerated to stay potent
Inactivated	• Usually do not require refrigeration • Can be easily stored and transported in a freeze-dried form	• Stimulate a weaker immune system response than live vaccines • Take several doses, or booster shots, to maintain a person's immunity

A major consideration is the time it takes a vaccine to provide protective immunity. This means, how many days, weeks or months after a full course of vaccine (number of doses required, which may be age specific) can the immune response be considered to be protective. In addition to host-related factors such as age, pregnancy and any immune-system related disorders, the time to protection is a function of the vaccine classification. Generally, as discussed in Table 6, live vaccines require only one or two doses and elicit a strong protective effect. For live vaccines, protection is generally considered to be acquired within a two-week window. Few inactivated vaccines induce high and sustained responses after a single dose, even in healthy young adults. Inactivated vaccines usually require at least two doses, spaced 3 to 4 weeks a part. This means, that in the case of some inactivated vaccines, there may be at least a delay of 4 weeks from first vaccine dose to a degree of protection conferred and in some instances even longer. Alternately, in individuals who previously received one or more doses of the same vaccine, protective immunity may be generated quickly (between 4-7 days).

As multiple vaccines may be delivered as a part of the same intervention, it is important to consider that provided separate syringes and different injection sites are used, all inactivated vaccines can be administered concurrently. Live vaccines may also be delivered concurrently. If not delivered concurrently, an interval of at least 4 weeks should be used. This means that if two live vaccines are to be delivered during the intervention, they should be delivered at the same time, or one delivered and then a second 4 weeks later. This is to ensure a sufficient immune response is mounted without interference. The exception to this rule is oral polio vaccine (OPV) (see Annex 3) which may be given without consideration of other live vaccines.

When several doses of vaccine are required, similar vaccines (same antigen), but produced by different manufacturers may be used interchangeably while following the any changes in specified number of doses or contra-indications.

4.4 Vaccine characteristics

Understanding vaccine characteristics and mode of vaccine delivery plays an essential part in determining whether a specific antigen is appropriate to include in the intervention. Each situation is unique, and it is impossible to determine one strategy valid for all situations, but there are certain common elements to be examined concerning the vaccines themselves. Consideration of these factors helps provide important information for whether vaccines for VPDs identified in the risk assessment can then be delivered. Tables 7 and 8 provide an overview of the criteria, their definitions and additional considerations.

Table 7: Definitions and considerations of vaccine characteristics concerning conferred protection

Criteria	Definition	Considerations
Efficacy[1] at full schedule	Protection and duration of immunity assuming entire course is given (e.g., 68% two-dose efficacy in adults lasting for 2 years).	It goes without saying that higher efficacy vaccines are preferable to lower efficacy vaccines.
Efficacy at less than full schedule	Efficacy of vaccine at less than full course (e.g., 50% one-dose efficacy in adults)	Although a full course of vaccine should be delivered, this is not always possible due to many different factors. Particularly in emergencies, populations may not be accessible due to security constraints or population movement making delivery of multiple dose vaccines difficult.
Exclusion criteria	Groups or ages to which the vaccine is contra-indicated (e.g., children under age 1 year or pregnant women or women of child-bearing age)	This criterion is important in the implementation of mass vaccination campaigns where the exact age of an individual may not be known or when only certain segments of a population may benefit from vaccination.
Administration Course	Schedule of administration and age (e.g., dose 1 at age 9 months and 2nd dose at 12 months or above)	The administration course of a vaccine (schedule) should be considered in the decision-making process. With population movements, or erratic access to populations it may not be possible or realistic to deliver the full-course of recommended vaccine. There may only be means or access for one mass vaccination campaign and therefore only one dose of supervised delivery. The possibility of non-delivery of subsequent doses (less than the full schedule) or doses delivered by another means (oral doses delivered at home) should be weighed in terms of their risks and benefits. It is also important to investigate whether there are different possible schedules for each specific antigen (e.g., one dose under the age of 1 year and a booster dose later in life)
Safety[2]	WHO prequalification	Vaccines which are prequalified have an assurance of safety. There may be specific age ranges or underlying conditions for which the vaccine is not considered safe.

[1] Efficacy in preventing disease in the immunized populations is obtained from controlled studies, where immunization is delivered under ideal conditions. In those trials, vaccines tend to be given to healthier people who may present a better immune response. Efficacy may also vary depending on age, nutritional status, co-infections, and other factors. As a result, the efficacy of some vaccines is lower in "real world" settings. Vaccine effectiveness is a different concept that describes protection under programmatic implementation and reflects the performance of the vaccine in the actual target population. Programmatic factors like errors in vaccine storage, preparation or administration, which can impair the vaccine, are more likely to occur in the field. Therefore, vaccine effectiveness is usually lower than vaccine efficacy. It is also important to note that although there may be instances of overdose (e.g., 3 doses instead of 2 in an individual with prior vaccination but undocumented vaccination status) the risks of overdose are minimal or absent.

[2] Vaccines being considered should meet international standards of quality and safety and have obtained WHO prequalification. However, under certain circumstances vaccines may be approved for use in a specific country, while not having WHO prequalification status. The decision to use vaccines not meeting WHO prequalification is a difficult and delicate decision which necessitates expert advice. Although the safety of a vaccine is assessed by clinical trials before it is considered for use, trials may not capture rare adverse events. Information on safety needs to be assessed carefully, weighing the risks against the benefit of the vaccine. The risk: benefit ratio may vary between situations, but in emergencies, where morbidity and mortality is high, the expected benefits may far outweigh the risk of adverse events.

In addition to the criteria listed above concerning protection conferred by the vaccines themselves, there are important factors to consider concerning the formulation, presentation, storage and cost of vaccine that play a role in deciding whether to include a vaccine in the intervention.

Table 8: Definitions and considerations of vaccine characteristics concerning formulation and delivery

Formulation	Combination, lyophilized, liquid	The formulation of the vaccine is important in terms of the need for trained staff to deliver the vaccine. Most freeze-dried (lyophilized vaccines) do not contain preservatives and consequently must not be kept more than the manufacturer's recommended limit and never longer than six hours after they are reconstituted. Death due to toxic shock syndrome has resulted when reconstituted live virus vaccines kept longer than the recommended period have been injected. Liquid injectable vaccines contain preservatives that prevent growth of bacterial contamination. Should contamination take place within the vial, the action of these preservatives prevents any increase in bacterial growth over time and actually decreases the level of contamination.[1]
Presentation	Individual or multi-dose presentation (vial/ampoule, prefilled injection device, vial size) and volume (e.g., glass multi-dose vial at 11 cm3)	Like formulation, the vaccine presentation plays a role in determining the type and number of staff required for delivery and the storage necessary for the vaccines.
Storage	Temperature and conditions of storage (e.g., 2-8°C in a dark room)	Cold-chain capacity for storage should be considered and if not present, whether there is the capacity to mount a cold-chain in the affected area.
Stability	Duration vaccine can be exposed to ambient temperatures (e.g., one month at 37°C). The Vaccine Vial Monitor (VVM) should be used as a guide.	The vaccine vial monitor (VVM) is a small sticker that adheres to the vaccine vial and changes colour as the vaccine is exposed to heat. The colour of the sticker tells health workers whether the vaccine is bad—or can be safely used for immunization.[2]
Current Price	GAVI listed price	

[1] See *http://www.path.org/vaccineresources/files/Getting_started_with_VVMs.pdf* for additional information on VVMs.

[2] See *http://extranet.who.int/ivb_policies/reports/open_vials.pdf* for additional information on open vial guidance for specific antigens.

In addition to those listed in Table 8, there are a few additional important considerations.

First, vaccines currently introduced or used in a country's routine program afford important benefits. There may be additional supply of the vaccine present in the country and more importantly less quantifiable factors, such as healthcare workers' and the populations' familiarity with the antigen can have important benefits. The same is also true for vaccines for seasonal diseases, such as meningitis where countries may have prior experience in conducting campaigns. Inversely, introducing vaccines into an intervention when they are not currently a part of EPI (for example, oral cholera vaccine) is important to consider. Vaccines that have not yet been introduced into EPI, or are not destined for inclusion in EPI, may necessitate a different approach in terms of procurement and community acceptance.

Second, supply (availability) is an important factor and ideally should be investigated prior to crises. Manufacturers have different capacities for supply of vaccine. The delay expected for the vaccine supply to be delivered may play a role in the decision-making process. Whether a vaccine is currently incorporated into a country's routine program and the supply of vaccine available are context dependent. Third, the shelf life of the vaccine is also important to consider. This is the time before the vaccine expires, or can no longer be considered protective under ideal conditions. Vaccine shelf-life may play an important role in insecure contexts, where plans for a mass vaccination campaign may need to be delayed or may occur in a "stop-start" manner with the target population receiving vaccination at irregular intervals over a long period of time. If the vaccine is to be incorporated into the intervention, it is important to note the time the shelf-life of the vaccine (this may vary by lots) to ensure that there is enough time for delivery.

4.5 Vaccine specific information

The previous tables present an overview of the different vaccine and delivery factors, which are interlinked and should then be used to consider which vaccines are feasible to implement through mass vaccination. The characteristics listed previously vary by vaccine and are presented in Annex 3. In some cases, evidenced-based information is not yet known or scanty for specific antigens. This is especially the case concerning protection afforded by delivery of less than the full-course of vaccine. As a result, in situations where there may not be sufficient access to the target population due to logistic and/or security constraints, the decision to include a vaccine in the intervention where a priori there is a realistic possibility of not delivering a full course of vaccine, the decision is not straightforward. The decision needs to balance known information about vaccine efficacy at full-course and best available information at less than full-course balanced with the potential benefits of vaccination. Further, if less than a full-course is delivered, this information should be documented during the intervention.

4.6 Deciding Which Vaccines to Consider

For each of the VPDs you have listed as definitely or possibly consider, this next step in the process aims to help determine whether the vaccine for each of these VPDs could be included in the intervention. In order to do this, what vaccines, for who to use them, where to use them and how to use them need to be considered. In order to do this, the first step is to answer the question: Does a vaccine exist for the VPDs listed as definitely or possibly to consider? Appendix X provides a list of available vaccines and their characteristics. If the answer to this question is yes, then the first step is to determine the target population for vaccination.

4.6.1 Age group targeted for vaccination and estimated doses needed

Estimating the target population is required to determine the number of vaccine doses needed. This information should have been obtained during the risk assessment step where the denominator (at-risk population) has been determined. Target populations vary by antigen, with some vaccines necessitating the vaccination of wide age ranges, and others a smaller subset. The target age range for vaccination should be based on the expected age distribution of cases or if the outbreak as started on the age profile of early cases. This information is then used to provide an estimate of the expected number of vaccines that are needed to afford protection to those at risk of death.

For example, it is recommended that all individuals 6 months to 15 years of age be vaccinated for measles (see WHO/UNICEF guidelines). However, for other antigens, such as an intervention where meningococcal disease has been identified as a high-risk, then the target group for vaccination includes those aged 2 to 30 years (see Annex 3). In both cases however, the target age range needs to be adapted based on both the epidemiologic risk and pragmatic issues. The target population at risk for all candidate vaccines should be listed in the following way:

Table 9: Worksheet for each vaccine corresponding to VPDs definitely and possibly to be considered for the intervention

Vaccine for VPD priority	Expected age distribution of cases (at-risk population)	Denominator estimate for at-risk population (include host population here if relevant)	Doses per person	Number of doses of vaccine needed (population	Estimated number of vaccines +10% wastage + 10% buffer
Ex. Measles	Ex. 6m to 15 years	Ex. 100,000	Ex. 1	Ex. 100,000	Ex. 100,000+10,000 + 10,000 = 120,000 doses

When different population figures are available, or the expected age distribution of cases is not known, it is better to over-estimate, rather than to under-estimate, the target population for vaccination. This means that the highest number available should be used as a precautionary measure.

4.6.2 Determining when and where to vaccinate

It is important to remember that all vaccination interventions identified from the risk assessment should be implemented as soon as possible. Failure to deliver these interventions is a sub-optimal intervention. However, this said there may be logistical, political or ethical barriers to delivering all interventions simultaneously. In these cases, interventions should be prioritized in terms of urgency (which interventions are most important to do first).

Prioritizing vaccine interventions in terms of urgency should be based on the epidemiologic risk. Vaccines for VPDs indicating a high risk should be prioritized in terms of the timing of their delivery. Following the same example of measles and meningococcal disease, measles vaccine should be delivered immediately due to the high risk of an epidemic. Meningitis vaccine, if the emergency occurs outside of the meningitis season, could be postponed until operational concerns are addressed. Although in most cases, vaccination will be considered an urgent need.

An additional criterion for prioritization includes geographic area. Certain high-risk populations may be located in a particular area. These include very crowded sites or areas with no access to safe water or sanitation or population sub-groups, such as children under the age of 5 years. Selecting specific geographic areas for vaccination needs to be balanced with ethical issues. Vaccination of only specific geographic areas may create tension among the population and leads to the need to justify why only certain groups are eligible for vaccination while others are not.

When looking at Table 10, when risk groups overlap, and they will do most of the time, it may be better and more efficient to deliver all vaccine interventions at the same time, rather than organizing individual campaigns for each antigen. Delivering multiple antigens at the same time may require better organization in terms of setting up the logistics of the campaign, but have the important advantage of maximizing the opportunities of delivering vaccine to individuals in one planned intervention.

4.6.3 Considerations for VPD priorities and inclusion of vaccines in the intervention

At this point in the process, after consulting the appendix listing available vaccines and filling in the worksheet in Table 10, there may already be some vaccines addressing the VPD priorities established in step one of this guide that may not be feasible. Considering responses in the worksheet, for each vaccine, the following questions are to be considered:

- Does a vaccine exist for the VPD?
- Is the vaccine available in sufficient quantities for those who need it including buffer stock for wastage and errors in the denominator?
- What are the cold chain requirements for the vaccine and is the cold chain adequate?
- Does the mode of delivery require skilled staff and can such staff be mobilized in adequate numbers for the campaigns?
  - Injectable vaccines require trained staff to deliver the vaccines. The number of vaccines an individual vaccinator can deliver varies by context and by the number of antigens to deliver. Different agencies and actors have different experience in delivering mass vaccination interventions and the experience of the staff plays a role in human resource needs. There are several guidelines available on planning of vaccination campaigns including estimation of needed human resources.
- Can injection safety and waste disposal be assured throughout the duration of the intervention?
  - If not considered from the start, poor injection safety can result in transmission of infection, eroding of donor and community confidence and most importantly, a lack of impact in terms of reduction of morbidity and mortality. For specific information on injection safety and waste disposal, refer to WHO/V&B/02.10 for specific information.

If the answer to any of the above questions is “no” for any of the antigens under consideration, then they should not be considered further.

The output for this section should be a list of the priority VPDs and their associate vaccines with the following information:

1) Timing of the intervention (are all antigens to be delivered simultaneously? Phased?)
2) Age range for each antigen
3) Size of target population for each antigen
4) Dosage and quantity of vaccine for each antigen

4.7 Implementation considerations

Although mass vaccination campaigns in acute emergencies are an intervention rather than a program, they still require the same components as other mass campaigns such as supplementary immunization activities. Mass campaigns have four key components that ensure campaigns are successful in reaching the target population:

1) **Planning:** A clear and comprehensive plan on how to reach populations and budgeting accordingly. Who will do what, at both the macro level and micro level, is clearly laid out and everyone is aware of their responsibilities. This stage also entails the decision of which antigens to include.

2) **Logistics:** The logistics of having the vaccine reach individuals is perhaps the most important component. Ensuring the safe transportation route of the vaccine from procurement through to injection must be ensured and clearly identified. Human resources must also be available for the campaign.

3) **Social mobilization:** Getting word of impending vaccination to a population is essential to ensure vaccines are delivered. Social mobilization may be limited only to word of mouth, but when circumstances permit, includes other formal and informal channels. Social mobilization also serves to provide the population with important information about the risks and benefits of vaccination.

4) **Monitoring and evaluation:** During a campaign, monitoring provides an essential component to trouble-shoot potential problems and provide information on the implementation of the campaign. After mass campaigns have been implemented and the target population has received vaccine, documentation of successes and failures is a critical step. The follow-up phase capitalizes on the experience to provide lessons learned and identify additional needs of the target population. The follow-up phase also serves as an important step in terms of documenting the rationale of the emergency intervention.

4.7.1 Planning mode of delivery

As discussed previously, mass vaccination can be divided into two main strategies: vaccine delivery from fixed sites and from mobile posts (mobile teams), or both.

1) **Fixed sites:** These sites are located at permanent health facilities or health posts. Vaccination can be provided at the facilities for at least the whole day (sometimes at night) throughout the duration of the campaign. These sites may also be storage areas and sites for vaccine distribution to mobile teams. Additional fixed sites, which may be specifically constructed as semi-permanent structures if necessary, may be located at schools, churches, mosques, bus depots, roadblocks, markets, village squares, etc. Villages and settlements with small populations may also be served through such temporary sites.

2) **Mobile posts:** Mobile posts, of mobile vaccination teams, move from community to community reaching populations that are living in hard–to–reach areas, which may not have access to a fixed site. Mobile teams may set up a vaccination posts at a fixed site for a few hours or a day, and then move the post to a new site after completing their task. A mobile vaccination team may also vaccinate from door-to-door or shelter-to-shelter.

Fixed sites have the advantage that they can be identified in advance (schools, health facilities) or constructed in the form of temporary structures. Fixed sites also provide additional advantages in terms of providing a secure shelter for vaccination teams and an identifiable location for the population to participate in the intervention. Further, due to their fixed nature, many people can be vaccinated in a short period. However, as fixed sites necessitate the population displacing to receive the vaccine, not all individuals may be able to reach the site to be vaccinated, due to restricted movement, lack of awareness about the intervention or simply not wanting to travel.

Mobile vaccination teams, which may either bring the vaccine to groups of people, or deliver the vaccine from door-to-door, have the advantage of bringing the vaccine directly to the target population. Vaccination teams bring the vaccine in vaccine carriers and vaccinate individuals where they are located. The advantages with mobile teams are clear in that difficult to reach populations may be accessed. However, the use of mobile teams requires additional resources as less of the population can be reached per day.

In most situations, a combination of fixed and mobile vaccination sites is necessary. Both strategies, fixed and mobile, should be identified in the planning stage and may require creative solutions to provide sufficient opportunities for the target population to be reached. In areas spanning a large geographic area, urban and densely populated areas may best be served by fixed sites, ensuring that a large portion of the target population can be vaccinated quickly. In a rural area, mobile teams may be more appropriate to reach the population.

In emergencies it is essential to consider different non-traditional places for vaccination and opportunities. This may mean that sites are opened during non-traditional hours and dispersed across the geographic area so that individuals across the area are able to access a site. A classical program based strategy may not be the most appropriate, but considering opportunities such as vaccination at registration if the emergency entails refugees, or vaccination within other interventions, such as food distributions, should also be considered. It is essential to remember that mass vaccination campaigns in emergencies need to be accomplished quickly and are not a replacement for routine programs.

4.7.2 Logistics

Campaign logistics entail the development of a specific and concrete plan to ensure that vaccines are delivered to individuals. There are numerous guidelines on how to plan campaigns, which include information on how to design an operational strategy. These include information on the size of vaccination teams, how to set up a fixed and mobile vaccination site and include information on how to calculate needs. This logistic exercise should try to come up with valid and realistic estimates of the resource needs based on the target population and the reality on the ground concerning existing and locally available resources – human as well as material. The goal of this guide is not to provide specific information on how to set up an operational strategy, but rather to ensure that logistic considerations are an integral part of the planning process.

4.7.3 Social Mobilization

Social mobilization activities, even in an emergency, are needed to ensure that the community is aware of impending vaccination activities. They need to be planned to enlist support from the population and include mobilization of support of religious and community or group leaders, groups that may be functioning in the area and other informal support networks. Contact with individuals and groups should be made prior to vaccination, asking for their views and support that they can provide so that they participate in the process. Leaders may be given specific tasks, which may include providing human resources, passing the word within their communities or even announcing the event formally. Clear messages therefore need to be designed and disseminated through methods suitable to reaching populations by those that can motivate or influence them. Specific activities will depend on each situation and may range from walking though the community, radio messages, religious gatherings and publicity by village or group leaders or town criers. Some countries have utilized mobile phone companies successfully to mobilize communities through the mass dissemination of text messages. Efforts should be tailored to reach underserved populations or special populations. These may include minority groups or marginalized populations, religious communities that may resist public health interventions, nomadic/migratory groups, refugees, elite groups and their staff.

4.7.4 Monitoring

Formal documentation of emergency response is often not a part of the standard operating procedure of many emergency organizations. Although documentation of interventions is often difficult, monitoring of interventions and documentation of specific decisions made is a critical component of ensuring that lessons are learned from interventions and ensuring that populations are reached. Monitoring provides an important tool to keep track of intervention progress and provides an opportunity to adjust plans if needed. This includes both quantitative and qualitative aspects of campaigns. The quantitative component of monitoring includes careful tallying and recording of doses administered, vials utilized, and doses wasted; and reviewing of the number of doses administered against the expected to be delivered on a daily basis. The qualitative component addresses observation of vaccination teams in action, with specific emphasis on the cold chain and handling of vaccines and injection practices. Empowering supervisors or teams with the necessary means of communication, where immediate and effective action to address issues related to vaccine stocks, injection safety, rumours and resistance, etc., will be crucial to the success of the campaigns.

4.7.5 Informed consent

Obtaining valid consent from individuals prior to offering medical intervention is an obligation created by the ethical principle of respect for the autonomy of persons. Under non-emergency circumstances, the consent process is often comprehensive and therefore time consuming. The nature of the consent process during an emergency will differ from a routine health setting. Information on risks and benefits must be communicated to target populations in sufficient depth, given the severity of the situation, to facilitate an informed decision on receiving the vaccine, while recognizing that health literacy levels, including a basic understanding of germ theory and immunology, will be limited in some affected communities.

The amount of information provided will need to be tailored if the process places others at risk by creating avoidable delays. However, any questions raised should be adequately and accurately addressed. This implies that those immunizing should be able to answer common questions relating to the diseases targeted, benefits offered, potential adverse events, follow up and alternative options available if vaccination is refused. They should also have the ability to refer undecided individuals with additional legitimate questions to others with particular expertise, although this requirement may not always be feasible and should not prevent programme implementation in an emergency setting. Group education prior to vaccination roll-out, or in the waiting space or line, using visual aids and other appropriate media may assist in providing necessary information in a more time efficient manner.

Vaccination should be voluntary unless compulsory vaccination is essential to "prevent a concrete and serious harm". Where there is an imminent threat of infectious disease that poses a significant risk of substantial harm to a large number of persons, individual liberties may be justifiably curtailed. The Siracusa Principles endorsed by the United Nations Economic and Social Council state that: "Public health may be invoked as a ground for limiting certain rights in order to allow a State to take measures dealing with a serious threat to the health of the population or individual members of the population. These measures must be specifically aimed at preventing disease or injury or providing care for the sick and injured."

Respecting the autonomy of persons implies that individuals may exert their choice to decline vaccination even though public health policy may encourage widespread vaccination. The right to autonomy is however not absolute. When members of a community decline to participate in a vaccination programme, they are risking not only their own health but also the health of others who either may not have access to vaccination or are unable to be vaccinated for medical reasons. Even if herd immunity is achieved, such people may be considered "free riders" because they benefit from herd immunity without contributing to herd immunity themselves. This places an unequal burden of the risks of adverse events from vaccination on those who participate.

As children are at particularly high risk in humanitarian crises, where there is substantial risk of significant harm to the child, parental authority may be overruled on the basis of the child's best interests.

5. Contextual considerations and competing needs

5.1 Chapter summary

This chapter adds to the preceding ones by factoring in to the Framework considerations that go beyond the diseases and the vaccines. It takes into account some of the political and social properties of the environment in which an emergency is unfolding. It suggests that proceeding with a vaccination intervention should be considered in relation to the many other interventions that need to be implemented in order to save the most lives in a disaster setting. Like the preceding chapters, it does not provide answers, but it does suggest that decision-makers need to consider broad array of evidence from non-vaccine areas of the health sector and from other sectors as well in order arrive at a decision that will result in the best possible outcomes of the emergency-affected population.

Specific factors examined include;

- Political considerations
- Security concerns
- Human resources
- Financial considerations
- Alternative interventions
- Target population
- Add-on interventions
- Research

5.2 Introduction

The preceding chapters of this Framework deal with issues pertaining to the risks posed by vaccine-preventable disease and to the vaccines that prevent them. However, even though an assessment of these characteristics may justify a mass vaccination intervention, the final decision will be influenced both by the context in which the emergency is unfolding and by ethical considerations. Every emergency setting is unique and what applies in one will not necessarily be appropriate to another. This chapter highlights some of the principal issues posed by context and discusses them briefly.

5.3 Political considerations

Many emergencies are associated with highly charged, unstable political conditions. Tensions may exist between a ruling government and parts of its population, or between local authorities and the international relief community, or between any other combination of actors, making both the delivery and the acceptance of humanitarian assistance of any kind problematic due to suspicion and mistrust. In these circumstances, vaccination interventions have been politicized and have become the subject of contention.

Authorities in charge of emergency relief must decide whether to advocate for with recalcitrant or slow moving civilian and/or military authorities for proceeding with mass vaccination of target populations when indicated, or to postpone this intervention, at least temporarily, in order to be able to deliver other forms of assistance more rapidly and effectively. Bypassing local authorities or proceeding without their approval can lead to significant problems.

5.4 Security concerns

The most serious potential political impediment to vaccination is the insecure environment that often characterizes humanitarian emergencies. Violence, or even the threat of violence, can have important adverse consequences for health interventions of any kind, but mass vaccination campaigns are especially vulnerable – experience has taught that large gatherings are desirable targets for those intent on social disruption, especially if the population consists largely of unarmed women and children. In addition, access of the population to organized services can be severely affected if insecurity affects travel and communications. Even where access is possible, the real fear of violence takes a toll on the rate of utilization of available services – people who are concerned for their physical safety may not risk travelling by themselves or with their children to places where vaccination is offered. Even if vaccination is offered in as many individual communities as possible, the risk of violence directed towards health workers is real. The probability of conducting a successful mass campaign is clearly higher if security concerns have been adequately addressed. A choice must be made, therefore, between pushing ahead with a vaccination campaign that is entirely justified on public health grounds and foregoing vaccination until the security situation becomes more stable, whether it be on the basis of a negotiated, temporary truce between warring parties or a longer-term settlement.

This consideration has led some to argue that addressing the security situation in an emergency setting is a higher priority than initiating public health interventions. Even some epidemiological studies have shown that reductions in mortality are associated with more secure environments as much as they are by the availability of primary health care services[2], including vaccinations. Of course, what should specifically be done in any particular setting in regard to the relative priorities of action in different sectors such as protection and health is entirely dependent on the context and only a careful analysis of the local situation by those working closest to it will result in the adoption of the best course of action.

[2] Coghlan B, Brennan RJ, Ngoy P et al. Mortality in the Democratic Republic of Congo: A Nationwide Survey. Lancet 2006 Jan 7;367:44-51.

5.5 Human resources availability

While political instability and physical insecurity are not prominent features of all emergencies, resource limitations are. The needs of emergency-affected populations always exceed the ability of national, regional, or international relief efforts to deliver appropriate and effective relief in a timely manner. Qualified public health personnel are consistently in short supply, especially at the onset of emergency. Program managers, logisticians, public health workers, drivers, and translators, among others, are all needed for the successful implementation of vaccination programs. However, these same people, with the same skills, are also needed for other health and non-health sector interventions that could be of great benefit to the same population. Deploying them for days or weeks to a vaccination campaign could adversely affect the relief effort and slow down scaling up of life saving health delivery capacity. The competition between priority programs for individuals with these qualifications can be fierce; strong and respected leadership is critical to ensuring that any intervention program undertaken in an emergency is adequately staffed in order to maximize its chances to succeed. It requires close collaboration with national and subnational health authorities, as in most cases qualified health workers and supervisors required for campaigns are recruited from the existing national health system.

Utilitarian considerations require that allocation decisions achieve maximal benefits in terms of aggregate wellbeing, i.e. achieving “the greatest good for the greatest number”.

5.6 Financial considerations

While political instability and physical insecurity are not prominent features of all emergencies, resource limitations are. The needs of emergency-affected populations always exceed the ability of national, regional or international efforts to deliver effective relief in a timely manner. Qualified local public health personnel are consistently in short supply, especially at the onset of emergency, when they themselves, or members of their families, might have incurred serious personal loss. Program managers, logisticians, public health workers, drivers, and translators, among others, are all needed for the successful implementation of vaccination interventions. However, these same people, with the same skills, are also needed for other health and non-health sector interventions that could be of great benefit to the same population. Deploying them for days or weeks to a vaccination campaign could adversely affect the relief effort by slowing the scaling-up of other life-saving interventions. The competition between priority interventions for qualified individuals can be fierce; strong and respected leadership is critical to ensuring that any intervention undertaken in an emergency is adequately staffed. Because most qualified health workers recruited to in these interventions will be recruited from the national health system, their most effective deployment requires, whenever possible, close collaboration with national and local authorities.

5.7 Alternative interventions

In regard to competition between interventions, unfortunately there is no algorithm that can determine the relative value of one intervention versus another, no mathematical formula that can be applied. The balance between the potential benefits and adverse consequences of implementing a mass vaccination campaign during the emergency phase of a crisis, compared to those of other interventions,, is specific to each setting. Good judgment, based on a careful and systematic consideration of a variety of contextual and ethical factors, is the key to arriving at an appropriate solution to what may seem to be an intractable problem.

Ultimately, the decision as to whether or not to proceed with a vaccination campaign should take into account the degree to which vaccination, weighed against other interventions, and assuming that not all interventions can be implemented, will result in reduced morbidity and mortality in the population. In any event, even if a vaccination campaign is delayed while other interventions, in the health sector or in other sectors such as food distribution, water and sanitation, and shelter are being implemented, planning and preparing for a vaccination campaign should proceed.

Within the health sector, the prioritization of specific services should be carefully considered. The distribution of human and financial resources between activities that provide immediate clinical care to the sick or wounded who are in grave danger of dying or of suffering severe disability needs to be weighed against the value of preventive interventions such as vaccination that may not have an immediate visible impact but that, if implemented in a timely manner, may save more lives in the longer term. Health authorities should never have to choose between offering clinical and preventive services – it is obvious that both are necessary to maintain the health of any population. However, emergencies such as those being considered in this Framework impact heavily on the health status of a population and the sad reality is that this choice often has to be made.

5.8 Target population

The extent of the target population for vaccination interventions must also be taken into account. In many emergencies, especially those in which displacement of large populations is a prominent feature, the risk of vaccine-preventable disease affecting the “host” population may be increased. Furthermore, especially where international emergency relief is provided, the level of services, including vaccination, available to the emergency-affected population may, in fact, surpass that which is available on a routine basis to the surrounding communities. This can result in heightened tensions in the area and can, at times, complicate the relief effort. For these reasons, it has become standard practice to try to include these communities in health interventions. Doing so means those resources must be devoted to those not directly impacted by the emergency, perhaps at the expense of providing more services to the affected population. The epidemiological, ethical, and political consequences of this decision are addition context-specific factors that must be taken into consideration.

5.9 Add-on interventions

In a somewhat similar vein, not only the population that benefits from vaccination may expand, but the vaccination intervention itself may be asked to expand into other areas. Once a decision is made that a mass vaccination campaign is warranted, there will always be a temptation to add additional antigens to those that have been selected. Even more than that, the argument is frequently heard that as long a people are going into communities to vaccinate, why do they not also distribute soap, jerry cans, shovels, mosquito nets, blankets, and so on as well? Indeed, in some cases, such as with the addition of vitamin A capsules to measles vaccine campaigns, "add-ons" have become routine. Yet, depending on the context, the addition of commodity distribution to a vaccination campaign should be approached warily as the risk of overwhelming limited human and logistical resources is real and fraught with risk.

5.10 Research

The acute setting following disasters presents a unique opportunity to conduct research that can be extremely beneficial in providing a better understanding of the health and humanitarian consequences of disasters, establishing the safest and most effective health interventions, and evaluating service delivery models for specific disaster settings. However, it is imperative that medical care and service delivery take precedence over research in resource limited settings during an acute humanitarian emergency.

Ideally a local research ethics committee should establish that care needs have been met before such personnel are permitted to conduct research Consideration should be given to developing regional or international ethical review boards to assist where there is no appropriate local expertise. In countries where research governance structures are not functioning researchers must use credible international ethics review boards.

The principle of justice dictates that communities that carry the burdens of research must stand to benefit. Research protocols should be relevant, methodologically sound and should make the benefits or potential harms for participants explicit. They should also contain clear plans for returning results to participants recognising that they may relocate in the months following the humanitarian crisis.

5.11 Conclusion

The decision to implement vaccination against one or more high-risk diseases during the acute phase of an emergency must be made on the basis of epidemiological, vaccine, political, and ethical considerations that are specific to the context in which the emergency is unfolding. The question of who makes that decision is an important one. In accordance with increasingly accepted standards of accountability such as those enunciated in the IFRC Code of Conduct and by the Inter-agency Steering Committee's "transformative agenda", emergency –affected communities should be as involved in the prioritization and decision-making process to the maximum extent possible. In emergencies, perhaps especially in emergencies, where lives are almost always at stake, winning and maintaining the trust of the population being served is crucial.

A decision to proceed with vaccination in emergencies should take into consideration all of the areas discussed in this chapter, from highly charged political situations to ones of overt conflict and general insecurity; from weighing the benefits and consequences of different interventions to dealing with how to distribute limited resources; and from selecting from among health interventions to considering the relative priority of interventions from other sectors. The ability to arrive at the decision that best serves the interest of the emergency-affected population will depend not only on epidemiological risk assessment, vaccine characteristics, or a consideration of context. In addition, that ability will be dependent on authoritative but respected leadership, on rapid but effective consensus building, and on a cautious and real respect from the entire relief community for decisions that have been made on the basis of the best available evidence, the lessons learned from prior experience, and considered judgment of the broadest consensus of all those involved.

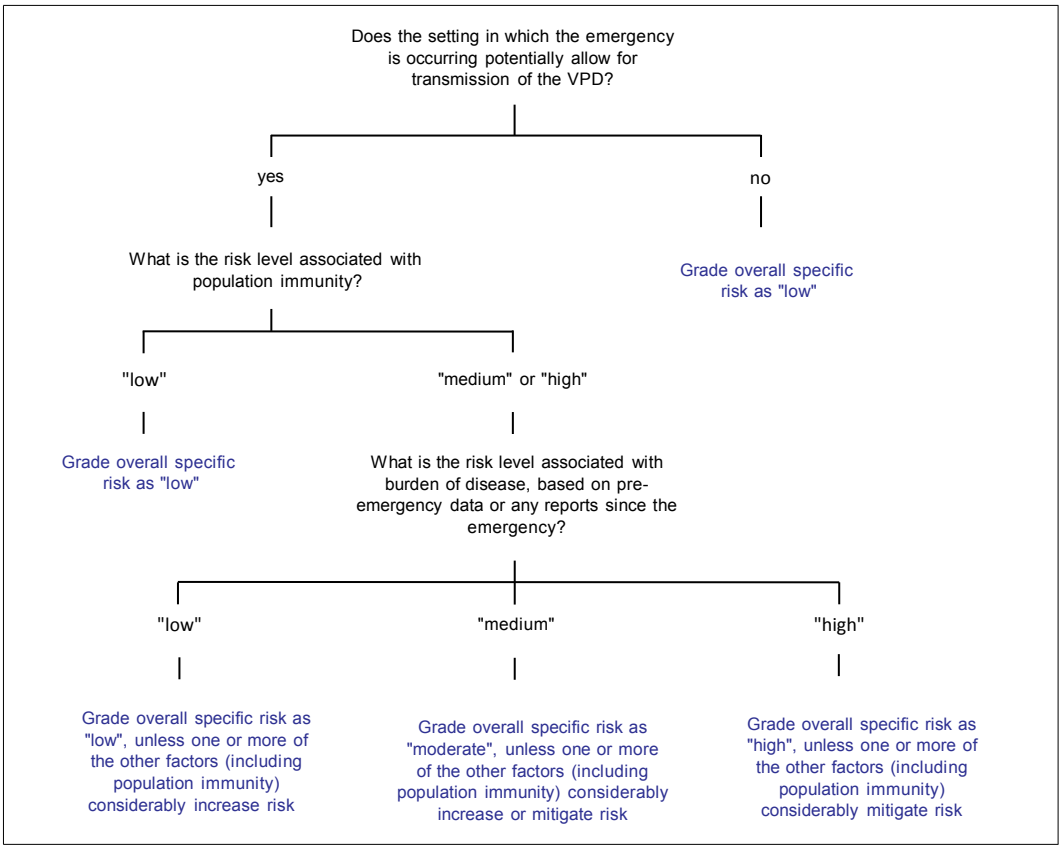
8. Annex 3: Disease-specific risk assessment worksheets

8.1 Guidance for going through each worksheet

While each worksheet differs, the overall procedure for going through each is similar:

- For each factor, the user should first consider whether the criteria suggested for the classification of "High" is met; if not, whether the criteria for the "Medium" classification are met; and if not, adopt a classification of "Low". Thus, the column for "Low" risk indicates absence of "High" or "Medium" level risk factors and is therefore the default for all situations not meeting "High" or "Medium" risk level criteria.
- Unless otherwise specified, the user is asked to assess whether any of the criteria listed under the High, Medium or Low categories, for any factor, are fulfilled (i.e. based on "and/or" logic). Note that for some criteria, and statements are instead made (these are explicitly stated whenever used).
- Having completed the worksheet, the user can refer to below as the basis for coming up with a summary classification of specific risk. Note that this flowchart is to be interpreted qualitatively, and that some recursive logic will be needed: for example, having established that the level of population immunity is insufficient in the second node of the flowchart, it may be necessary to reconsider its contribution to overall risk when coming up with the overall grading after the third node.

Figure 2: Algorithm for qualitatively synthesising VPD-specific worksheets into an overall grading of specific risk, for any VPD



Note also the following specific points:

- The criteria suggested to classify the level of risk due to population immunity are, as all other criteria in these worksheets, arbitrary and, as such, may occasionally be superseded by best judgment and special considerations specific to the emergency in question; however, thresholds suggested for the classification of “low” risk broadly reflect existing evidence on what is required to ensure a level of immunity sufficient to probably confer either herd (community) protection or a high level of individual protection.
- The occurrence of a ‘large’ outbreak, either in the past or in the present, is listed in some of the worksheets as a criterion for determining risk level, and a case definition of what constitutes a large outbreak (based on number of cases or deaths) is suggested where appropriate as a rough guide. Judgment should however be used to decide whether in a given setting an outbreak should be considered large or not (e.g. in a country where surveillance is known to be very incomplete, one should expect that the reported number of cases is a considerable underestimate of the true number, and adjust the case definition accordingly).
- ‘n/a’ in any risk column indicates ‘not applicable’, i.e. the for the VPD and specific factor in question risk should never be classified at that level.
- Sources for all data reported are the latest relevant WHO position papers unless otherwise indicated.

8.2 Risk assessment worksheets

8.2.1 Cholera

Table to assess risk from VPD-specific factors:

Factor	Risk level			Comments
	High	Medium	Low	
Population immunity	• The population does not experience year-round cholera transmission; and – No vaccination has taken place before; or – A primary series campaign was conducted ≤3 y ago with a VC <50%; or – A primary series campaign was conducted >3 y ago, and ♦ No booster campaign was conducted ≤3 y ago; or ♦ A booster dose campaign was conducted ≤3 y ago with a VC <50%	• A primary series campaign was conducted ≤3 y ago with a VC of 50-74%; or • A primary series campaign was conducted >3 y ago with a VC ≥50%, and a booster dose campaign was conducted ≤3 y ago with a VC of 50-74%	• All other situations, i.e. absence of criteria warranting "high" or "medium" classification	The primary series consists of 2 doses, with a 1 dose booster. Current vaccines afford relatively short-lived immunity (about 2-3 years), but seem to confer strong transmission reduction effects, even at low VC. VC should be assessed among people ≥ 2y old.
Burden of disease	• The area has experienced one or more large outbreaks in the past 5y; • An outbreak is currently ongoing	• The area has experienced one or more outbreaks in the past 5y, but none of them large	• All other situations	The area refers to where emergency-affected people are currently living, and could be a city or a district/ region.
Geography, climate and season	• Widespread flooding resulting in potential large-scale contamination of water supply with excreta; dry weather	• The population lives alongside a large body of water (river, estuary, lake); • Warm surface water temperatures; • El Niño year; • Limited flooding	• All other situations	

Risk characterization:

Type of threat: Epidemic, either in a setting with no prior transmission or superimposed on an endemic pattern of transmission.

Timeframe: An outbreak could start within days of the onset of an acute emergency, particularly if sudden environmental change occurs (e.g. due to flooding) or there is mass displacement into a camp. Risk would remain high as long as risk factors, particularly overcrowding and insufficient water, sanitation and hygiene, persist. Any outbreak would propagate very quickly in a camp or urban setting, with local peaks within a few days; and diffuse more slowly (peaking within weeks) in a rural setting.

Age-specific burden: All age groups are at risk.

8.2.2 Diphtheria

Table to assess risk from VPD-specific factors:

Factor	Risk level			Comments
	High	Medium	Low	
Population immunity	• Primary series coverage* for children <1 yr old is <70%	• Primary series coverage* for children <1 yr old is 70-89% and there is no booster dose or natural boosting is low	• All other situations	*Primary series = 3 doses of DTwP- or DTaP-containing vaccine (DPT) provided through EPI • Achieving herd immunity requires >85% VC • Infection is thought to provide long-lasting, possibly lifelong immunity
Burden of disease	• The area has experienced one or more large outbreaks in the past 5y; and/or • An outbreak is currently ongoing	• The area has experienced one or more outbreaks in the past 5y, but none of them large	• All other situations	Global burden estimated at 140,000 deaths/year. • CFR can range from <1% to 5-6% (especially in Africa, SE Asia); CFR >10% have occurred in refugee camps
Geography, climate and season	• The disease is endemic in the area • Cold seasons	• High transmission season within the next 3-6 months	• All other situations	Perennial transmission in tropical countries Transmission increased during cold seasons in temperate countries

Risk characterization:

Type of threat: Diphtheria mainly occurs as sporadic cases or small outbreaks in endemic settings. Most cases are asymptomatic or have a mild clinical course (some fever, and diminished activity and irritability in some children). However, in severe cases pseudo-membranes form in the throat may cause airway obstruction. CFR from respiratory diphtheria is 5-10%.

Timeframe. The incubation period for diphtheria is typically 1-5 days. Onset is relatively slow and characterized by moderate fever and mild exudative pharyngitis. Communicability is generally <2 weeks, and rarely >4 weeks for respiratory diphtheria. Rare chronic cases of diphtheria may transmit for 6 or more months.

Age-specific burden. Pre-school and school-age children are the most commonly affected by respiratory diphtheria in endemic settings. Diphtheria is generally rare among both infants, presumably due to the presence of maternal antibody, and adults as a result of acquired immunity.

8.2.3 Hepatitis A

Table to assess risk from VPD-specific factors:

Factor	Risk level			Comments
	High	Medium	Low	
Population immunity	• Low transmission areas (see below) • Travel to (humanitarian relief workers) or displacement to high transmission areas (see below)	• Intermediate transmission areas (see below)	• High transmission areas (see below)	• Vaccine is not routinely used in EPI. Recommended as a 2 dose series. • Infection is thought to induce lifelong immunity. In high transmission areas, lifetime risk of infection is >90% and occurs mainly in childhood and is asymptomatic. Therefore, individual susceptibility, disease severity and thus burden of disease actually increase as transmission decreases.
Burden of disease	• Low transmission areas such as America, Canada, Europe, Japan, Australia and New Zealand with <30% seroprevalence	• Intermediate transmission areas such as North Africa, Middle East, Central Asia and South America with 30-70% seroprevalence	• High transmission areas such as Sub-Saharan Africa; Indian sub-continent; and Central America with >70% seroprevalence	• Global burden 1.5 million cases per year
Geography, climate and season	• Widespread flooding and destruction of sanitary infrastructure	• Limited flooding and damage to sanitary Infrastructure	• All other situations	Even within regions of high transmission, seroprevalence may be low due to variable economic development and status of sanitary infrastructure within a country or sub-region.

Risk characterization:

Type of threat: Not epidemic prone, although time-space clusters of cases could occur following poor hygienic and sanitary conditions in acute humanitarian emergencies. CFR is 0.1-0.3%, but can reach 1.8% for adults over 50. No chronic infection is known to occur. Disease severity generally increases with age, but complete recovery without recurrence is the rule.

Timeframe. The average incubation period is around 28 days (range: 15-50 days). Increase in incidence would mirror access to inadequate water and sanitation facilities in acute humanitarian emergencies.

Age-specific burden. Age-specific profiles of anti-HAV prevalence and disease incidence are endemicity-dependent. In highly endemic areas, most infections occur in early childhood (<5 years) and are asymptomatic. In intermediate endemicity countries, most cases occur in late childhood and early adulthood. In areas of low endemicity, hepatitis A occurs mainly in adolescents and adults in high risk groups.

Global Support for New Vaccine Implementation in Middle-Income Countries

Miloud Kaddar [a], Sarah Schmitt [b], Marty Makinen [c], Julie Milstien[d]

[a]Corresponding Author
World Health Organization
20 Avenue Appia
1211 Geneva 27, Switzerland
Telephone: +41 22 791 1436
Email: kaddarm@who.int

[b]WHO Consultant
World Health Organization
20 Avenue Appia
1211 Geneva 27, Switzerland
Telephone: +41 78 838 4573
Email: sarahlschmitt@hotmail.com

[c]Results for Development Institute
1100 15th St NW, Suite 400
Washington, DC 20005, USA
Telephone: +1-202-470-5724
Email: mmakinen@resultsfordevelopment.org

[d]University of Maryland School of Medicine
3 bis rue des Coronilles Batiment C
34070 Montpellier, France
Telephone: +334 6706 5779
Email: milstien@medicine.umaryland.edu

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ABSTRACT

Middle-income countries (MICs) as a group are not only characterized by a wide range of gross national income (GNI) per capita (US$1,026 to $12,475), but also by diversity in size, geography, governance, and infrastructure. They include the largest and smallest countries of the world—including 16 landlocked developing countries, 27 small island developing states, and 17 least developed countries—and have a significant diversity in burden of vaccine-preventable diseases. Given the growth in the number of MICs and their considerable domestic income disparities, they are now home to the greatest proportion of the world's poor, having more inhabitants below the poverty line than low-income countries (LICs). However, they have little or no access to external funding for the implementation of new vaccines, nor are they benefiting from an enabling global environment. The MICs are thus not sustainably introducing new life-saving vaccines at the same rate as donor-funded LICs or wealthier countries. The global community, through World Health Assembly resolutions and the inclusion of MIC issues in several recent studies and important documents—including the Global Vaccine Action Plan (GVAP) for the Decade of Vaccines—has acknowledged the sub-optimal situations in some MICs and is actively seeking to enhance the situation by expanding support to these countries. This report documents some of the activities already going on in a subset of MICs, including strengthening of national regulatory authorities and national immunization technical advisory groups, and development of comprehensive multi-year plans. However, some additional tools developed for LICs could prove useful to MICs and thus should be adapted for use by them. In addition, new approaches need to be developed to support MIC-specific needs. It is clear that no one solution will address the needs of this diverse group. We suggest tailored interventions in the four categories of evidence and capacity-building, policy and advocacy, financing, and procurement and supply chain. For MICs to have comparable rates of introduction as other wealthier countries and to contribute to the global fight against vaccine-preventable diseases, global partners must implement a coordinated and pragmatic intervention strategy in accord with their competitive advantage. This will require political will, joint planning, and additional modest funding.

INTRODUCTION

Middle-income countries (MICs)[1] determined by the World Bank classification based on gross national income (GNI) per capita, are more than ever on the global public health agenda because 1) the number of low-income countries (LICs) is declining, 2) most of those living in poverty now reside in the 111 MICs, 3) these countries have a slower uptake of new and priority vaccines against diseases of public health importance, and 4) the prices available to MICs for new vaccines differ significantly and may affect the rate of new vaccine introduction in some cases.

Since 2000, the GAVI Alliance has provided effective support to poorer countries, including 40 of the 111 MICs, to assist them with improving immunization infrastructure and introduce these new vaccines. Eligible countries pay only a fraction of the GAVI price for new vaccines obtained by the UNICEF Supply Division (SD) as a co-financing amount to complement GAVI's support.

Countries with a per capita GNI less than $1,000 were eligible for GAVI support from its start to 2011, when the threshold was raised to $1,500. Countries with a per capita GNI that rises above the threshold lose eligibility for additional GAVI support (and are referred to as "graduating countries"). Of the 111 MICs, 3 MICs have already graduated and 16 more are graduating in 2015 and will need continued assistance in the transition phase to immunization self-sufficiency.

The focus of donors and activities of global partners on the poorest countries with little extension to the MICs poses equity and ethical questions. There are several additional reasons why it makes good public health sense to address the uptake of new vaccines in MICs:

1. Public health impact: failure to introduce priority vaccines leaves these countries vulnerable to infectious diseases which can then threaten neighboring countries even if they have been able to begin immunization.
2. Immunization equity: with the changes in economic growth rates and levels leading to the emergence of a "new bottom billion" [1] in MICs, the poorest populations are again losing out.
3. A healthy vaccine market: MICs could provide a large stable demand volume for vaccine supply promoting competition and a healthy vaccine market to the benefit of both recipient countries and suppliers. Because of the competing priorities, MICs are burdened fiscally by the vaccine prices paid by high-income countries and do not have the access to the lower prices paid by LICs and donors. A more rapid uptake of new vaccines in MICs will increase the predictability of demand and level of funding available and, in the case of pooled procurement, reduce transaction costs to suppliers. In combination, these two factors could make the production investment less risky.
4. The threat of inappropriate decision-making: because of inadequate information, capacity, or support, MICs may (1) wait to adopt and put their populations at avoidable risk or (2) choose to adopt but pay unsustainably high prices to access these new vaccines and then could be forced to discontinue or reconsider their use, with deleterious consequences for the vaccine market and the health of their populations.

[1] Abbreviations: cMYP = comprehensive, multi-year plan for immunization, EMRO = WHO Eastern Mediterranean Regional Office, GNI = gross national income, GVAP = Global Vaccine Action Plan, Hib = *Haemophilus influenzae* type B, HPV = human papillomavirus, LIC = low-income country, LMIC = lower-middle-income country, MIC = middle-income country, NRA = national regulatory agency, ODA = official development assistance, PAHO = Pan American Health Organization, PCV = pneumococcal conjugate vaccine, R4D = Results for Development Institute, RF = revolving fund, RV = rotavirus vaccine, SAGE = strategic advisory group of experts on immunization, SIVAC = Supporting National Independent Immunization and Vaccine Advisory Committees, UMIC = upper-middle-income country, UNICEF SD = United Nations Children's Fund Supply Division, V3P = Vaccine Product, Price, and Procurement Project, WHA = World Health Assembly, WHO = World Health Organization.

Many partners are now beginning to intervene, but the vision so far has been limited. A coordinated effort is needed to accelerate sustainable new vaccine implementation by MICs.

The objective of this paper, one of the companion papers to the Global Vaccine Action Plan (GVAP) [2], is to bring attention to this issue. Section 1 deals with the MICs, who they are, and why they are important; Section 2 considers actions taken to date at the global level as part of this focus on MICs; Section 3 describes new vaccine implementation in MICs; Section 4 details specific partner initiatives to gain information and provide support to MICs; and Section 5 provides a way forward to a coordinated global immunization policy for MICs.

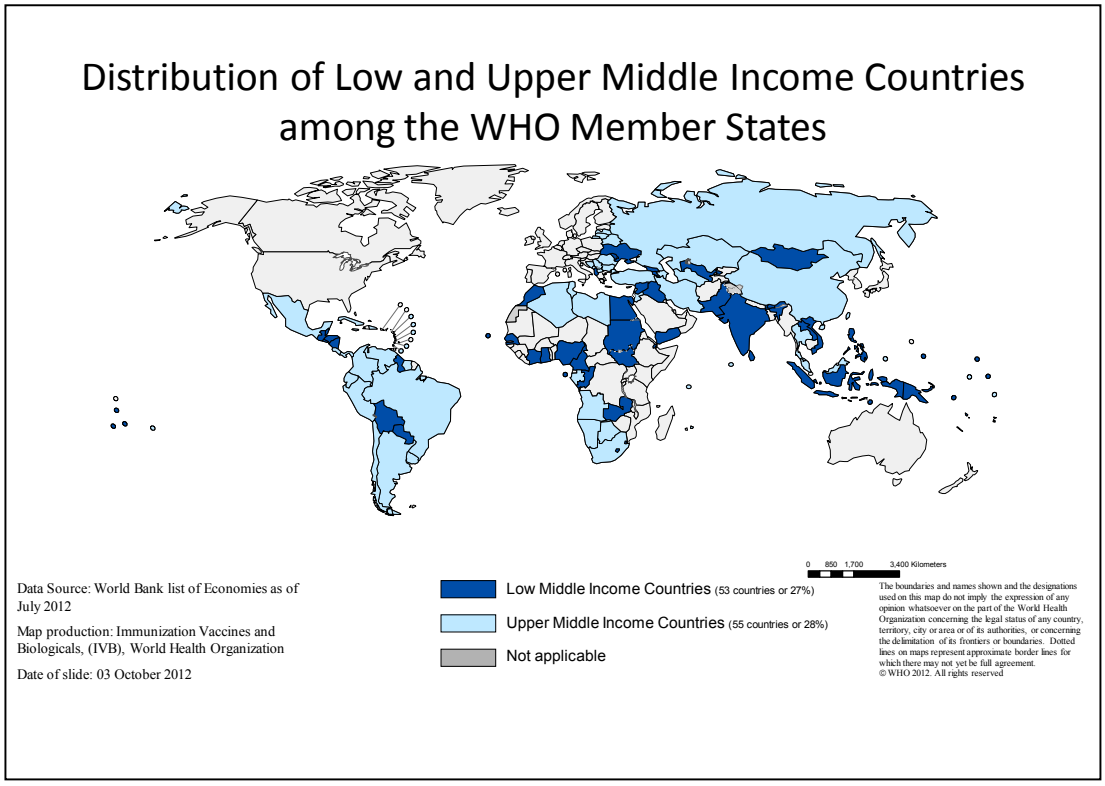
1. THE MIDDLE-INCOME COUNTRIES

Who are the middle-income countries?

The World Bank classifies 111 countries in all regions of the world as lower- (55) or upper- (56) middle-income countries (LMICs or UMICs). Selected data on the MICs (the LMICs and UMICs grouped together—a formulation that we use throughout this paper) are shown in Annex 1. As of July 1, 2012, the World Bank income classifications by GNI per capita are as follows:

- Lower-middle-income: $1,026 to $4,035.
- Upper-middle-income: $4,036 to $12,475.

Figure 1. World map highlighting location of middle-income countries[2], 2012.



[2] Source:http://data.worldbank.org/data-catalog/GNI-per-capita-Atlas-and-PPP-table

It is of note that:

- GNI figures for some countries are estimated and allocated to classification of LMICs or UMICs on this basis.
- The World Bank classifies only countries with a population greater than 30,000.
- There are discrepancies in the number of countries and availability of data between the World Bank and United Nations organizations.

Where possible, all available data have been included and referenced.

Basic data about the MICs compared to LICs are shown in Table 1. The MICs have a population of about 5 billion compared to about 0.8 billion in LICs, a mean GNI per capita of $6,751 and a life expectancy of 69 years in 2010, compared to $302 and 56 years in LICs. LICs receive official development assistance (ODA) equal to 10% of their GNI; LMICs receive ODA equal to 1% of their GNI, and UMICs receive no ODA at all.

Table 1. Summary of characteristics of lower- and upper-middle-income countries as subsets of total middle-income countries and compared to low-income countries[3]

Item	Year	MIC	UMIC	LMIC	LIC
Total population (millions)	2010	4,970	2,452	2,518	796
GNI per capita (US$)	2010	$6,751 ($1,026-$12,475)	$6,247 ($4,036-$12,475)	$1,716 ($1,026-$4,035)	$302 (under $1026)
Life expectancy at birth (years)	2010	69	73	65	56
Infant mortality rate (per 1,000 live births)	2010	27	16	39	70
Under-five mortality rate (per 1,000 live births)	2010	35	19	52	109
Official development assistance/GDP (%)	2010	0	0	1	10
Population living on less than $2 per day (%)	2008	10.6	5.2	15.8	67.7
Population living on less than $2 per day (millions)	2008	526	128	398	539
Population living on less than $1.25 per day (%)	2008	4.3	1.8	6.7	41.9
Population living on less than $1.25 per day (millions)	2008	213	44	169	333
Landlocked developing countries		16	5	11	
Small island developing states		25	13	12	
Birth cohort (millions)	2010	74.7	34.3	60.4	26.3
DTP3 coverage (%)	2009	89	91	86	78
Total health expenditure per capita (US$)	2009	$295	$471	$120	$29
Government health expenditure as share of total government expenditure (%)	2009	10.8	11.5	10.0	9.6

Despite MICs having a lower poverty rate (10.5% of MIC populations lived on less than $2 per day in 2008, compared to 67.7% of LIC populations) [3], they had nearly as many poor people within their populations as did LICs in 2008. Since 2008 more poor people live in MICs than in LICs, a trend that is projected to increase [1], while the numbers of LICs are projected to decrease as incomes grow, from 63 in 2000 to 20 in 2025 [4]. In particular, five large MICs—Pakistan, India, Nigeria, China, and Indonesia—are home to 60% of the world's poor [1].

Although grouped as MICs this set of countries is very diverse in terms of size, economy, health status, governance, infrastructure, and development [5]. The highest-income MICs have more than ten times the GNI per capita than the lowest-income MICs (for example, compare Chile at $12,000 to Vietnam at

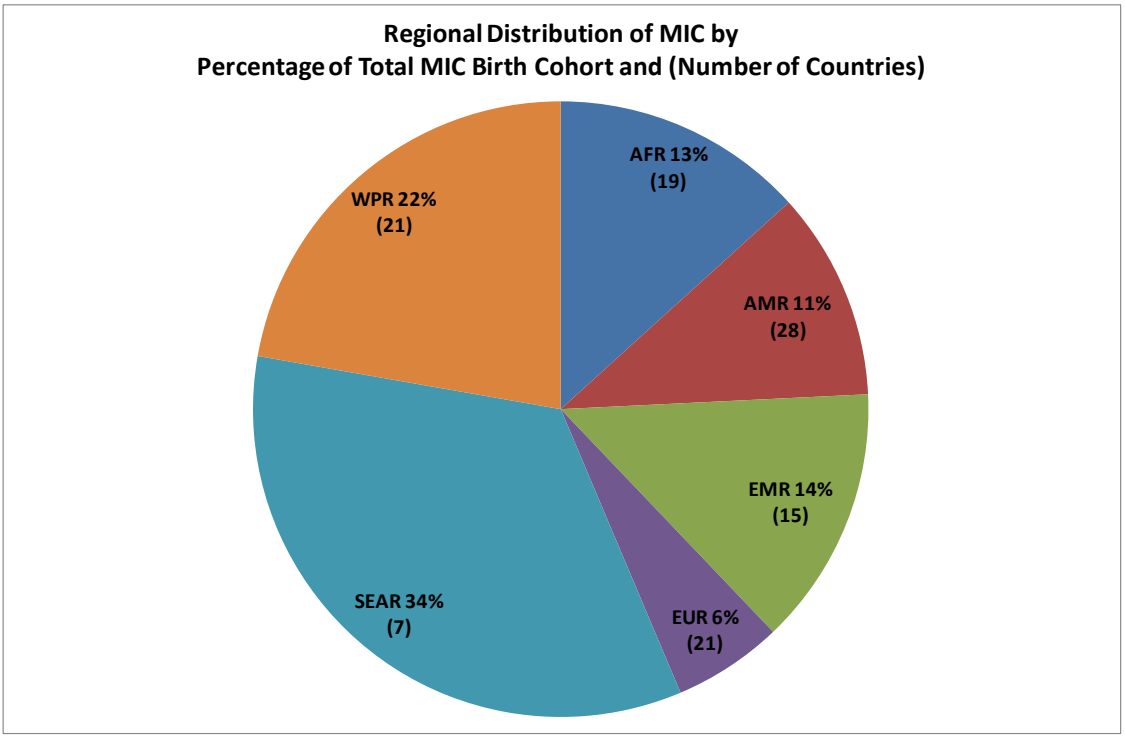
[3] Sources : Figures were obtained using the database at http://iresearch.worldbank.org/PovcalNet/index.htm, accessed 27 July, 2012 or http://www.who.int/immunization_monitoring/data/en/, accessed 29 July, 2012

$1,300) and similarly varying health indicators and disease burdens (for example, compare Malaysia's infant mortality rate of 5 to Egypt's 19 and Congo Republic's 61). Some UMICs even have begun providing development assistance to LICs. However some MICs face similar issues to LICs and the distinction based solely on GNI separating the two groups does not indicate an ability to reduce social disparities and to sustainably implement new vaccines.

In terms of potential vaccine uptake, the MICs 2011 birth cohort (approximately 95 million) was almost three times that in the LICs (due for the most part to the graduation of large countries such as India, China, Nigeria, and Indonesia to the MIC group). In 2009, the MICs reached immunization coverage for the third dose of DTP vaccine (DTP3) of 89% compared to 78% in LICs [6].

Figure 2 shows the geographical distribution of the MICs and LMICs in terms of birth cohort and number of countries in WHO regions (Africa, Americas, Eastern Mediterranean, Europe, South East Asia, and Western Pacific). The Americas Region has the most MICs (28) while the birth cohort of the seven MICs in the South East Asian region is the largest with 34% of the total MIC birth cohort.

Figure 2. Regional distribution of middle-income countries in WHO regions by birth cohort and number of countries.[4]



Abbreviations: WPR = Western Pacific Region, AFR = Africa Region, AMR = Americas Region, EMR = Eastern Mediterranean Region, EUR = Europe Region, SEAR = South-East Asia Region.

[4] Birth Cohort Data from WHO/UNICEF JRF 2012

Why should the global community be considering middle-income countries?

Those MICs with a GNI per capita of less than $1,520 (adjusted from $1,500 due to inflation in July 2012) are eligible for assistance with the introduction of new vaccines and other forms of support from the GAVI Alliance. Those countries that begin with a GNI per capita of less than $1,520 benefit from economic growth that pushes them above this threshold but they lose their eligibility for GAVI assistance. Nevertheless, these GAVI-graduating countries still have the opportunity to buy some priority vaccines at special GAVI prices. Prior to graduation they pay an increasing percentage of this price (co-financing). Post-graduation they will have access to pay the full GAVI price, while some of the 71 MICs that have never been eligible for GAVI but have similar per capita incomes must pay higher prices (i.e., market prices).

Some of the GAVI graduating countries that have had rapid economic growth have higher per capita GNI than a number of countries that were never eligible for GAVI support. Twenty-eight countries that have never been eligible for GAVI support have a GNI lower than the highest GNI graduating country (Azerbaijan had a $5,290 per capita GNI in 2011).

In addition, as shown in Table 1, other forms of ODA beyond immunizations also drop off quickly once the MIC threshold is passed, so the higher incomes earned can be, in some cases, counterbalanced by lost external assistance. MICs not eligible for GAVI assistance get almost no specific technical and financial assistance for immunization. Donors and technical agencies see this group of countries having the technical capabilities to manage their immunization programs well and sufficient financial resources to pay for vaccines and related costs of delivery. The MICs national immunization programs overall are managed well, without external help, and are quite successful in reaching high coverage with traditional vaccines, but this masks weaknesses in the capability to assess whether, how, and when to add new vaccines to the program. MICs have no problem in funding the traditional vaccine programs, but the addition of newer vaccines, especially when purchasing them on the open global market, means that large increments of funding must be mobilized for vaccines compared to the amounts needed for traditional vaccines. However, the increments are small relative to overall health budgets in MICs. Thus, MICs do not generally require financial help to adopt new vaccines but are in need of technical assistance and appropriate information given the increasing complexity and sophistication of the vaccine pipeline.

Of the 111 MICs, 41 have benefited from eligibility for funding support from the GAVI Alliance of which 36 are currently still receiving support and 21 can apply for new programmes. These 21 countries equate to 49% of the total birth cohort of the MICs and include large population countries such as India and Nigeria. Figure 3 below indicates the GAVI eligibility of the MICs in terms of percentage of total MIC birth cohort and number of countries.

Figure 3. GAVI eligibility status[5] in middle-income countries[6], 2012.

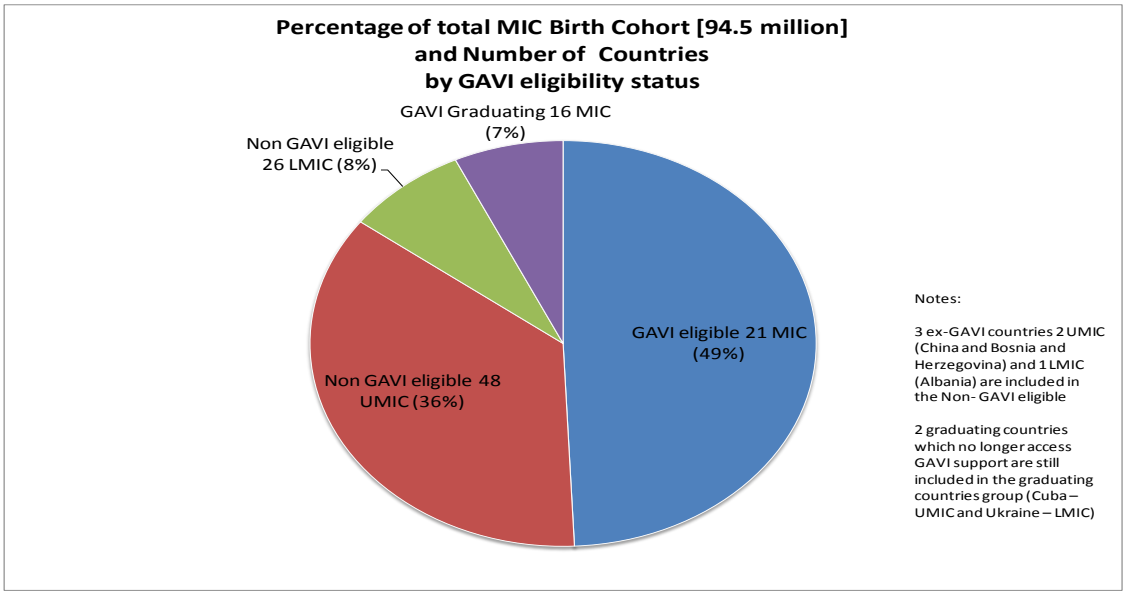
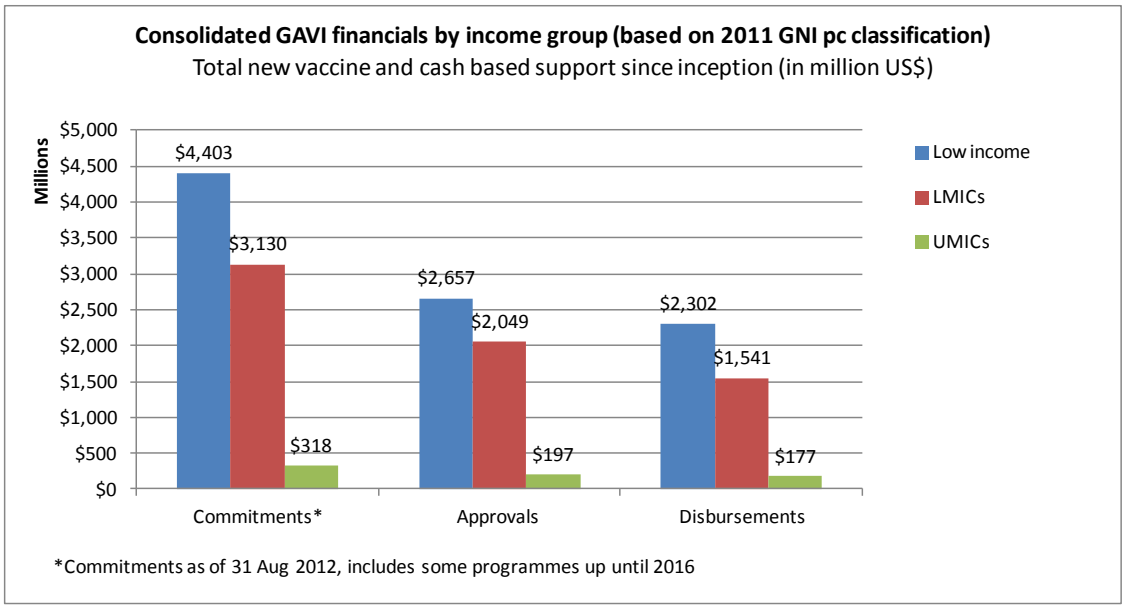


Figure 4 indicates the funds committed, approved, and disbursed by GAVI to eligible countries since 2000 for new vaccine support and cash-based support.

Figure 4. GAVI financial commitments, approvals, and disbursements by lower-income, lower-middle-income, and upper-middle-income countries [7].



[5] Source:http://www.gavialliance.org/support/apply/countries-eligible-for-support/ accessed June 2012
[6]Source: WHO Regional Updates, WHO/UNICEF Joint Reporting Form 2012
Source:http://data.worldbank.org/data-catalog/GNI-per-capita-Atlas-and-PPP-table
[7] GAVI Secretariat Data provided September 2012

GAVI-graduating countries are a priority group for activities by GAVI Alliance partners. These countries will progressively take over the funding of vaccines with, in principle, domestic resources replacing the subsidies provided through GAVI support. GAVI and its partners are working together to individually assess the needs of these countries during and after graduation to develop transition plans and secure the immunization gains made during the period of GAVI eligibility. These countries include a range of GNI per capita from $1,970 to $5,290, and cover a total population of approximately 383 million with a birth cohort of 7.1 million.

Table 2. GAVI-graduating countries, 2012

Country	World Bank Category[2]	GNI 2011[2]	WHO Region	UN Population Estimate 2010 (000)[3]	Birth Cohort[4]	Priority Activity Country 2012
Angola	UMIC	4,060	AFR	19,082	803,274	YES
Armenia	LMIC	3,360	EUR	3,092	47,148	
Azerbaijan	UMIC	5,290	EUR	9,188	183,787	
Bhutan	LMIC	2,070	SEAR	726	14,832	YES
Bolivia	LMIC	2,040	AMR	9,930	264,140	
Congo, Republic	LMIC	2,270	AFR	4,043	144,632	YES
Cuba[1,5]	UMIC	No Data	AMR	11,258	109,642	
Georgia	LMIC	2,860	EUR	4,352	50,850	YES
Guyana[1]	LMIC	No Data	AMR	754	13,466	
Honduras	LMIC	1,970	AMR	7,601	204,512	
Indonesia	LMIC	2,940	SEAR	239,871	4,331,100	
Kiribati	LMIC	2,110	WPR	100	2,047	
Moldova	LMIC	1,980	EUR	3,573	43,549	YES
Mongolia	LMIC	2,320	WPR	2,756	65,221	YES
Sri Lanka	LMIC	2,580	SEAR	20,860	373,262	
Ukraine[5]	LMIC	3,120	EUR	45,448	494,153	

[1] Estimated WB Category without GNI Listed[2] http://data.worldbank.org/data-catalog/GNI-per-capita-Atlas-and-PPP-table.
[3] http://esa.un.org/unpd/wpp/Excel-Data/population.htm.
[4] WHO/UNICEF Joint Reporting Form Data 2011.
[5] No longer accessing GAVI financial support for new vaccines.

All 111 MICs are listed in Annex 1 which shows some key official data points including WHO region, GNI status, GAVI eligibility, birth cohort, and current partner projects conducted in each country.

The characteristics of the six priority countries selected by the GAVI immunization financing and sustainability task team for assessment and transition planning in 2012 (indicated in Table 2) have demonstrated that the needs in relation to technical and financial preparedness for graduation differ significantly between the countries.

The infant and under-five mortality rates (Table 1) in MICs are lower than in LICs, but those in the LMICs in particular still lead to concern about the health of young children in these countries. To address child mortality, MICs have had—in addition to other health interventions—strong immunization programs with DTP3 coverage that is at or near 90% using the "traditional" vaccines. LMICs have been slower to adopt new vaccines, such as *Haemophilus influenzae* type b (Hib)-containing, pneumococcal conjugate (PCV), or rotavirus (RV) vaccines, into their national programs than either high-income countries or LICs [7]. Using a systematic analysis of global, regional, and national child mortality in 2008 [8] to provide data on the burden of disease in MICs that is preventable by RV, PCV, and Hib-containing vaccines, it is observed that pneumonia represents 18.4%, rotavirus 2.4%, and meningitis 2% of all causes of mortality for all MICs not eligible for GAVI support.

The Results for Development Institute (R4D) study [13] conducted an analysis of the rates of adoption of hepatitis B and Hib-containing vaccines by LICs, LMICs, and UMICs. The study constructed step-wise Kaplan-Meier curves on the percentage of countries in each category that had adopted each vaccine annually from the year of first adoption to 2010. Statistical tests showed the following relationships:

- LMICs and UMICs adopted hepatitis B vaccines at statistically similar rates that were about twice as fast as (and statistically different from) LICs.

- LICs and LMICs adopted Hib vaccines at statistically similar rates that were about 30% slower (statistically significant) than UMICs.

The difference in the rates of adoption indicates that LMICs adoption of Hib vaccines has been slower compared to UMICs and similar to the rate of adoption by LICs. This is a change from the pattern of adoption of hepatitis B vaccines, where LMICs kept up with UMICs and were well ahead of LICs. Thus, LMICs seem to have slowed in their adoption of Hib vaccines compared to hepatitis B vaccines.

Further data in relation to inclusion of new vaccines into national immunization schedules are provided in section 3 on new vaccine implementation.

Where the vaccines are neither publicly funded nor included in the national immunization schedule, they are available and used by small percentages (usually less than 10%) of the MIC populations mainly through private purchases.

The 74 MICs not eligible for any GAVI support must buy their vaccines on open international markets, with the exception of those 21 in the Americas Region that are able to use the Pan American Health Organization's (PAHO) Revolving Fund (RF) and the 19 that utilize UNICEF SD either partially or for all vaccine procurement.

GAVI has arranged for those 16 countries graduating from its support to continue to access some of the GAVI-eligible country prices for certain vaccines after graduation, but only for procurement made through UNICEF SD. These arrangements (as reported by GAVI Secretariat) include:

- The ability to purchase PCV under the terms and conditions of the Advance Market Commitment until 2020. Countries will therefore pay a maximum of $3.5 per dose.
- Countries approved for support for the GlaxoSmithKline RV will continue to benefit from the current GAVI price ($2.50 per dose for a two-dose course) after graduation.
- Countries receiving pentavalent vaccine from Crucell can access the GAVI-eligible price until 2020.
- Access to prices provided to GAVI-eligible countries through UNICEF for all products supplied by Sanofi Pasteur and its affiliated manufacturer in India, Shantha Biotech.
- For other manufacturers and vaccines, including human papillomavirus (HPV), discussions are ongoing and further price commitments by manufacturers will be communicated to countries once agreed.

Other newer vaccines available to MICs on the open market are available at a much higher price per dose than those offered to GAVI-eligible and GAVI-graduating countries. Even if MICs that never had GAVI support could obtain the GAVI price per dose for PCV as the GAVI graduating countries can, this price is much higher than the per-dose prices of traditional vaccines (typically a few cents to less than $1 per

dose), meaning that the budgets assigned by MICs to vaccine purchases must be increased dramatically if the newer vaccines are adopted for national programs.

MICs have at least the beginnings of the bodies and procedures to make evidence-based decisions about whether and when to adopt new vaccines for their national programs, including national regulatory authorities (NRAs) for drugs and biologicals and national immunization technical advisory groups. In many instances, however, these institutions and procedures are relatively new, sometimes uncoordinated and unpracticed, so they function with uneven efficiency and speed. Further, external technical help from bilateral partners, WHO and UNICEF, abundantly offered for immunization programs in LICs and GAVI-eligible countries, is relatively absent for most MICs. The great majority of bilateral aid is provided to LICs. WHO and UNICEF tend to focus on other important issues in MICs—WHO responds to health agendas that MICs set themselves that often prioritize systems issues and emerging demands to address non-communicable diseases, and UNICEF focuses on child rights and education issues. This leaves MICs largely on their own concerning the question of adopting and sustaining newer vaccines.

2. A MIDDLE-INCOME COUNTRY FOCUS IN NEW VACCINE IMPLEMENTATION AND PRIORITIZATION OF IMMUNIZATION

The primary impetus for an MIC focus has been the concern that MICs are relatively lagging behind other income groupings in the introduction of new and priority vaccines. The one exception to lagging adoption by MICs is the Americas region which has moved forward with a package of enabling interventions in combination with high political commitment and allocation of domestic resources with successful outcomes. The Americas region does not prioritize technical assistance to its countries on the basis of GNI level [9].

In response to lagging adoption, the regions of Europe and the Eastern Mediterranean have championed the cause of MICs. In 2007, following the first global meeting on implementing new and under-utilized vaccines [10], a "WHO plan of action for new and under-utilized vaccines implementation: 2007–2010" was developed, including a specific work area to "develop an approach to assist middle income countries with new vaccines implementation."

During its November 2008 session, the Strategic Advisory Group of Experts (SAGE) [11] advisory to the WHO Director General on immunization considered the issues raised and requested that "WHO conduct further situation analysis of financial challenges for low and middle-income countries and consultation with countries concerned and partners to distill issues to more actionable activities." The same year, in its resolution regarding immunization, the 61st World Health Assembly (WHA) [12] requested the Director General "to collaborate with international partners, donors as well as vaccine producers to mobilize necessary resources to support low income and middle income countries with the aim of increasing supply of affordable vaccines of assured quality."

In response to calls from the WHA and SAGE, WHO initiated, with the support of the Bill & Melinda Gates Foundation, a study on new vaccine adoption by LMICs. The study [13] was undertaken by R4D and overseen by an advisory group consisting of vaccination experts, representatives of vaccine producers, WHO, UNICEF SD, and the Gates Foundation, which assisted and provided input to the project team.

The R4D report identified barriers to new vaccine adoption by MICs and formulated recommendations for improvements to decision-making at the country, regional, and global levels under the following themes:

- Evidence and capacity-building.

- Policy and advocacy.
- Financing.
- Procurement and supply [7].

The study and its recommendations were presented to SAGE in November 2010 [14]. SAGE then made the following recommendation: "Noting the high number of poor households in lower to-middle-income countries and the need for these households to have equitable access to low-priced vaccines, SAGE supports the study's high priority recommendations, many of which have utility beyond lower middle-income countries." The current paper builds upon the R4D study endorsed by SAGE to try to take forward the recommended agenda for improving decision-making.

In 2012 SAGE reviewed and endorsed the Global Vaccine Action Plan (GVAP) elaborated for the Decade of Vaccines [2], which was endorsed during the May 2012 WHA. The GVAP states, in Paragraph 72 that:

> *Innovations [innovative pricing and procurement mechanisms] will be particularly important for those lower-middle-income countries that do not have access to the PAHO, UNICEF and GAVI Alliance pricing and procurement mechanisms. Mechanisms to explore include differential pricing using new approaches to define price tiers and pooled negotiation or procurement methods for lower-middle-income countries. . . One example is the PAHO revolving fund pooled procurement and short-term credit mechanism. This and other models could be assessed and modified to best suit the needs of the lower-middle-income countries and the individual vaccine markets.*

Along with these efforts, the publication of the paper identifying the new bottom billion [1] has heightened the urgency.

With this increased focus immunization partners have begun to consider the MIC issues and extend activities and projects to determine MIC-specific needs and identify possible interventions.

3. NEW VACCINE IMPLEMENTATION IN MIDDLE-INCOME COUNTRIES

Table 3 shows data on the introduction of new vaccines, specifically Hib, PCV, RV, and HPV. The data come from the WHO/UNICEF Joint Reporting Form, an annual reporting system issued to all member states collecting data on a number of immunization indicators. The data were further validated by WHO through its communications with regions and countries. These data indicate the degree of reduced implementation of new vaccines in the MICs despite the efforts made since 2007, and they illustrate the impact of GAVI eligibility and access on new vaccine implementation.

The assumptions utilized in these analyses include:

- The total MIC birth cohort of 94.5 million.
- One hundred and eight countries are included in this analysis as no data are available for West Bank and Gaza, American Samoa, and Kosovo.
- Birth cohort data are not available for South Sudan so it is included only in reference to the number of countries but not as part of the birth cohort calculations.

Table 3. New vaccine introduction status in middle-income countries, September 2012[8]

New Vaccine Introduction Status	Number of Middle-Income Countries	% of Total MIC Birth Cohort
Hib		
Introduced	96	37%
Partially introduced	4	38%
Not introduced	8	26%
PCV		
Introduced	28	14%
Partially introduced	4	2%
Not introduced	76	84%
RV		
Introduced	25	15%
Partially introduced	4	5%
Not introduced	79	80%
HPV		
Introduced	10	N/A
Partially introduced	3	N/A
Not introduced and no reported plan to introduce	67	N/A
Pilot study	12	N/A
Suspended introduction	2	N/A
Planned or interested in introducing	14	N/A

Summary of new vaccine implementation in middle-income countries, as of September 2012:

- 96 MICs, 37% of the total MIC birth cohort, have fully implemented Hib vaccine into their national immunization schedule, 32 of which have done so with GAVI support.
- 28 countries, 14% of the total MIC birth cohort, have fully implemented PCV, 6 of which have done so with GAVI support.
- 25 MICs, 15% of the total MIC birth cohort, have implemented RV, 8 of which have done so with GAVI support.
- 10 MICs have fully introduced HPV and a further 12 are currently conducting pilot studies.

Hib introduction

Ninety-six MICs have fully implemented Hib into their national immunization schedules. While commendable as a percentage of the total number of countries, these 96 countries make up only 37% of the total MIC birth cohort as several large-population countries have yet to implement (China, Indonesia, Thailand, Iran, and Egypt).

Partial introduction has begun in two GAVI-eligible countries (India and Nigeria) and two non-GAVI-eligible countries (Philippines and Belarus). These countries make up a further total of 38% of the birth cohort. Scale-up to cover all children within these countries would have a significant impact on mortality or morbidity reduction due to pneumonia and meningitis.

Of the 26% of the birth cohort (eight countries) that have yet to introduce Hib vaccine, two are GAVI eligible (Timor Leste and South Sudan), one is GAVI graduating (Indonesia), one is no longer GAVI eligible (China), and four have never been GAVI eligible (Egypt, Maldives, Iran, and Thailand). While some of these countries indicate a plan to introduce Hib, the introduction process has yet to begin.

[8] WHO Regional Updates, WHO/UNICEF Joint Reporting Form 2011.

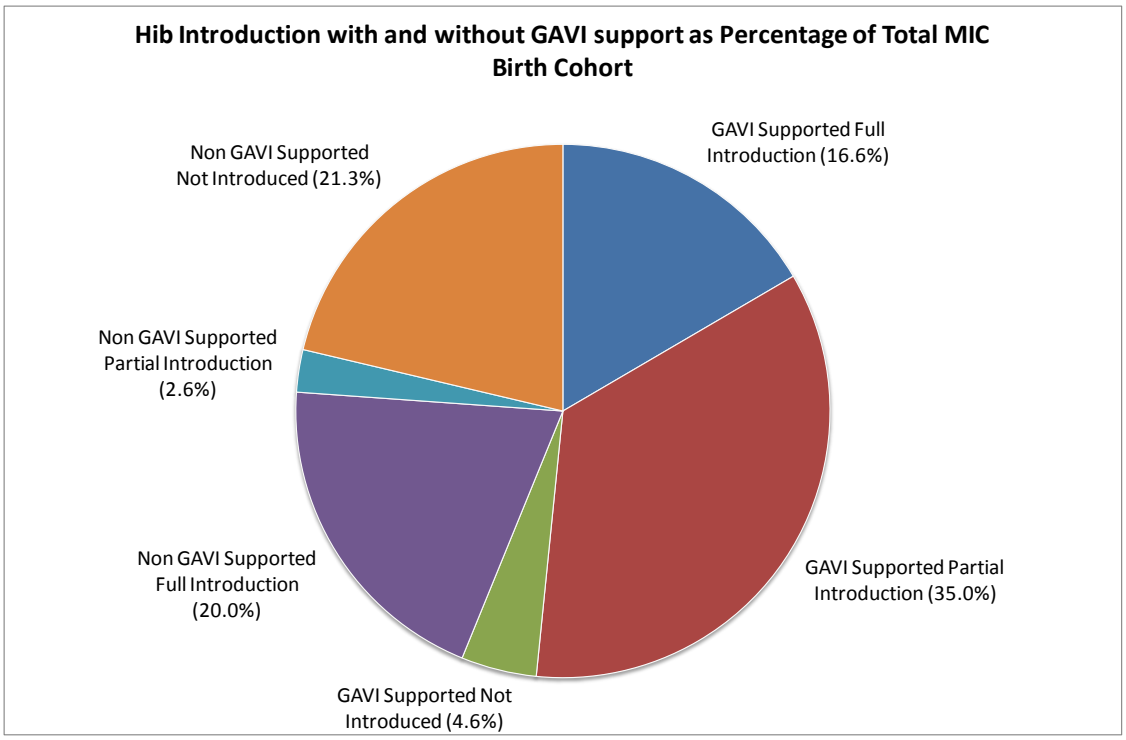
From Figure 5 below it can be seen that 17% of the birth cohort has been fully covered with assistance from GAVI for Hib introduction, a further 35% could be covered if the eligible countries continue to implement Hib, and a further 5% of the birth cohort that are currently GAVI eligible have yet to implement Hib.

All 49 MICs in the Americas and European regions have implemented or started to implement (Belarus only) Hib-containing vaccines.

Of the 43.8% of the MIC birth cohort not eligible for GAVI support:

- 20% of the MIC birth cohort is covered by the introduction of Hib.
- 2.6% of the MIC birth cohort resides in a country that has partially implemented Hib.
- 21.3% of the MIC birth cohort resides in a country which has not yet implemented Hib.

Figure 5. Hib vaccine introduction[9] in middle-income countries, September 2012.



PCV introduction

Of the 108 countries providing data, 28 countries (14% of the total MIC birth cohort) have fully implemented PCV, and 6 countries (3% of the MIC birth cohort) have implemented PCV with GAVI support—4 of which are GAVI eligible and 2 are GAVI-graduating countries. Of the 28 countries that have implemented PCV, 14 countries are from the Americas.

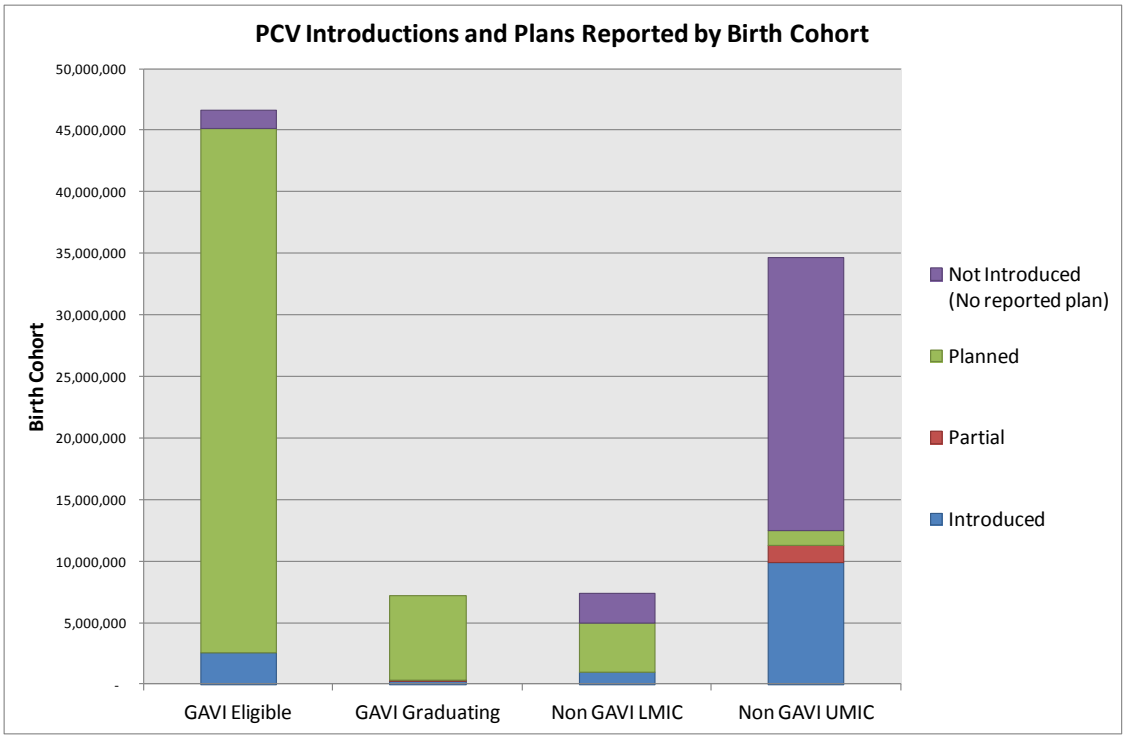
[9] Source: WHO Regional Updates until September 2012, WHO/UNICEF Joint Reporting Form 2011

An additional 4 countries (2% of the MIC birth cohort) have partially implemented PCV. One of these is a GAVI-graduating country (Mongolia) and the remaining 3 are non-eligible (Kazakhstan, Colombia, and Dominican Republic).

A total of 76 countries (86% of the MIC birth cohort) have not yet implemented PCV. Although 39 countries (57% of the total MIC birth cohort) have indicated a plan or interest in implementing PCV in the future, 12 of these are not eligible for GAVI support (6 LMICs and 6 UMICs), 13 are GAVI-graduating countries (including Indonesia), and 14 are GAVI eligible (including India, Pakistan, and Nigeria).

The 16 GAVI-graduating countries were given the opportunity to apply for support for the implementation of PCV and RV in 2011. Most of them took up this opportunity, were approved, and have indicated plans to implement in the coming years.

Figure 6. PCV introduction[10] in middle-income countries, September 2012.



RV introduction

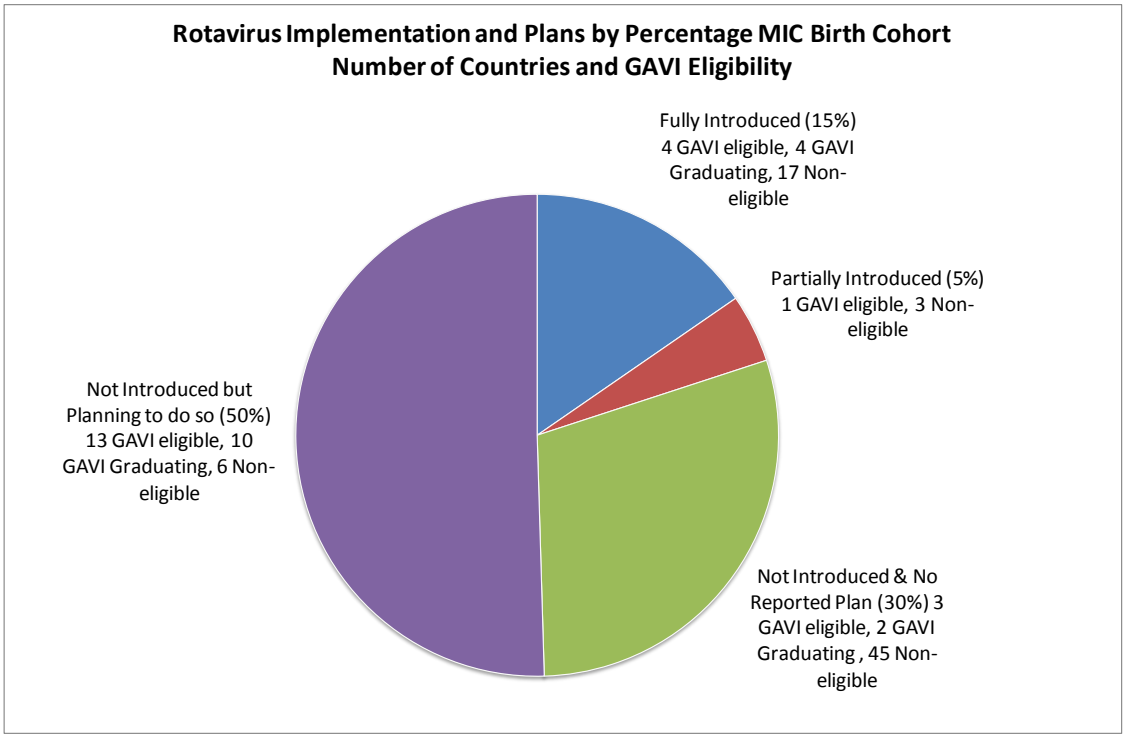
Twenty-five MICs, representing 15% of the total MIC birth cohort, have implemented RV. More than half of the countries, 14 of the 25, are from the Americas. Another 5% of the MIC birth cohort reside in four countries that have partially implemented RV; one that is GAVI eligible (Zambia), and three that are not eligible (Thailand, Philippines, and Peru).

Eighty percent of the MIC birth cohort are not currently covered by RV vaccination, however, 29 countries—making up 50% of the total MIC birth cohort—report they are planning to introduce it in the

[10] Source: WHO Regional Updates until September 2012, WHO/UNICEF Joint Reporting Form 2011

future. This group is made up of 13 GAVI-eligible countries, 10 GAVI-graduating countries, and 6 non-eligible countries.

Figure 7. Rotavirus vaccine introduction[11] in middle-income countries, September 2012.



HPV introduction

Twelve MICs are currently conducting pilot studies for HPV. Of these, two are GAVI-graduating countries, two are not eligible, and eight are eligible.

A total of ten countries (one GAVI eligible, two graduating, and seven non-eligible) have fully introduced HPV, a further three countries (one graduating and two non-eligible) have partially implemented HPV. Two countries that implemented HPV have suspended the implementation. Nine countries have indicated plans to implement HPV in the future and a further five report being interested in implementation.

In some MICs, support for the introduction of HPV has been provided from external sources other than GAVI, such as manufacturer donations and supported program-assisted funding.

Of the 108 MICs reporting, 67 countries have not indicated any intention at this point to introduce HPV. Ten of these are GAVI eligible, eight are GAVI graduating (and are unable to apply for funding for HPV from GAVI) and 49 are not eligible for any support from GAVI.

[11] Source: WHO Regional Updates until September 2012, WHO/UNICEF Joint Reporting Form 2011

4. PARTNER ACTIVITIES WITH MIDDLE-INCOME COUNTRIES

To enhance the decision-making process on the sustainable implementation of new vaccines, a number of partners are extending their activities to a limited number of MICs.

Partners are conducting projects or offer services that benefit some MICs for some of the issues identified to inhibit vaccine adoption. Most of the projects and services principally target LICs, but unevenly support a subset of LICs. Some countries are benefiting from a number of programs while others do not currently have access to any. Annex 1 indicates global partner activities for each of the MICs.

Utilization of UN-pooled procurement systems by middle-income countries

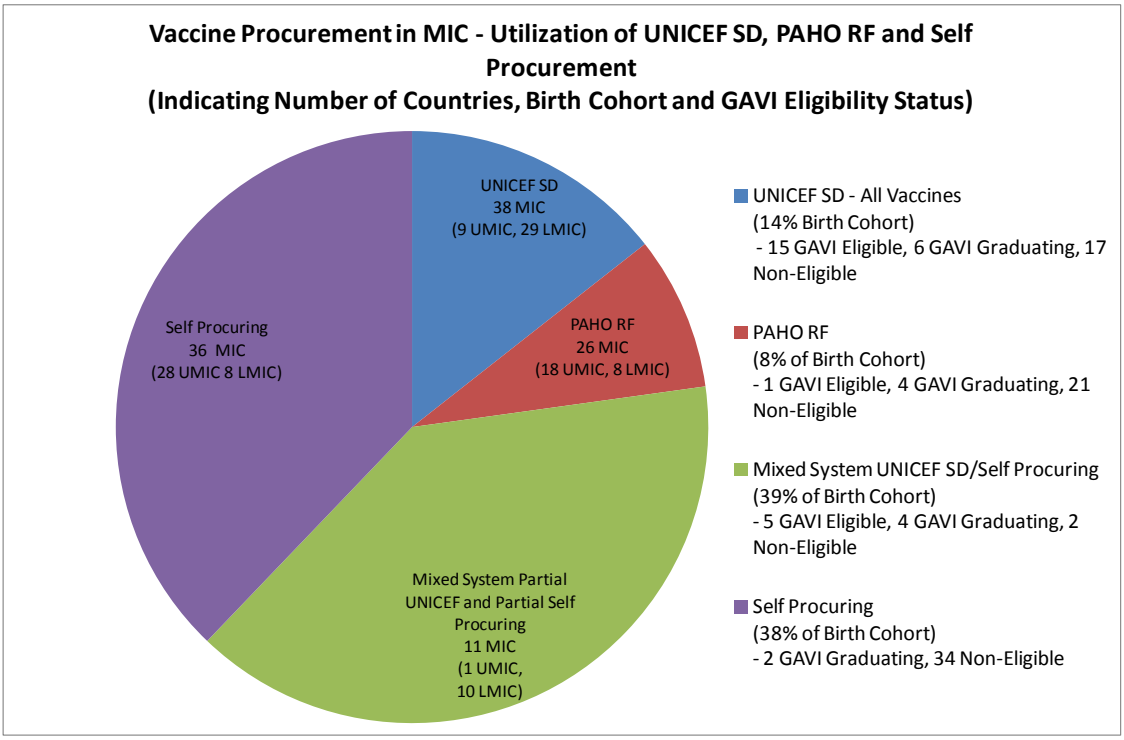
Of the 111 MICs, 75 benefit either partially or fully from the pooled procurement activities of UNICEF SD and the PAHO RF. Forty of the 75 countries involved with pooled procurement are neither GAVI eligible nor GAVI graduating. With data provided from the two procurement agencies, Figure 8 shows the utilization of the pooled procurement mechanisms by both LMICs and UMICs, indicating the MIC birth cohort covered by the procurement systems and the GAVI eligibility status.

Seventy-seven percent of the total MIC birth cohort is being provided with some or all vaccine through self-procurement; these 47 countries are procuring on the open global market. More than half of the UMICs are self-procuring vaccines while 33% of the LMICs are self-procuring for some or all vaccines. Some GAVI-eligible and GAVI-graduating countries are utilizing UNICEF SD solely for GAVI-supported vaccines and are otherwise self-procuring.

Use of UNICEF SD procurement services for the procurement of some or all vaccines is not limited to GAVI countries as indicated by the 17 non-eligible countries, nor is this service being utilized only by LMICs, as 9 UMICs are procuring some or all vaccines through UNICEF SD [15].

Figure 8. Reported procurement modalities in middle-income countries[12], July 2012.

[12] Source: UNICEF SD, PAHO RF July 2012 Self Procurement assessed by elimination



Utilization of UNICEF SD by MICs has increased, and now represents a significant share of the volume and value of UNICEF SD vaccine procurement. This in part is due to increasing GNI of previously low-income countries advancing into the MIC category. UNICEF SD does not have defined criteria for access to its services by countries and some continued utilization is based on historical use.

PAHO RF provides procurement services and technical assistance to countries and territories in the Americas region regardless of GNI. With the exception of Mexico, all other MICs in the Americas region are utilizing the PAHO RF for some or all of their vaccine procurement; these 26 MICs make up 8% of the total MIC birth cohort. The PAHO system has been a catalyst for rapid introduction of new vaccines in the region and combined with appropriate country planning and budgeting, the RF mechanism has contributed toward financial sustainability of the immunization programs.

Potential vaccine procurement interventions

Pacific Island countries pooled vaccine procurement utilizing UNICEF Vaccine Independence Initiative Mechanism. Thirteen Pacific Island countries—the majority of which are MICs—procure vaccines, autodisable syringes, and safety boxes utilizing the UNICEF Vaccine Independence Initiative mechanism through UNICEF SD. The mechanism has been and is currently utilized by other countries; however it was initiated in the Pacific Island countries in 1995 to assist with the procurement of the region's vaccine requirements, and to facilitate logistic and supply issues given the very low populations and vast geographical dispersion. This is an innovative mechanism adapted to suit the specific needs of these small, isolated island nations [16].

UNICEF proposals. UNICEF SD, in response to the increasing awareness of the specific needs of the MICs, has begun consulting with countries, industry, and partners on possible interventions it could make within the vaccine market on behalf of the MICs. UNICEF SD is committed to the concept of tiered pricing for vaccines and offers the lowest prices it obtains to the poorest countries as determined (in most cases) by

GNI. The UNICEF options for MICs include pooling demand from MICs and conducting MIC-specific procurement processes, and negotiating price ceilings for MICs to access under certain criteria. UNICEF is also considering possible innovative financing and funding mechanisms to provide security to industry on the commitment to the forecast demand. Acknowledging that some of the current UNICEF requirements for utilization of its procurement services are difficult for some countries to utilize under government financing and public procurement rules, UNICEF is also considering options to address these concerns.

Following the outcome of a consultation process, UNICEF considers that any activities would be evolutionary, starting with a limited number of products and interested countries. [15].

WHO Vaccine Product, Price, and Procurement (V3P) Project. With funding from the Bill & Melinda Gates Foundation, WHO initiated the V3P project in 2011 to address product and price information and procurement options as obstacles to sustainable MIC introduction of new vaccines and in response to the WHA and SAGE recommendations. V3P collects, collates, and disseminates accurate and reliable data and information on vaccine pricing, procurement, and product characteristics. The focus countries are MICs and GAVI-graduating countries. The ultimate goal of the V3P project is to create a collaborative, functional, and valuable source of vaccine product, price, and procurement data and information that is available to and appropriately used by countries to aid informed decision-making.

Pooled Vaccine Procurement in the Eastern Mediterranean. In response to requests from the governments of regional MICs, the WHO Eastern Mediterranean regional office (EMRO) initiated a feasibility study on implementing a pooled procurement mechanism for these countries. The member states were concerned at the high prices being offered to them and the limited prioritization of some countries to access supply, particularly in emergency situations.

Considerable work was conducted by EMRO and partners with the countries to determine their needs and the best course of action for a phased approach to implementation. The member states endorsed the proposed process during side meetings of the WHA, Regional Committee meetings, and regional and global technical meetings, most recently during the 58th Regional Committee in October 2011 [17]. EMRO is working closely with partners on its pooled procurement considerations including UNICEF SD, as part of its MIC strategy.

Progress on specific technical activities required to move toward a sustainable pooled procurement system have been significantly slowed due to the political situation in many of the MICs of the region. The member states of the region consider, however, that this is an appropriate and needed mechanism in the region which would assist in the sustainable implementation of new vaccines, which a number of the MICs have been slow to introduce.

Technical assistance projects

During the past ten years a number of specific technical assistance tools and projects have been developed and used mainly in GAVI-eligible countries.

Comprehensive Multi-Year Planning (cMYP). One of the tools is the cMYP, developed by WHO and UNICEF, and is now a prerequisite for applications to GAVI for its new vaccine subsidy. cMYPs help to ensure comprehensive, simplified, and harmonized immunization planning, including cost estimates and financing source identification at the national level. However, only five non-GAVI-eligible MICs have implemented a cMYP (Botswana, Cape Verde, Seychelles, Swaziland, and Syrian Arab Republic). Of the 111 MICs, 41 report having a current cMYP—20 of these are currently GAVI eligible, 15 are graduating, and 1 is no longer GAVI eligible.

cMYPs have the potential to be useful to non-GAVI countries, with some adaptation, to improve decision-making, planning, and financing processes. Funding for assistance with cMYP development is currently limited, in the most part, to GAVI-eligible countries.

NRA strengthening. Since 1997 WHO has conducted a five-step capacity-building program to strengthen national regulatory systems to regulate vaccines at international standards of quality, safety, and efficacy. This program aims to help countries to develop the necessary regulatory functions for vaccines. Needs differ depending on whether the country is procuring its vaccines from UN agencies (mainly UNICEF SD and PAHO RF), using its own direct self-procuring system or producing its own vaccines. The WHO prioritizes activities in vaccine producing, self-procuring, and UN agency countries [18].

Nine MICs that produce vaccines have NRAs that have been assessed by WHO as being functional (Brazil, Bulgaria, China, Cuba, India, Indonesia, Russian Federation, Senegal, and Thailand). This allows manufacturers operating under the oversight of these NRAs to apply for WHO prequalification for individual products, so that these products would be eligible for purchase by UN agencies.

Two further MIC NRAs where vaccines are produced have been assessed as functional but no products manufactured in these countries have been awarded prequalified status. Five non-producing MIC NRAs have been assessed as functional for procurement. In total, 11 of the NRAs assessed as functional are in UMICs and 7 in LMICs.

Other MICs are actively working with WHO to develop functionality of their NRA both to meet recommended functions of a producing country (9 countries) but also to meet the recommended functions for self-procuring countries (12 countries) and UN agency procurement of vaccines (22 countries). In total, 58 MICs have or are currently working with WHO prequalification on NRA functionality (30 UMICs and 28 LMICs).

The NRA status will be particularly important for new vaccine introduction, for countries to be able to assure the quality of the vaccines they produce and procure, especially new products. There are several priority vaccines in the pipelines of some MIC vaccine producers. Specifically, at least one rotavirus vaccine and a dengue vaccine are being developed.

Additional technical support

The Gates Foundation has provided funding for technical intervention projects to improve sustainable immunization implementation. The projects have varied approaches and some of these have been extended to include some MICs, but they are not available to all MICs. Annex 1 indicates the countries in which these projects are currently being conducted. Five of the Gates Foundation–funded projects (ProVac, SIVAC, SIF, OPTIMIZE, and V3P) are indicated there as they are operating in MICs.

Four initiatives that might be more systematically applied to middle-income countries:

ProVac. PAHO's ProVac Initiative is funded by the Bill & Melinda Gates Foundation. Its goal is to strengthen the national capacity to make evidence-based transparent and objective decisions on new vaccine introduction with special emphasis on cost-effectiveness analysis. Twenty-four MICs are involved in ProVac. ProVac is specifically referenced in the GVAP as an example of strengthening countries to make informed decisions. An important development from the initial focus of ProVac on the Americas is the formation of the ProVac International Working Group, a consortium of partners (WHO, CDC, Sabin Vaccine Institute, Agence de Médicine Préventive, and PATH). ProVac received additional funding from the Gates Foundation for a two-year pilot phase (2012–2013) for the working group to use ProVac tools and methodologies in LICs and MICs in Africa, the Eastern Mediterranean, and Europe.

SIVAC. The SIVAC Initiative is a project implemented by the Agence de Médicine Préventive in partnership with the International Vaccine Institute to support the development of sustainable national immunization technical advisory groups (NITAGs) in low- and middle-income countries. NITAGs institutionalize evidence-based decision-making processes for immunization programs and policies. Eight MICs are involved in the SIVAC Initiative. The activities fall into two core areas:

1. Support for NITAG establishment, development, and strengthening. SIVAC directly operates in about 15 countries in Africa, Asia, Europe, and the Middle East, 8 of which are MICs.
2. Knowledge sharing through the NITAG Resource Center (a multilingual website that offers information, tools, and short learning modules), the development of articles and tools, and the organization of regional technical workshops.

SIF. The Sustainable Immunization Financing project managed by the Sabin Institute advocates for parliamentary prioritization of immunization and domestic financing for immunization activities. The program operates on a country-specific basis, working with parliamentarians and sub-national stakeholders to develop information and data to utilize in advocacy with decision makers. In some countries assistance is provided to draft and implement legislation to indicate government commitment to immunization. Begun with a focus on LICs, SIF has been extended to work with eight LMICs.

Project Optimize. Optimize is a collaboration between WHO and PATH to identify ways in which supply chains can be optimized to meet the demands of an increasingly large and costly portfolio of vaccines. Optimize works directly with national governments and other institutions to identify problems in the supply chain and demonstrate innovative solutions. Their goal is to help define an ideal vaccine supply chain that can be used to develop stronger, more adaptable, and more efficient logistics systems, extending the reach of lifesaving health technologies to people around the world.

As part of its efforts to guide key stakeholders at country, regional, and global levels in their work to strengthen supply and logistics systems, Optimize works to ensure that vaccine products and their packaging are designed with characteristics that best suit the needs and constraints of countries.

US Agency for International Development (USAID). In addition to these projects funded by the Gates Foundation, USAID and the US Centers for Disease Control and Prevention both conduct and fund immunization activities in a number of countries. Other bilateral donors and nongovernmental organizations provide funding and in some cases technical assistance to national immunization programs within MICs; however these have not been mapped for this paper as they vary widely and can be difficult to determine.

Despite the number of activities to provide technical assistance to MICs for the sustainable implementation of new vaccines, decisions regarding partner activities conducted in MICs are being made in relative isolation with limited coordination or prioritization. Some countries are benefiting from a

number of activities while others in need of assistance are not included in any. Addressing the specific technical assistance, data, and information needs of MICs can require individual needs assessment and tailoring.

5. DEVELOPMENT OF MIDDLE-INCOME COUNTRY GLOBAL POLICY AND COORDINATION

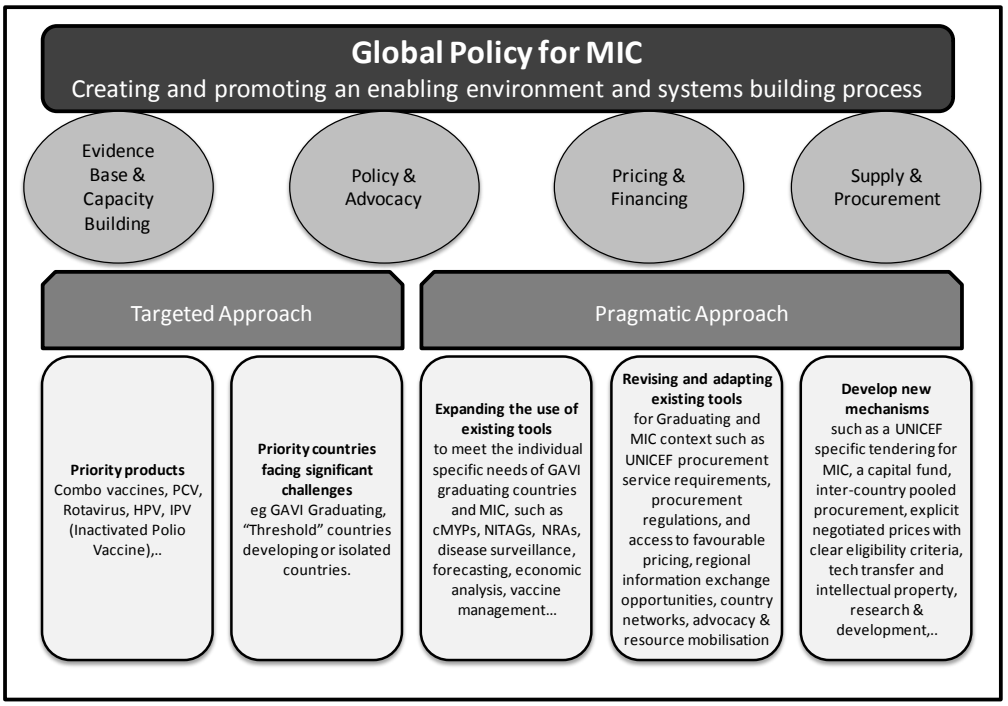
The immunization community is motivated to assist MICs to make informed decisions, but even with all the best intentions of global and regional partners a lack of coordination could result in a distortion of effort creating an inequitable focus on some areas and some countries while completely missing others. A global policy and coordination framework for appropriate targeting of activities of partners would assist in defining roles and responsibilities and maximizing efficiency of actions. The goal of any global policy for MICs should be to improve the capacity of countries to make informed decisions regarding national immunization programs to achieve the best possible outcomes in the prevention of vaccine-preventable diseases.

A global policy toward middle-income countries

The previous sections and the information gained from the study on MIC vaccine uptake decisions [7] indicate that there are three main gaps for new vaccine implementation in MICs:

1. An information gap on vaccine products, pipelines, the vaccine market, prices, innovative ideas and mechanisms, and best practices.
2. A capacity gap on applied research, institutional development, economic and epidemiologic data analysis, production and technology transfer, assurance of quality, and performance evaluation.
3. A networking gap with very few opportunities for countries to benefit from peer review, and intra- and inter-regional exchanges.

Figure 9. Possible global middle-income countries policy structure.



A global policy for MICs as shown in Figure 9 could include creating and promoting an enabling environment and a systems-building process to the benefit of all MICs. This includes sharing information on a variety of aspects of experiences with immunization and vaccines; providing technical support and mutual assistance; setting up a clear pricing strategy based on explicit agreed criteria; and promoting best standards, policies, and practices.

The study by Makinen et al. [7] referred to four pillars for support that can provide a framework for global policy:

- Evidence and capacity-building.
- Policy and advocacy.
- Costing, pricing, and financing.
- Procurement and supply chain management.

In addition to these pillars, a framework could incorporate a *targeted approach* based on criteria for selecting priority countries or products for specific action and activities and/or a *pragmatic approach* extending the use of available tools and mechanisms, adapting such tools and mechanisms for MIC particular needs, and developing MIC-specific technical assistance.

A. Targeted approach

Targeting specific countries and products: prioritization of countries for activities could include developmental indicators, burden of disease, population impact, influence on neighboring countries, and willingness and capacity to implement. Some specific priority countries could be selected based on these and other defined criteria, although it is clear that each country will need an individually tailored strategy.

To promote sustained implementation, the targeting of specific products that would have high epidemiological, market, and economic impact could also be considered.

B. Pragmatic approach

MICs are seeking an enabling environment and systems-building support, but (with a few exceptions) not direct financial assistance. Solutions exist and have already been identified [11, 12]. However, much more work is needed.

The implementation of policy should proceed pragmatically by:

1. Using existing tools. Expanding the use of existing tools to meet the individual specific needs of GAVI-graduating countries and MICs, such as cMYPs, ProVac, SIVAC, NRA strengthening, V3P, etc.
2. Revising existing mechanisms. Revising and adapting existing tools for the MICs and GAVI-graduating country context, needs and constraints, such as UNICEF procurement service requirements, procurement regulations, and access to favorable pricing for priority vaccines including access to the Advance Market Commitment price.
3. Developing new options. Design and develop innovative mechanisms and tools to better respond to MICs and GAVI-graduating country needs, such as a UNICEF specific window for MICs, a capital guarantee fund, inter-country pooled procurement, explicit negotiated prices with clear eligibility criteria, active technology transfer, intellectual property rights management, and support to research and product development efforts in MICs.
4. Ensure optimal coordination. Ensure coordination through a task team of partners who work together regularly and are supported with adequate funding to move forward with the greatest efficiency.

Conclusion

The 111 MICs are a key group of countries in the global fight against vaccine-preventable diseases. MICs are increasing in number and by proportional representation of the world's poor. The MICs have not benefited as appreciably from donor and partner activities in decreasing vaccine-preventable disease and are starting, as a group, to lag behind significantly in the sustainable implementation of new life-saving vaccines. Many reasons, beyond but including donor support and financial constraints, explain this situation.

The work conducted by R4D with support from the Bill & Melinda Gates Foundation and WHO identified the issues and concerns faced by MICs and recommended focus areas to improve national immunization programs. SAGE endorsed the R4D report on the plight of these countries acknowledging and raising awareness of the issues they face at regional and global levels.

The R4D report recommended that technical assistance and capacity-building efforts be extended to MICs. Some partners have begun to do so, but the scope of these activities is still limited to a small sub-set of countries and funding for activities in MICs is very limited. Other partners are looking toward developing strategies to assist MICs.

To ensure the best possible outcomes with limited resources, partners need to organize activities under a global framework to address the information, capacity, and networking gaps; utilize and expand existing tools; develop new tools and mechanisms; and utilize the comparative advantage of each of the partners in a coordinated and efficient manner.

The cost of targeted technical assistance to MICs would come at a fraction of the cost of the investment made to subsidize vaccines in the poorest GAVI-eligible countries. The potential benefits from enhanced decision-making and faster implementation of new vaccines would have a significant impact on the populations of these countries and a substantial share of the world's poor, and would contribute to the global fight against vaccine-preventable disease.

A global policy should assist partners to mobilize resources in a challenging financial environment by identifying the strategies and activities to achieving global immunization targets and reducing the vaccine-preventable disease burden in both low- and middle-income countries.

Annex 1

Middle-income countries: GNI, GAVI eligibility, total population, procurement through UNICEF SD and PAHO RF, and involvement in selected immunization projects

Country Name	World Bank Category[2]	GNI 2011[2]	WHO Region	UN Population Estimate 2010 (000)[3]	GAVI Eligibility	UNOHRLLS LDC, LLDC SIDs [10]	Birth Cohort[4]	Projects Reported as Operating in MIC	Vaccine Procurement Mechanism[6]
Albania[9]	LMIC	3,980	EUR	3,204	ex-GAVI		41,007	PROVAC, OPTIMIZE	UNICEF
Algeria	UMIC	4,470	AFR	35,468	NO		712,254	EMRO PVP, V3P	SELF
American Samoa[1]	UMIC	No Data	WPR	68	NO		No Data		SELF
Angola	UMIC	4,060	AFR	19,082	Graduating	LDC	803,274	V3P	UNICEF
Antigua and Barbuda	UMIC	12,060	AMR	89	NO	SIDS	1,597		PAHO RF
Argentina	UMIC	9,740	AMR	40,412	NO		693,484	PROVAC	PAHO RF
Armenia	LMIC	3,360	EUR	3,092	Graduating	LLDC	47,148	V3P	UNICEF
Azerbaijan	UMIC	5,290	EUR	9,188	Graduating	LLDC	183,787	PROVAC	MIXED
Belarus	UMIC	5,830	EUR	9,595	NO		106,750		SELF
Belize	LMIC	3,690	AMR	312	NO	SIDS	7,727		PAHO RF
Bhutan	LMIC	2,070	SEAR	726	Graduating	LLDC / LDC	14,832	Sabin SIF, V3P	UNICEF
Bolivia	LMIC	2,040	AMR	9,930	Graduating	LLDC	264,140	PROVAC, V3P	PAHO RF
Bosnia and Herzegovina	UMIC	4,780	EUR	3,760	ex-GAVI		31,558		SELF
Botswana	UMIC	7,480	AFR	2,007	NO	LLDC	47,208		SELF
Brazil	UMIC	10,720	AMR	194,946	NO		2,995,976	PROVAC	PAHO RF
Bulgaria	UMIC	6,550	EUR	7,494	NO		75,042		SELF
Cameroon	LMIC	1,210	AFR	19,599	Eligible		715,773	Sabin SIF	UNICEF
Cape Verde	LMIC	3,540	AFR	496	NO	SIDS	10,194		UNICEF
Chile	UMIC	12,280	AMR	17,114	NO		245,427		SELF
China	UMIC	4,930	WPR	1,341,335	ex-GAVI		16,431,611	PROVAC	SELF
Colombia	UMIC	6,110	AMR	46,295	NO		910,296	PROVAC	PAHO RF
Congo, Rep.	LMIC	2,270	AFR	4,043	Graduating	LDC	144,632	Sabin SIF, V3P	UNICEF
Cook Islands[9]	UMIC	No Data	WPR	20	NO		430		UNICEF
Costa Rica	UMIC	7,660	AMR	4,659	NO		73,376	PROVAC	PAHO RF
Côte d'Ivoire	LMIC	1,100	AFR	19,738	Eligible		678,778	SIVAC	UNICEF
Cuba[1,5]	UMIC	No Data	AMR	11,258	Graduating		109,642		PAHO RF
Djibouti[1]	LMIC	No Data	EMR	889	Eligible	LDC	26,031		UNICEF
Dominica	UMIC	7,090	AMR	68	NO	SIDS	1,206		PAHO RF
Dominican Republic	UMIC	5,240	AMR	9,927	NO	SIDS	215,528	V3P	PAHO RF
Ecuador	UMIC	4,140	AMR	14,465	NO		297,868	PROVAC, V3P	PAHO RF
Egypt, Arab Rep.	LMIC	2,600	EMR	81,121	NO		1,885,631	PROVAC, EMRO PVP, V3P	SELF
El Salvador	LMIC	3,480	AMR	6,193	NO		125,686	PROVAC, V3P	PAHO RF
Fiji	LMIC	3,680	WPR	861	NO	SIDS	18,369	PIC VII	UNICEF
Gabon	UMIC	7,980	AFR	1,505	NO		41,620		UNICEF
Georgia	LMIC	2,860	EUR	4,352	Graduating		50,850	PROVAC, USAID, V3P	SELF
Ghana	LMIC	1,410	AFR	24,392	Eligible		776,010	PROVAC, USAID	UNICEF

Country Name	World Bank Category[2]	GNI 2011[2]	WHO Region	UN Population Estimate 2010 (000)[3]	GAVI Eligibility	UNOHRLLS LDC, LLDC SIDs [10]	Birth Cohort[4]	Projects Reported as Operating in MIC	Vaccine Procurement Mechanism[6]
Grenada	UMIC	7,220	AMR	104	NO	SIDS	2,037		PAHO RF
Guatemala	LMIC	2,870	AMR	14,389	NO		473,216	PROVAC, OPTIMIZE	PAHO RF
Guyana[1]	LMIC	No Data	AMR	754	Graduating		13,466		PAHO RF
Honduras	LMIC	1,970	AMR	7,601	Graduating		204,512	PROVAC	PAHO RF
India	LMIC	1,410	SEAR	1,224,614	Eligible		27,098,275	USAID	MIXED
Indonesia	LMIC	2,940	SEAR	239,871	Graduating		4,331,100	SIVAC, USAID	SELF
Iran[1]	UMIC	4,520	EMR	73,974	NO		1,255,194	EMRO PVP	SELF
Iraq	LMIC	2,640	EMR	31,672	NO		1,143,989	EMRO PVP	SELF
Jamaica	UMIC	4,980	AMR	2,741	NO	SIDS	50,146	PROVAC	PAHO RF
Jordan	UMIC	4,380	EMR	6,187	NO		153,808	EMRO PVP	SELF
Kazakhstan	UMIC	8,220	EUR	16,026	NO	LLDC	344,858	SIVAC	SELF
Kiribati	LMIC	2,110	WPR	100	Graduating	LDC / SIDS	2,047	PIC VII	UNICEF
Kosovo[12]	LMIC	3,520	EUR	1,794	NO		No Data		SELF
Lao PDR	LMIC	1,130	WPR	6,201	Eligible	LLDC / LDC	140,398		UNICEF
Latvia	UMIC	12,350	EUR	2,252	NO		24,326	V3P	SELF
Lebanon	UMIC	9,110	EMR	4,228	NO		64,673	SIVAC, EMRO PVP	UNICEF
Lesotho	LMIC	1,220	AFR	2,171	Eligible	LLDC / LDC	60,426		UNICEF
Libya[1]	UMIC	No Data	EMR	6,355	NO		143,762	EMRO PVP	SELF
Lithuania	UMIC	12,280	EUR	3,324	NO		35,239		SELF
Macedonia, FYR	UMIC	4,730	EUR	2,061	NO	LLDC	21,955		SELF
Malaysia	UMIC	8,420	WPR	28,401	NO		579,122		SELF
Maldives	UMIC	6,530	SEAR	316	NO	LDC / SIDS	5,335		UNICEF
Marshall Islands	LMIC	3,910	WPR	54	NO	SIDS	1,110		SELF
Mauritius	UMIC	8,240	AFR	1,299	NO	SIDS	16,466		SELF
Mexico	UMIC	9,240	AMR	113,423	NO		2,194,666		SELF
Micronesia, Fed. Sts.	LMIC	2,900	WPR	111	NO	SIDS	2,732		UNICEF
Moldova	LMIC	1,980	EUR	3,573	Graduating	LLDC	43,549	V3P	MIXED
Mongolia	LMIC	2,320	WPR	2,756	Graduating	LLDC	65,221	SIVAC, Sabin SIF, V3P	UNICEF
Montenegro	UMIC	7,060	EUR	631	NO		7,674		SELF
Morocco	LMIC	2,970	EMR	31,951	NO		620,253	EMRO PVP, V3P	MIXED
Namibia	UMIC	4,700	AFR	2,283	NO		60,036		SELF
Nauru[9]	UMIC	No Data	WPR	10	NO	SIDS	209		UNICEF
Nicaragua	LMIC	1,170	AMR	5,788	Eligible		137,860	PROVAC	PAHO RF
Nigeria	LMIC	1,200	AFR	158,423	Eligible		6,457,908	Sabin SIF, USAID	UNICEF
Niue[10]	LMIC	No Data	WPR	1	NO		30		UNICEF
Pakistan	LMIC	1,120	EMR	173,593	Eligible		4,763,694	USAID	MIXED
Palau	UMIC	7,250	WPR	20	NO	SIDS	417		UNICEF
Panama	UMIC	7,910	AMR	3,517	NO		69,810		PAHO RF
Papua New Guinea	LMIC	1,480	WPR	6,858	Eligible	SIDS	208,495		MIXED
Paraguay	LMIC	2,970	AMR	6,455	NO	LLDC	157,651	PROVAC	PAHO RF
Peru	UMIC	5,500	AMR	29,077	NO		590,552	PROVAC	PAHO RF
Philippines	LMIC	2,210	WPR	93,261	NO		2,357,583	PROVAC, V3P	MIXED
Romania	UMIC	7,910	EUR	21,486	NO		220,534		SELF

Country Name	World Bank Category[2]	GNI 2011[2]	WHO Region	UN Population Estimate 2010 (000)[3]	GAVI Eligibility	UNOHRLLS LDC, LLDC SIDs [10]	Birth Cohort[4]	Projects Reported as Operating in MIC	Vaccine Procurement Mechanism[6]
Russian Federation	UMIC	10,400	EUR	142,958	NO		1,688,954		SELF
Samoa	LMIC	3,190	WPR	183	NO	SIDS	4,457	PIC VII	UNICEF
São Tomé and Principe	LMIC	1,360	AFR	165	Eligible	LDC / SIDS	5,189		UNICEF
Senegal	LMIC	1,070	AFR	12,434	Eligible	LDC	470,836	PROVAC, SIVAC, Sabin SIF, OPTIMIZE, USAID	UNICEF
Serbia	UMIC	5,680	EUR	9,856	NO		109,767		SELF
Seychelles	UMIC	11,130	AFR	87	NO	SIDS	1,094		SELF
Solomon Islands	LMIC	1,110	WPR	538	Eligible	LDC / SIDS	17,301	PIC VII	UNICEF
South Africa	UMIC	6,960	AFR	50,133	NO		1,052,420	V3P	SELF
South Sudan[1, 11]	LMIC	No Data	EMR	8,260	YES		No Data		UNICEF
Sri Lanka	LMIC	2,580	SEAR	20,860	Graduating		373,262	Sabin SIF, V3P	MIXED
St. Lucia	UMIC	6,680	AMR	174	NO	SIDS	3,053		PAHO RF
St. Vincent & the Grenadines	UMIC	6,100	AMR	109	NO	SIDS	1,836		PAHO RF
Sudan[1]	LMIC	No Data	EMR	43,552	Eligible	LDC	1,446,755	USAID	UNICEF
Suriname[1]	UMIC	7,630	AMR	525	NO	SIDS	9,603		PAHO RF
Swaziland	LMIC	3,300	AFR	1,186	NO	LLDC	34,970		SELF
Syrian Arab Republic[1]	LMIC	No Data	EMR	20,411	NO		465,516	EMRO PVP	SELF
Thailand	UMIC	4,420	SEAR	69,122	NO		824,017	V3P	SELF
Timor-Leste[1]	LMIC	No Data	SEAR	1,124	Eligible	LDC / SIDS	44,488	USAID	UNICEF
Tonga	LMIC	3,580	WPR	104	NO	SIDS	2,777	PIC VII	UNICEF
Tunisia	UMIC	4,070	EMR	10,481	NO		179,434	PROVAC, SIVAC, OPTIMIZE, V3P	SELF
Turkey	UMIC	10,410	EUR	72,752	NO		1,288,624		SELF
Turkmenistan	UMIC	4,110	EUR	5,042	Ex-GAVI	LLDC	109,493		UNICEF
Tuvalu	UMIC	5,010	WPR	10	NO	LDC / SIDS	207	PIC VII	UNICEF
Ukraine[5]	LMIC	3,120	EUR	45,448	Graduating		494,153	USAID	SELF
Uruguay	UMIC	11,860	AMR	3,369	NO		49,495	PROVAC	PAHO RF
Uzbekistan	LMIC	1,510	EUR	27,445	Eligible	LLDC	588,666		MIXED
Vanuatu	LMIC	2,870	WPR	240	NO	LDC	7,179	PIC VII	UNICEF
Venezuela, RB	UMIC	11,920	AMR	28,980	NO		598,472		PAHO RF
Vietnam	LMIC	1,260	WPR	87,848	Eligible		1,457,775	PROVAC, SIVAC, Sabin SIF, OPTIMIZE	MIXED
West Bank and Gaza[1]	LMIC	No Data	EMR	4,039	NO		No Data	EMRO PVP	UNICEF
Yemen, Rep.	LMIC	1,070	EMR	24,053	Eligible	LDC	939,589		UNICEF
Zambia	LMIC	1,160	AFR	13,089	Eligible	LLDC / LDC	622,268	USAID	UNICEF

[1] Estimated WB Category without GNI Listed/or Estimated GNI http://data.worldbank.org/about/country-classifications
[2] http://data.worldbank.org/about/country-classifications, accessed 27 July 2012, for the World Bank's explanation of its classification of countries by income.
[3] http://esa.un.org/unpd/wpp/Excel-Data/population.htm accessed 3 August 2012 for UN Population estimations
[4] WHO/UNICEF Joint Reporting Form Data 2011
[5] No Longer accessing GAVI Financial Support for New vaccines
[6] UNICEF PAHO Reported July 2012, Self Procurement estimated by Elimination
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[10] Least Developed Countries, Landlocked Developing Countries, Small Island Developing States http://www.unohrlls.org/

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New vaccine adoption in lower-middle-income countries

Marty Makinen,[1]* Miloud Kaddar,[2] Vivikka Molldrem[3] and Lara Wilson[1]

[1]Results for Development Institute, Washington, DC, USA, [2]World Health Organization, Geneva, Switzerland and [3]Independent consultant

*Corresponding author. Results for Development Institute, 1100 15th Street NW, Suite 400, Washington, DC 20005 USA.
Tel: +1-202-470-5724. Fax: +1-202-470-5712. E-mail: mmakinen@resultsfordevelopment.org

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Objectives Lower-middle-income countries (LMICs) are lagging behind both high-income and low-income countries in new vaccine adoption. Our study involved the following objectives: (1) understand the decision-making processes of LMICs on new vaccine adoption, (2) identify the factors influencing LMIC decisions, (3) obtain the views of vaccine manufacturers about LMIC markets for new vaccines, and (4) make recommendations concerning how to speed up and improve decision making, including proposing mechanisms for implementation of the recommendations.

Methods Collect and analyse qualitative data from participants in decision making in 15 case study countries [12 LMICs and three upper-middle-income countries (UMICs)] and multinational and developing country vaccine manufacturers.

Findings Interviews of actors in decision making indicate that the aspects deemed most important for adoption are: World Health Organization (WHO) recommendations, the existence of local epidemiological data and a set of factors comprising affordability, cost-effectiveness and overall cost of the new vaccine for the programme. National Immunization Technical Advisory Groups (NITAG) have a key role in advising decision-makers, although their resources and capacity vary. Country decision-makers and manufacturers both see advantages in pooled procurement mechanisms for vaccine purchasing. Recommendations for countries and the international community involve assisting with making epidemiological data and vaccine market information accessible to countries, building and reinforcing related analysis capacity, and assisting with purchasing mechanisms and practices such as pooled procurement.

Keywords Immunization, middle income countries, vaccines, GAVI, pooled procurement

KEY MESSAGES

- Of particular importance in new vaccine adoption decisions in lower-middle-income countries (LMICs) are local burden of disease data, vaccine prices and the cost implications of adopting a new vaccine.
- LMICs use a technically-focused decision-making process that places National Immunization Technical Advisory Groups in a key advisory role.
- Recommendations include making epidemiological data and vaccine market information accessible to countries, building and reinforcing related analysis capacity, and promoting more efficient procurement mechanisms such as pooling.

Introduction

Lower-middle-income countries[1] (LMICs) receive little external support for their vaccination programmes, despite representing about 57% of annual global births and a more than commensurate share of the burden of disease. The World Health Organization (WHO) has estimated that there were 8.1 million cases of *Haemophilus influenzae* type b (Hib) worldwide in 2000, before widespread use of vaccines against Hib by other than high-income countries, and that 5.6 million (69%) were in LMICs (WHO 2011a).

Until a recent revision in eligibility in 2011, the GAVI Alliance was assisting 41 lower-income countries and 31 at the lower-income end of the LMIC category. On 18 July 2011, among the World Bank's countries classified as lower-middle-income, 40 were not GAVI eligible while 16 were deemed to be 'graduating' from GAVI support in the coming years, as their per capita Gross National Income (GNI) was above the GAVI threshold of US$1500.

Since 2000, GAVI has assisted the countries it supports for the adoption of new vaccines, such as the pneumococcal conjugate and rotavirus vaccines, through the purchase of vaccines with only a small requirement of co-financing from countries. GAVI eligibility has been associated with accelerated adoption of Hib vaccine (Shearer *et al.* 2010). Many GAVI eligible countries are currently introducing these new vaccines and a majority of the remainder has submitted applications to do so. New vaccines such as pneumococcal and rotavirus have already been introduced into the immunization schedule of the vast majority of high-income countries. By contrast, very few non-GAVI LMICs have adopted them. For instance, 86% of GAVI-assisted countries (whether low-income or lower-middle-income) had adopted the Hib vaccine in their national immunization programmes by 2010, but only 54% of the non-GAVI LMICs had done so (WHO 2011b). Few of the latter countries had adopted new vaccines such as rotavirus and pneumococcal (see Table 1).

National immunization programmes in non-GAVI-eligible LMICs generally have strong managerial capacity and perform well in delivering basic Expanded Program on Immunization (EPI) vaccines to their birth cohort, although there is some heterogeneity within the group of countries. Coverage rates reported to WHO[2] are high; half of the 24 countries achieve over 90% coverage (WHO 2011b) (see Table 1). The programmes are financially self-sufficient, since all costs are paid from national budgets (Lydon *et al.* 2008). Thus there is a strong base to build upon, although adding new vaccines would often mean a substantial increase in the vaccine budget.

Non-GAVI-eligible LMICs must fund from their national budgets future purchases of vaccines that they add. A study reported that the average routine immunization expenditures worldwide increased from US$6 to US$18 annually per infant between 2000 and 2010 (Lydon *et al.* 2008). In the open market, the prices of these vaccines are substantially higher than the traditional EPI vaccines. For example, Morocco obtained prices of US$22 per dose for pneumococcal and US$7 per dose for rotavirus vaccines through international tendering in 2009 vs

Table 1 Adoption of new vaccines by lower- and upper-middle-income countries (LMICs and UMICs)

Country		Decided to adopt vaccine?					2009 DTP3 coverage
		HepB	Hib	HPV	Pneumo	Rota	
LMIC country case studies							
Country visits	Armenia*	✓	✓	–	–	–	93
	China	✓	–	–	–	–	97
	Ecuador	✓	✓	–	✓	✓	75
	Egypt, Arab Rep.	–	–	–	–	–	97
	Indonesia*	✓	–	–	–	–	82
	Morocco	✓	✓	–	✓	✓	99
	Syrian Arab Republic	✓	✓	–	–	–	80
Remote	Cape Verde	✓	✓	–	–	–	99
	Philippines	✓	✓	–	–	–	87
UMIC country case studies							
Country visits	Panama	✓	✓	✓	✓	✓	84
	Thailand	✓	–	–	–	–	99
	Turkey	✓	✓	–	✓	–	96
Remote	Albania*	✓	✓	–	✓	–	98
	South Africa	✓	✓	–	✓	✓	69
	Tunisia	✓	–	–	–	–	99

Sources: WHO Vaccine Preventable Diseases Monitoring System, Updated 3 October 2011; cited 8 December 2011. Online at: http://apps.who.int/immunization_monitoring/en/globalsummary/scheduleselect.cfm.

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Notes: ✓ = Yes; – = No.

*Indicates a country that has benefited from GAVI support.

US$0.124 to 0.34 per dose in 2008 for BCG, measles, DTP, oral polio and hepatitis B (Morocco Direction of Population and Division d'Approvisionnement 2011, pers. comm.). The majority of non-GAVI-eligible LMICs must procure their vaccines on the open market. However, the non-GAVI-eligible LMICs in the Americas purchase through a 'pool' via the Revolving Fund of the Pan American Health Organization (PAHO). A few other non-GAVI LMICs buy vaccines through UNICEF's Supply Division.

In 2008, the WHO's World Health Assembly and Immunization Strategic Advisory Group of Experts noted that there was little literature and knowledge on the obstacles faced by LMICs in adopting new vaccines. They acknowledged the importance of vaccination in LMICs to global health goals and recommended that WHO investigate obstacles and mobilize resources for LMIC adoption of new vaccines. A study was designed to validate the hypothesis that LMICs were falling behind in vaccine adoption and to understand the decision-making processes of LMICs in new vaccine adoption. It sought to identify factors explaining adoption with the aim of making recommendations to the countries and the global health community.

The research focused primarily on exploring the factors behind adoption of the most recently introduced vaccines such as Hib, pneumococcal conjugate, rotavirus and human papillomavirus (HPV) as well as some vaccines of specific regional interest, such as Japanese Encephalitis. The study methodology built on previous work analysing factors in vaccine adoption (DeRoeck *et al.* 2003; DeRoeck 2004). This paper provides a timely analysis of reasons and decision-making processes for new vaccine adoption in LMICs and offers practical recommendations at the global, regional and national levels to address the issues identified.

Methods

The study used qualitative semi-structured key informant interviews. Additional selected quantitative analysis was performed[3] but is reported elsewhere (Results for Development 2011). The interviews were conducted in 2010 with a total of 204 key informants in 15 countries (see Table 2). The 15 countries chosen included 12 classified as LMICs and three classified as UMICs in 2008[4] (see Table 1 for the case study countries). Headquarters staff at 10 vaccine manufacturers were separately interviewed, using a guide to canvass their views on the factors influencing adoption and concerns around LMIC markets.

The case-study countries were selected purposively by the study team in consultation with its Advisory Group to achieve diversity in geographical location, population size, Gross Domestic Product (GDP) per capita and history of new vaccine adoption. The countries included three that have previously benefited from GAVI support: Albania, Armenia and Indonesia. Three UMICs were included (Panama, South Africa and Turkey) because the Advisory Group thought lessons could be learned from their vaccine adoption experiences. Nine of the country case studies were conducted with visits and face-to-face interviews, and remote data collection methodology was employed in the six remaining countries. The remote data

Table 2 Key informants interviewed

Type of interviewee	Lower-middle-income countries (LMICs)[a]										Upper-middle-income countries (UMICs)[a]							Total
	Country visits						Remote				Country visits			Remote				
	Armenia	China	Ecuador	Egypt	Indonesia	Morocco	Cape Verde	Philippines			Panama	Thailand	Turkey	Albania	South Africa	Syria	Tunisia	
National EPI staff	2	1	1	3	4	–	–	1			3	1	4	–	1	1	1	**23**
NITAG members	2	2	3	3	3	–	–	–			–	4	2	–	1	–	1	**21**
Other national government staff (e.g. MOH, MOF, Parliamentarians)	11	2	5	4	2	16	2	1			6	5	5	–	1	–	–	**60**
International agency staff (e.g. WHO, UNICEF, CHAI)	4	1	3	6	4	4	2	3			2	–	6	4	–	–	1	**40**
National organizations (e.g. academics, civil society, professional associations)	–	4	3	1	–	8	–	1			2	4	2	2	–	2	–	**34**
Sub-national MOH staff	1	1	2	–	–	–	–	–			–	–	–	–	–	–	–	**4**
Others (e.g. pharmaceutical companies)	–	–	1	6	4	13	–	–			1	–	2	–	1	–	–	**28**
Total	**20**	**10**	**18**	**23**	**17**	**41**	**4**	**6**			**14**	**14**	**21**	**6**	**4**	**3**	**3**	**204**

Notes: [a]The LMIC and UMIC classifications here are for 2011. In the 2008 classifications used to select countries for inclusion in the study, Albania, Syria, Thailand and Tunisia all were LMICs.
EPI = Expanded Programme on Immunization; NITAG = National Immunization Technical Advisory Group; MOH = Ministry of Health; MOF = Ministry of Finance; WHO = World Health Organization; UNICEF = United Nations' Children's Fund; CHAI = Clinton Health Access Initiative.

collection (by phone and email) was used in case study countries with smaller populations and in one country (Philippines) for which substantial information was already available through a recent WHO vaccine procurement assessment. The six case studies conducted remotely involved fewer interviews than those using site visits (see Table 2).

All interviews in the visited and remotely studied countries were conducted with the same set of interview guidelines (Results for Development 2011). Interviews were open ended and probed when necessary. The interview guide focused on factors of adoption, constraints and enabling factors concerning vaccine adoption, and the decision-making process in recent vaccine adoptions. It also explored suggestions by key informants on how decision-making processes could be improved. The hypothesized factors explored by interviewers were based on previous studies' findings (DeRoeck *et al.* 2003; DeRoeck 2004; Munira and Fritzen 2007; Griffiths and Miners 2009). They included epidemiological information, prices and costs, recommendations by international bodies, experience with vaccines in private markets, the role of the media, procurement options and whether neighbouring countries had adopted. Factors in the decision-making process were classified in five categories: 'factors reported by interviewees to be critically important'; 'factors considered to be important'; 'factors considered a bit important'; 'factors considered not important'; and factors that were 'not available or not considered'.

Key informants were selected in consultation with the relevant WHO Regional Office and the local immunization programme manager in each country and also used a snowball methodology. Key informants were informed that individual comments would not be directly attributed.

The country and remote interviews were conducted by teams with skills and experience of working on immunization issues and new vaccine adoption from a multiple disciplinary background, including economics, policy and public health. All teams used the same interview guide and had overlapping membership to ensure adequate consistency of approach, but differed because of language skills required and availability. Interviews took between 30 and 90 minutes each. The interviewers took notes and compiled results, charting data thematically and analysing results on a cross-country basis. On some occasions follow-up emails or phone calls were employed to clarify responses or to fill gaps.

Findings

Decision-making process in lower-middle-income countries

All countries appear to take a systematic and technical approach in deciding whether or not and when to adopt a new vaccine. Almost all countries have established a National Immunization Technical Advisory Group (NITAG) or equivalent technical body that makes recommendations on the adoption of new vaccines.

> *"The task force on immunizations (NITAG equivalent) takes up new vaccines that are available, studies the evidence about them, and makes recommendations to the Minister of Health. Once the Minister is convinced, he goes to the Council of Ministers for the final decision."* (Cape Verde national informant on the adoption of Hib and MMR vaccines)

However, this technical approach to decision making often has imperfections. The membership and skills of NITAG members tend to vary as well as the way they operate (see Table 3). Some NITAGs meet only when called upon by the Ministry of Health, while others meet on a regular basis. Some can set the agenda, while others require the Ministry of Health to propose a new vaccine for adoption. Seven of the 15 countries allowed international agencies to be members of the committee, while the remainder does not. Seven included members with some economic analysis skills.

The role of the NITAG or equivalent committee was found to be key in all countries studied, except in two cases where a new vaccine was introduced prior to the set up of the advisory committee (Hib vaccine in Armenia and rotavirus vaccine in Panama) and the decision made was more political.

In all countries studied, the Minister of Health played a critical role, either initiating the decision to take up the new vaccine, for example in Panama and Turkey, or responding to recommendations of the NITAG. In some countries there was support at higher political levels. In Morocco, the first lady of the Kingdom championed HPV vaccine (see Box 1). Ministry of Finance buy-in was deemed important to adoption, since it had to approve overall health budgets, although specific allocations

Table 3 Characteristics of National Immunization Technical Advisory Groups (NITAGs) in case-study countries

Country	It has resources to gather research and to commission research when local data are not available	It has local cost-effectiveness data and members with economics skills	International organizations, such as WHO and UNICEF, are formal members
Albania	✓	✓	✓
Armenia	✓	✓	–
Cape Verde	–	–	✓
China	✓	–	–
Ecuador	✓	✓	✓
Egypt	–	–	–
Indonesia	✓	✓	–
Morocco	✓	–	✓
Panama	✓	✓	✓
Philippines	–	–	✓
South Africa	✓	–	✓
Syria	✓	–	–
Thailand	✓	✓	–
Tunisia	✓	–	–
Turkey	✓	✓	✓

Key: ✓ The statement applies to the country; – The statement does not apply to the country.

within the health budget usually remained within the Ministry of Health's decision-making power.

> *"The major obstacle to increasing the health budget [sufficient to pay for new vaccines] is having good indicators of performance that would enable us to judge programme effectiveness."* (Armenian Ministry of Finance)

Unlike in low-income countries, we found that external partners, such as WHO, UNICEF and bilateral donors, only provide limited support on immunization policy in non-GAVI LMICs, despite global and regional recommendations and advocacy for new vaccines by WHO and others.

> *"We no longer work on immunizations per se; we are focused on issues around children's rights."* (International Agency in Egypt)

Other key aspects of the decision-making process involved the development of government multi-year plans and budgets and the enacting of vaccine-related legislation, notably in countries in the Americas that made universal access to immunizations a mandatory obligation of governments (Ecuador, Panama).

Box 1 Decision-making process in Morocco

The interest of the Moroccan first lady's Lalla Salma Foundation in cancers was instrumental in putting HPV vaccine on the agenda for adoption. However, the decision to introduce pneumococcal conjugate and rotavirus vaccines in 2010 was aided by a more technocratic process. Early and in-depth discussions between the Ministry of Health and the Ministry of Finance resulted in a shared conclusion that the economic justification for the vaccines was solid. Another key step in the decision-making process was inclusion of these vaccines in the 2008–2012 National Health Plan. In addition the Ministry of Health developed advocacy documents that showed graphically the burden of disease of the two diseases locally and regionally, the savings obtainable through prevention and the projected cost for the vaccines.

Once NITAGs recommend a new vaccine for adoption, the decision whether to accept the recommendation also was subject to discussions and iterations. Health ministries were confronted with the need to balance between financing the new vaccine and other priorities that often involved a growing and more visible burden of chronic and non-communicable diseases, in the context of a perception that high child mortality largely has been solved. A key informant in Egypt for instance noted that mortality from pneumonia and diarrhoea was low on the government's priority list because good access to low-cost treatment had reduced the disease burden. The importance of local evidence, notably in relation to burden of disease, was reported in all countries. Twelve out of 15 NITAGS reported that they had access to resources to commission research when local data were not available. However, these key informants reported variability in accurately interpreting data on the burden of disease and cost-effectiveness studies.

Factors influencing decisions

Our findings on the factors deemed critically important or important in explaining vaccine adoption decision-making will be reported in four categories: those reported by interviewees to be important in every country studied, those important in many countries, those important in a limited number of countries, and those that were hypothesized to be important *ex ante* but found in fact to be of importance in only a few countries (see Table 4). Key informants reported that the critical drivers in adopting a new vaccine were burden of disease information, the price of the vaccine and funding for the new vaccine. The WHO estimate of burden of disease and related recommendations on use were also deemed important factors in every country studied.

Burden of disease

Key informants in all countries reported that although WHO recommendations were important, they considered it essential to have their own country-specific burden of disease data. Some give weight to burden information from neighbouring countries, but this is decidedly less valuable than having their own data, particularly for large countries. Availability of burden data had implications for the decision to adopt. For instance, Morocco decided to adopt HPV vaccine in 2015 on condition that the local burden of disease could be demonstrated. In Thailand, an analysis of burden of disease and costs led to the decision not to adopt the Hib vaccine. But only in a few countries were efforts being made to collect data when it was not available. Large countries, such as China, South Africa, Thailand and Turkey, and those with strong academic and research capacity were more likely to have access to country-specific epidemiological studies. In contrast, smaller countries such as Cape Verde tended to rely more on WHO recommendations. Finally, four of the case-study countries saw the epidemiological burden in terms of morbidity rather than mortality level for diseases that are preventable with pneumococcal, rotavirus and Hib vaccines.

Cost-related drivers

Issues identified as important in final decision making included vaccine price, cost-effectiveness, budget impact and affordability, and available financing. All countries reported in one form or another that financial considerations were very important in the decision-making process, generally after the vaccine had been recommended on epidemiological, safety and effectiveness grounds.

Price of vaccines was cited as an important factor by 9 of the 15 countries. The six countries that did not cite price as an *important* factor were Albania, China, Ecuador, Indonesia, Panama and Turkey. Among these Indonesia and China rely mainly on domestic vaccine manufacturers and negotiate or set prices for them. Two others, Ecuador and Panama, use the PAHO Revolving Fund.

Value for money was a factor in the majority of the countries studied. Cost-effectiveness was cited by 11 of the 15 countries, although only in two countries could cost-effectiveness studies be sourced. Thailand decided not to adopt Hib-containing vaccine because of an unfavourable cost-effectiveness analysis result. The cost-effectiveness analysis in Tunisia was cited

Table 4 Summary of critically important and important factors influencing vaccine adoption

Country	Broadly important factors					Factors important in multiple countries			Factors important in a few countries						
	Epidemiology	Cost-related concerns			WHO BOD ests. & recommendations	Neighbours' experience	UNICEF, PAHO or GAVI procurement	Engagement by global and regional organizations	Champions	NIP strength	Local production	Local events	Perception of vaccine safety	MDG 4 progress	Private market
		Cost-effectiveness	Budget resources devoted to vaccines	Price											
Albania	✓	✓	✓		✓		✓	✓		✓					
Armenia	✓	✓	✓	✓	✓	✓	✓						✓		✓
Cape Verde	✓		✓	✓	✓	✓	✓	✓		✓		✓		✓	
China	✓	✓	✓	✓	✓	✓					✓	✓	✓		
Ecuador	✓		✓		✓		✓	✓							
Egypt	✓	✓	✓	✓							✓				
Indonesia	✓	✓	✓		✓						✓				
Morocco	✓			✓	✓			✓	✓					✓	
Panama	✓	✓			✓	✓	✓		✓						
Philippines	✓	✓	✓	✓	✓		✓								
South Africa	✓	✓	✓		✓	✓			✓	✓		✓		✓	✓
Syria	✓	✓	✓	✓	✓	✓		✓							
Thailand	✓	✓		✓	✓										
Tunisia	✓	✓		✓	✓										
Turkey	✓	✓	✓		✓	✓			✓				✓		
Total	15	12	11	9	14	7	6	5	4	3	3	3	3	3	2

Notes: WHO BOD ests. = World Health Organization burden of disease estimates; NIP = National Immunization Programme; MDG 4 = Millennium Development Goal 4.

by nearly all national respondents as giving a clear priority to which new vaccines to adopt first, second and third.

In addition, Ecuador performs cost-effectiveness analysis prior to adopting a new vaccine and, if a favourable ratio is found, then price is not a key factor in the decision. Turkey also conducts cost-effectiveness analyses and, further, feels that its birth cohort size gives it bargaining power on prices. Having a secure source of funding for vaccines was also reported as important. Eleven out of 15 countries said having a budget line for vaccines was a key factor and those that did not have budget lines specifically for vaccines stated they had concerns over the sustainability of financing. GAVI graduating countries indicated that the challenge of raising the resources to add new vaccines would be particularly difficult, since the increases in vaccine spending needed to pay for previously GAVI-subsidized vaccines and for additional new vaccines were so large.

> *"I don't know how we will be able to achieve such a big increase in vaccine funding from the Ministry of Finance once the GAVI assistance ends."* (Armenian Ministry of Health)

Eleven of the case-study countries indicated that they did not have a reliable source to go to for vaccine prices and market conditions. However, PAHO countries such as Panama and Ecuador felt confident that they could rely on the PAHO Revolving Fund for price information and, as mentioned above, China and Indonesia negotiated prices for vaccines from domestic manufacturers. Interviews showed that there was a degree of confusion over the prices to be paid for new vaccines. Countries often cited prices and market conditions that were incorrect or long out of date. It was often assumed by country informants that prices would be the same as those paid by high-income countries or domestic private markets. Impact on vaccine price of large volume orders or the agreement of multi-year contracts that include other services bundled (such as technical assistance) with the vaccine price were often misunderstood. Finally there was uncertainty and speculation among key informants on the future level of prices.

> *"We are unsure whether the price we get this year will be similar to the prices we'll get over the next few years."* (Ministry of Health official, Egypt)

Other decision-making factors

Other less important factors cited by key informants included the experience of neighbouring countries (7/15), access to adequate procurement mechanisms (6/15) and the role played by global/regional bodies to engage countries (5/15).

Those countries with access to pooled procurement (in the Americas) or UNICEF's Supply Division services (e.g. Morocco) saw this as advantageous. Smaller population countries, such as Cape Verde and Armenia, expressed worries that they might be taken advantage of without the benefit of pooled procurement mechanisms, such as those offered by UNICEF and PAHO. Panama, which participates in PAHO's Revolving Fund, had no such concerns. Some countries expressed an interest in pooling arrangements, such as respondents in Egypt who expressed interest in joining a regional pool.

Factors that were found to be important in few countries included leadership by local champions and advocacy by other influential parties (4/15); local vaccine production (in countries with production capacity) (3/15); precipitating local events (such as outbreaks of vaccine-preventable diseases) (3/15); perception of vaccine safety (3/15); strength of the existing routine immunization programme (3/15); insufficient progress towards Millennium Development Goal (MDG) targets (3/15); and experience of the private sector vaccine market (2/15).

The role of local vaccine production was deemed important as a factor for decision making in countries that have local production. Countries with local production capacity include Egypt, China, Indonesia and Thailand. To date only China produces rotavirus vaccine among the new vaccines. While not explicitly a condition for adoption, the issue of whether local manufacturers could be suppliers came up in many of the interviews conducted in these countries.

The capacity to achieve the MDGs was cited by three countries, and notably by Morocco, whose Ministry of Health sees the adoption of pneumococcal and rotavirus vaccines as a key intervention to accelerate progress to reach the goals by 2015.

The strength of the existing routine immunization programme was cited by four countries as a factor in their decision-making process. Some key informants in countries such as Thailand and Turkey expressed concern that a too rapid adoption could jeopardize the effectiveness of their programmes.

Many of the new vaccines are available in the private markets of all 15 countries (5–10% of birth cohort). A majority of informants indicated the presence of the vaccines in these markets, and the perception that they are used safely and effectively was a positive influence on attitudes of decision-makers toward national adoption.

Factors of limited importance

Factors that the study found to be of limited importance (in single countries or mentioned only indirectly in interviews) included: (1) vaccine characteristics (including presentation, cold chain and other infrastructure requirements as well as less traditional characteristics such as injection schedule and location of production), and (2) the role of the media. However, Panama ran into cold chain capacity issues when it began to implement national use of new vaccines. The case studies found that several countries use the media to promote new vaccines and to disseminate information to the public about them, but in none of them did we hear that there is pressure from the media to adopt new vaccines.

Manufacturer views

Key informant interviews of multinational and developing country manufacturers (MNMs and DCMs, respectively) showed that they view LMICs as attractive markets, although they market vaccines by geographical zones rather than by income levels. Manufacturer informants reported that they do not see a capacity problem in supplying LMICs as long as there is advance forecasting of when adoption will take place. The manufacturers noted that GAVI's success in 'creating a market' was based on its strong procurement practices, including

accurate demand forecasting, multi-year contracting and assured funding.

Both groups of manufacturers reported support for pooled procurement by LMICs, despite their responses indicating unhappiness with the PAHO Revolving Fund pooling procurement across its member countries with widely varying levels of per capita income. DCMs see pooled procurement as giving them access to markets (as GAVI's procurement through UNICEF's Supply Division has done) and MNMs appreciate the likely reduction of transaction costs, ease of procurement and more-reliable forecasting resulting from pools. MNM respondents said that the ability for individual MNMs to maintain a tiered pricing approach, however, is important to them. Tiered pricing[5] means charging higher prices to countries with higher per capita income (said to allow manufacturers to recover investment costs of developing and increasing capacity for new products) and lower prices to countries with lower per capita income (to make products more accessible).

DCMs view themselves as disadvantaged compared with MNMs in terms of their ability to produce and market the new vaccines. DCMs are reportedly eager to see more technology transfer agreements between themselves and biotechnology companies, public health institutes and MNMs. MNMs said that they, too, are interested in technology transfers with DCMs, provided that the agreements are based on 'economics' (both reasonable financial compensation to the MNMs and paying attention to the scale economies of supplying the recipient) and not political factors (e.g. being required to transfer technology as a condition to supply a country). The DCMs also see some LMICs favouring longer-standing relationships with MNMs, even though the DCMs have WHO pre-qualified products to offer.

Some of the larger-population LMICs with vaccine industries, such as China, India and Indonesia, are likely to access new vaccines through various technology transfer arrangements to their local manufacturers. Technology transfers, however, take time, which may delay new vaccine introduction if the countries are unwilling to source vaccines externally in the interim.

Discussion

Our study found that the burden of disease data, vaccine prices and the cost implication of including the new vaccine in the immunization schedule were the most important factors in new vaccine adoption decisions in LMICs. This is consistent with previous studies (DeRoeck *et al.* 2003; DeRoeck 2004; Walsh and Mitu 2006; Griffiths and Miners 2009; Burchett *et al.* 2012).

The study showed that NITAGs play an increasingly important role in technically-focused decision-making processes in advising the Ministries of health and finance whether to adopt a new vaccine. This confirms previous findings by Munira and Fritzen (2007), Schoub *et al.* (2010) and Senouci *et al.* (2010), although NITAGs or their equivalent remain uneven in their capacity and resources across the 15 countries.

As mentioned previously, LMICs lag behind developed and GAVI-eligible countries in the consideration and adoption of new vaccines such as pneumococcal, rotavirus and HPV. As a result it will be critical to strengthen the current decision-making process to allow these countries to make evidence-based appropriate decisions. This involves the development of local evidence, in line with the perception that local burden of disease is key to the decision-making process. This could involve reinforcing country capacity, increased co-operation between LMICs and additional support from regional or global agencies. A particular emphasis may be placed on promoting the use of cost-effectiveness and economic benefit analysis of vaccination (Bloom 2011), which has been identified as critical in the decision-making process (Walsh and Mitu 2006) and was cited by a clear majority of the countries included in the study as a factor important in decision making. This will also mean that NITAGs are better supported and resourced.

Recommendations by WHO on vaccine adoption are valued by a majority of countries surveyed. However, our study also highlighted the lack of support by international agencies to LMICs. These agencies do not tend to focus on immunizations in LMICs, with studies showing instead that they have been increasingly focused on chronic and non-communicable diseases. This might account for the finding that advocacy was of lesser importance compared with other factors for the countries studied, not because it was not listened to, but because of its absence from the agenda of WHO, UNICEF and others.

A key finding of the study is the lack of understanding by many LMICs of pricing mechanisms for new vaccines, and the lack of procurement mechanisms to ensure affordable and reliable supplies. Our study showed that pooled procurement was viewed as a good strategy to obtain better prices for vaccines, while also economizing on procurement effort by sharing costs. The study concluded from manufacturers' interviews that LMICs with smaller populations lacked bargaining power and information about prices, suppliers and procurement options. The smaller-population LMICs could be the greatest beneficiaries of joining a pooled procurement mechanism and having access to comprehensive information about vaccine markets, though pooled procurement could also be attractive to larger-population LMICs such as Egypt. Our survey of vaccine manufacturers indicated that they also see certain advantages to pooled procurement. However, pooled procurement raises organizational and political challenges (DeRoeck *et al.* 2006). It requires participating countries to agree and co-ordinate on matters including the choice of vaccines, regulation, presentations and, potentially, schedules. This means that countries would give up some sovereignty and renounce individual procurement. Stronger regional or international leadership would be critical to push pooled procurement development forward, with UNICEF being in a good position to procure on behalf of LMICs that would request it.

The study heard from case-study countries that they did not have a reliable source to go to for vaccine prices and market information. Thus, there is a need to organize and maintain a clearinghouse to provide reliable and accurate information to LMICs, possibly based on the further development of the WHO's Vaccine Product, Price, and Procurement Project.[6] This clearinghouse could build on and expand the model of the price information provided by PAHO or by UNICEF's Supply Division. This would allow countries both to benchmark prices, thus

gaining useful insight of the marketplace, and to advocate for higher domestic financing. However, a limitation would be that there remain limited incentives for countries to submit procurement and price information to the clearinghouse.

The specific case of countries graduating from GAVI support needs to be highlighted. These countries stressed the challenge of raising additional resources to add new vaccines in the context of having to take over financing from GAVI of the existing vaccines. It remains to be seen whether the termination of external subsidies will cause a lag in new vaccine adoption by GAVI graduates compared with never-GAVI-eligible LMICs that had a similar or lower ability to pay.[7]

We have shown that financial considerations, not surprisingly, are important in decisions on whether to adopt by LMICs. However, this is not a simple question of price per dose or cost per fully immunized child. There are many uncertainties in decision making, such as the affordability of the new vaccine, the overall cost and funding requirements of the immunization programme, the uncertainty about the future level of prices, and the price available depending on different procurement arrangements. Countries need guidance and improved information on how to better address these particular issues. Further discussions with the vaccine manufacturers are needed to address tiered-pricing policy and technology transfer.

Strengths and limitations

The strength of this study lies in the high number of LMICs surveyed and in the wide range of decision-makers and key influential actors that were interviewed using a standard research protocol. By drawing on a large set of key informants we were able to satisfactorily triangulate information. Another strength was that the study collected the views of vaccine manufacturers at the national and global levels, allowing recommendations to address both demand and supply issues around new vaccine adoption. However, there are several limitations to the study that we would like to highlight.

A first limitation is that we had a two-tier approach to the research, with some countries being surveyed with field visits and others remotely. This was mitigated by the use of a single protocol. Differing numbers of people were interviewed in each country, reflecting both varying stakeholders' landscape and availability of interviewees. This is mitigated by taking the country, not the individual respondent, as the unit of analysis. Overall our findings were broadly consistent across countries, although each country has its own specific conditions to address. A second limitation is that although many themes highlighted by the research were common to the 15 countries, the results may not extend to all vaccines and countries. However, we consider that our findings based on a set of diverse countries do provide a valuable contribution to understanding of why LMICs lag behind in new vaccine adoption, and provide recommendations on how some of the current constraints to vaccine adoption can be alleviated.

Recommendations

The information produced by the study has led to the formulation of practical recommendations at the country, regional and global levels to assist LMICs in improving the decision-making process for new vaccine adoption. The recommendations formulated by the study team in close consultation with the study's Advisory Group address four themes: (1) evidence and capacity building, (2) policy and advocacy, (3) financing, and (4) procurement and supply. Table 5 details the study's highest priority recommendations.

The first set of recommendation calls for LMICs with the support of regional and global agencies to strengthen their capacities in epidemiological and economic analysis so that decisions can be backed by evidence-based analyses. The second and third sets of recommendations address funding for new vaccines. At the country level, recommendations involve improved access to information on prices and possible procurement arrangements to ensure affordable and sustainable supply. Recommendations for global and regional stakeholders

Table 5 Lower-middle-income country and new vaccine study; first priority recommendations

Theme	Level		
	Country	Regional	Global
Evidence and capacity building	Strengthen epidemiological and economic analysis capacities	Actively promote and strengthen regional information-sharing and joint research on burden of disease, pricing, cost-effectiveness, etc. (regional clearinghouse)	Create a technical and reliable source for global vaccine market information including vaccine pipeline, vaccine prices, pricing policies, procurement principles and practices
Policy and advocacy	Improve procurement regulation to promote competition, quality and sustainability	Conduct advocacy to strengthen political will and support champions for new vaccines	Conduct advocacy to strengthen political will, regulation and policy development
Financing	Take steps to increase domestic funding and capacities to negotiate with Ministries of Finance and other potential funders	Increase countries' and partners' awareness of the value of vaccination in the broader context of government investment and achievement of the MDGs	Promote transparency and access to comparatively low and affordable vaccine prices with sustainable domestic financing
Procurement and supply	Consider using or joining a pooled procurement mechanism	Develop inter-country and regional processes for achieving pooled procurement (where desired by countries), vaccine quality, safety and diversified and sustainable base of supply	Support regional and country activities for efficient and effective procurement systems through assessment, and identification of improvement to current practices and policies

involve assisting LMICs to create the conditions to make evidence-based decisions about new vaccine adoption, and the promotion of transparent and healthy markets for vaccines. The last recommendation involves strengthening pooling mechanisms to ensure both access to favourable vaccines prices and reliable supply for countries, and better forecasting, standardized procurement practices and economies of scale for manufacturers.

Conclusion

Our study found that LMICs are using a technically-focused decision-making process that places the NITAGs in a key advisory role. Factors deemed important to country stakeholders in the adoption of new vaccines include the burden of disease, cost-related drivers such as affordability and overall costs of the new vaccines and access to adequate procurement mechanisms. There is an opportunity for the international community to harness the role played by NITAGs in these countries to further strengthen the use of evidence in decision-making concerning new vaccine adoption. Actions to improve access to more affordable prices and suitable products and supply need to be taken at country, regional and global levels. These might involve increasing awareness and understanding by countries of vaccine pricing, and promoting better transparency of prices and more efficient procurement mechanisms including pooling. It is reasonable to argue that the cost of implementing these recommendations would represent only a small fraction of the current cost of GAVI's support to low-income and lower-middle-income countries.

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Conflict of interest

None declared.

Endnotes

[1] This study uses the World Bank's definition of a lower-middle-income country for 2008, GNI per capita of US$976–3855.

[2] Specific vaccine coverage surveys sometimes show lower rates than the figures reported to WHO.

[3] The quantitative analysis sought to examine the relationship between measurable hypothesized factors (many of those shown in Table 4 of this paper) and the actual adoption decisions of countries for Hepatitis B and Hib vaccines.

[4] The 2008 classification of countries was the most recent available when the study began in 2009. Note that four of the 2008 LMICs became UMICs by the 2011 classification (Albania, Syria, Thailand and Tunisia).

[5] See http://www.who.int/immunization_financing/options/en/briefcase_pricingtiers.pdf, accessed 27 May 2011.

[6] The World Health Organization's Vaccine Product, Price, and Procurement Project (V3P) was established in 2011 and took up some of this study's recommendations about a clearinghouse.

[7] Some of the rapidly growing graduating countries now surpass in per capita income some of the countries that never were eligible for GAVI support.

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