SAGE April 2011

This booklet contains key background documents for the meeting of the Strategic Advisory Group of Experts on Immunization (SAGE), 5 - 7 April 2011

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

http://workspace.who.int/sites/sage/default.aspx

For password, please send an e-mail to:

sageexecsec@who.int
# Table of Contents - April 2011

<table>
<thead>
<tr>
<th>Agenda</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of SAGE members</td>
<td>6</td>
</tr>
<tr>
<td>Terms of Reference</td>
<td>8</td>
</tr>
<tr>
<td>Current SAGE working groups</td>
<td>17</td>
</tr>
<tr>
<td>List of participants</td>
<td>22</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>34</td>
</tr>
</tbody>
</table>

**Session 1: Report from IVB Director including status of implementation of recommendations**

2. SAGE tracking record of recommendations and action points. 54
3. WHO. 64th World Health Assembly. Global Immunization Vision and Strategy: Draft of Progress report and strategic direction for the 'Decade of Vaccines'. Report by the Secretariat. 73

**Session 2: Regional priorities, major policy and implementation issues: reports from AFR, EMR and SEAR**

AFR

1. WHO. Recommendations from the 17th-18th Task Force on Immunization (TFI) Meetings held in Addis Ababa, Ethiopia, 20th-21st April 2010 and Ouagadougou, Burkina Faso, 3rd-4th December 2010. (Full report available on the website) 83

EMR

1. WHO. 26th meeting of the regional technical advisory group on immunization. Cairo, Egypt 8 July 2010 92

SEAR

1. None

**Session 3: Report from the GAVI Alliance Secretariat**

1. GAVI Alliance Board Meeting 30 November to 1 December 2010: Final Minutes 96

**Session 4: Reports from other Advisory Committees in Immunization**

**GACVS report**

2. GACVS. Statement on Fluzone and febrile seizures. 24 January 2011. 120
3. GACVS. Statement on narcolepsy and vaccination. 8 February 2011 121

**Session 5: Pandemic and seasonal influenza vaccines**

1. WHO draft of Preview Report (draft) of the Review Committee on the Functioning of the International Health Regulations (2005) and on Pandemic Influenza A (H1N1) 2009, 7 March 2011 123
3. WHO. Open-ended working group of member states on pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. Executive summary. Technical studies under resolution WHA63.1 167

**Session 6: Tick-borne encephalitis**

1. WHO draft position paper: Vaccines against Tick-borne-encephalitis 171
## Session 7: Meningococcal meningitis vaccine

1. Background paper on Meningococcal Vaccines. SAGE working group. March 15, 2011

## Session 8 Rubella vaccination:


## Session 9: Polio eradication


## Session 10: Update on evidence-based review process and GRADing of quality of scientific evidence

1. Draft guidelines for WHO and SAGE development of evidence-based vaccine related recommendations

## Session 11: Cholera vaccine: Feed-back on implementation of SAGE recommendations.

## Draft agenda

Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)

5 - 7 April 2011

CCV/CICG, Geneva

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Purpose of session, target outcomes and questions for SAGE</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td><strong>Welcome - introduction</strong></td>
<td></td>
<td>20 min.</td>
</tr>
<tr>
<td></td>
<td>H. Rees, Chair of SAGE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>09:20</td>
<td><strong>Report from IVB Director - Session 1</strong></td>
<td>FOR INFORMATION</td>
<td>1 h 10 min.</td>
</tr>
<tr>
<td></td>
<td>Discussion: 50 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td><strong>Coffee/tea break</strong></td>
<td>Break</td>
<td>30 min.</td>
</tr>
<tr>
<td>11:00</td>
<td><strong>Regional priorities, major policy and implementation issues: reports from AFR, EMR, SEAR - Session 2</strong></td>
<td>FOR INFORMATION AND DISCUSSION</td>
<td>2 h</td>
</tr>
<tr>
<td></td>
<td><strong>AFR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presentation: D. Nshimirima, WHO, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 25 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EMR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presentation: N. Teleb, WHO, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 25 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:20</td>
<td><strong>Lunch</strong></td>
<td>Break</td>
<td>1 h 10 min.</td>
</tr>
<tr>
<td>13:30</td>
<td><strong>Regional priorities, major policy and implementation issues (contd.) - Session 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SEAR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presentation: N. Abeysinghe, WHO, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 25 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Description</td>
<td>Duration</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>14:10</td>
<td><strong>Report from the GAVI Alliance secretariat - Session 3</strong></td>
<td>FOR INFORMATION</td>
<td>50 min.</td>
</tr>
<tr>
<td></td>
<td>Presentation: N. Schwalbe, GAVI Alliance, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 35 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:00</td>
<td><strong>Reports from other Advisory Committees in Immunization - Session 4</strong></td>
<td>FOR INFORMATION AND DISCUSSION</td>
<td>50 min.</td>
</tr>
<tr>
<td></td>
<td>Report from the Advisory Committee of the Initiative for Vaccine Research (IVAC), P. Ndumbe, Chair of IVAC, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:25</td>
<td><strong>Coffee/tea break</strong></td>
<td>Break</td>
<td>30 min.</td>
</tr>
<tr>
<td>15:55</td>
<td><strong>Reports from other Advisory Committees in Immunization (contd.) - Session 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Report of the Global Advisory Committee on Vaccine Safety (GACVS), P. Smith, Chair of GACVS, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:20</td>
<td><strong>Pandemic and seasonal influenza vaccines - Session 5</strong></td>
<td>FOR INFORMATION AND DISCUSSION</td>
<td>1 h 30 min.</td>
</tr>
<tr>
<td></td>
<td>International Health Regulations Review Committee (IHR): conclusions and recommendations, H. Fineberg, Chair of the IHR Review Committee, by telephone connection, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 30 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H1N1 update: use of deployed vaccine, L. Hedman, WHO, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- epidemiology, T. Mounts, WHO, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAGE Working Group on influenza vaccines and immunization. Update on process, L. Miller, Chair of Working Group, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17:50</td>
<td><strong>Cocktail</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Wednesday, 6 April 2011**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30</td>
<td><strong>Tick-borne encephalitis - Session 6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction: context and process, J. Hombach, WHO, 5 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease epidemiology &amp; burden of disease, J. Suess, Friedrich Loeffler Institute, Jena, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vaccine effectiveness and safety, H. Kollaritsch, University of Vienna, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Draft recommendations on the use of tick-borne encephalitis vaccines, J. Eskola, SAGE, 10 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 45 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td><strong>Coffee/tea break</strong></td>
<td></td>
<td>30 min.</td>
</tr>
<tr>
<td>11:00</td>
<td><strong>Meningococcal meningitis vaccines - Session 7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Update on the epidemiology of meningococcal disease, N. Messonnier, CDC, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Availability, safety and effectiveness of conjugated meningococcal A and C vaccines, M. Ramsay, UK Health Protection Agency, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Availability, safety and effectiveness of serogroup B/protein meningococcal vaccines, R. Borrow, UK Health Protection Agency, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Draft recommendations on the use of meningococcal vaccines, J. Abramson, Chair of SAGE Working Group, 15 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion: 1 h 30 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30</td>
<td><strong>Lunch</strong></td>
<td></td>
<td>1 h</td>
</tr>
</tbody>
</table>

**FOR DECISION**

- Review evidence on epidemiology and burden of tick-borne encephalitis, and on tick-borne encephalitis vaccines and their performance.
- Recommendations on the use of tick-borne encephalitis vaccines leading to the publication of a vaccine position paper.

- Recommendations on the use of meningococcal meningitis vaccines in different settings (endemic, non-endemic, and outbreak regions) with a view to update the WHO vaccine position paper.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:30</td>
<td>Meningococcal meningitis vaccines (contd.) - Session 7</td>
<td>FOR DECISION</td>
</tr>
<tr>
<td>14:30</td>
<td>Rubella vaccination - Session 8</td>
<td>FOR DECISION</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Propose necessary updating of WHO recommended vaccination strategies for use of rubella vaccines according to the disease control goal for rubella and congenital rubella syndrome (CRS).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The specific questions to be addressed are:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- What are the possible disease control goals for rubella and congenital rubella syndrome?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- For each goal, what are the most appropriate vaccination strategies?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- What is the minimum required immunization coverage that should be achieved and maintained to ensure that the introduction of rubella-containing vaccine does not increase the risk of CRS?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The recommendations from SAGE will be used to update the WHO Rubella Vaccines position paper.</td>
</tr>
<tr>
<td>15:30</td>
<td>Coffee/tea break</td>
<td>Break</td>
</tr>
<tr>
<td>16:00</td>
<td>Rubella vaccination (contd.) - Session 8</td>
<td></td>
</tr>
<tr>
<td>17:30</td>
<td>End of meeting</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>Details</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>08:30</td>
<td>Polio eradication - Session 9</td>
<td>Outcomes from the Independent Monitoring Board for the Global Polio Eradication Initiative, L. Donaldson, Chair of the Independent Monitoring Board, by telephone connection, 10 min. Discussion: 20 min. New breakthroughs in assuring affordable IPV options for low-income countries in the post-eradication era, R. Sutter, WHO, 10 min. Discussion: 20 min. SAGE IPV Working Group: potential pre-requisites if cessation of type-2 oral poliovirus vaccine is to be considered before global certification, E. Miller, Chair of the SAGE IPV Working Group, 10 min.</td>
</tr>
<tr>
<td>10:00</td>
<td>Coffee/tea break</td>
<td>Break</td>
</tr>
<tr>
<td>10:30</td>
<td>Update on evidence-based review process and GRADING of quality of scientific evidence - Session 10</td>
<td>Update from the SAGE discussion group, D. Durrheim, SAGE, 15 min. Discussion: 45 min.</td>
</tr>
<tr>
<td>12:50</td>
<td>Closing</td>
<td></td>
</tr>
<tr>
<td>13:10</td>
<td>End of meeting</td>
<td></td>
</tr>
</tbody>
</table>
### Meeting of the WHO Strategic Advisory Group of Experts on Immunization (SAGE)

5 - 7 April 2011  
Geneva, Switzerland

#### SAGE members

<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Information</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Professor Jon S. Abramson</strong></td>
<td>Chair, Wake Forest University Baptist Medical Centre</td>
<td>tel: +1 336 716 2512, fax: +1 336 716 9699, e-mail: <a href="mailto:jabrams@wfubmc.edu">jabrams@wfubmc.edu</a></td>
</tr>
<tr>
<td><strong>Professor Narendra K. Arora</strong></td>
<td>Executive Director, The INCLEN Trust International</td>
<td>tel: +91 11 477 300000, fax: 91 11 47730001, e-mail: <a href="mailto:nkarora@inclentrust.org">nkarora@inclentrust.org</a></td>
</tr>
<tr>
<td><strong>Professor Hyam N. Bashour (Vice-Chair)</strong></td>
<td>Faculty of Medicine, Damascus University</td>
<td>tel: +963 11 6618328, fax: +963 11 6116953, e-mail: <a href="mailto:hbashour@scs-net.org">hbashour@scs-net.org</a></td>
</tr>
<tr>
<td><strong>Professor Zulfiqar Ahmed Bhutta</strong></td>
<td>Head Maternal and Child Health Division, The Aga Khan University</td>
<td>tel: +92 21 493 9202, fax: +92 21 493 4294, e-mail: <a href="mailto:Zulfiqar.bhutta@aku.edu">Zulfiqar.bhutta@aku.edu</a></td>
</tr>
<tr>
<td><strong>Professor David Durrheim</strong></td>
<td>Director of Health Protection, Hunter New England Area</td>
<td>tel: +61-2492 46395, fax: +61492 46048, e-mail: <a href="mailto:David.Durrheim@newcastle.edu.au">David.Durrheim@newcastle.edu.au</a></td>
</tr>
<tr>
<td><strong>Professor Juhani Eskola</strong></td>
<td>Deputy Director General, THL Health Protection</td>
<td>tel: +358 206106006, fax: +358 20 610 6020, e-mail: <a href="mailto:juhani.eskola@thl.fi">juhani.eskola@thl.fi</a></td>
</tr>
<tr>
<td><strong>Professor J. Peter Figueroa</strong></td>
<td>Public Health, Epidemiology &amp; AIDS, Department of Community Health &amp; Psychiatry, University of the West Indies</td>
<td>tel: +1 876-970 6542, fax: +1 876 977 6346, e-mail: <a href="mailto:peter.figueroa10@gmail.com">peter.figueroa10@gmail.com</a></td>
</tr>
<tr>
<td>Name</td>
<td>Title / Institution</td>
<td>Contact Information</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Dr Xiaofeng Liang</td>
<td>Director of National Immunization Programme</td>
<td>tel: +86 10 631 76 737 fax: +86 10 631 71 724 e-mail: <a href="mailto:liangxf@hotmail.com">liangxf@hotmail.com</a></td>
</tr>
<tr>
<td>Professor Elizabeth Miller</td>
<td>Head, Immunisation Department</td>
<td>tel: +44 208 327 7430 (direct) fax: +44 208 327 7404 e-mail: <a href="mailto:Liz.Miller@hpa.org.uk">Liz.Miller@hpa.org.uk</a></td>
</tr>
<tr>
<td>Professor Malik Peiris</td>
<td>The University of Hong Kong</td>
<td>tel: +852 2855 4888 fax: +852 2855 1241 e-mail: <a href="mailto:Malik@hkcc.hku.hk">Malik@hkcc.hku.hk</a></td>
</tr>
<tr>
<td>Professor Helen Rees (Chair)</td>
<td>Executive Director, Reproductive Health and HIV Research Institute</td>
<td>tel: +27 11 358 5344 fax: +27 86 639 4305 e-mail: <a href="mailto:scorrent@rhru.co.za">scorrent@rhru.co.za</a>; <a href="mailto:hrees@rhru.co.za">hrees@rhru.co.za</a>;</td>
</tr>
<tr>
<td>Professor Arthur Lawrence Reingold</td>
<td>Head, Division of Epidemiology School of Public Health University of California</td>
<td>tel: +1 510 642 0327 fax: +1 510 643 5163 e-mail: <a href="mailto:Reingold@uclink4.berkeley.edu">Reingold@uclink4.berkeley.edu</a>; <a href="mailto:reingold@berkeley.edu">reingold@berkeley.edu</a></td>
</tr>
<tr>
<td>Professor Claire-Anne Siegrist</td>
<td>Head, WHO Collaborating Centre for Neonatal Vaccinology Department of Pediatrics &amp; Pathology-Immunology Centre Médical Universitaire</td>
<td>tel: +41 22 379 5778 fax: 41 22 379 58 01 e-mail: <a href="mailto:claire-anne.siegrist@unige.ch">claire-anne.siegrist@unige.ch</a></td>
</tr>
<tr>
<td>Dr Piyanit Tharmaphornpilas</td>
<td>Senior Medical Officer Ministry of Public Health</td>
<td>tel: +66-89 969 0852 fax: 66 2 590 3196 e-mail: <a href="mailto:piyanit@live.com">piyanit@live.com</a></td>
</tr>
<tr>
<td>Professor Oyewale Tomori</td>
<td>Vice Chancellor, Redeemer's University</td>
<td>tel: +234 1 791 3890 fax: +263 4 746 867 e-mail: <a href="mailto:oyewaletomori@yahoo.com">oyewaletomori@yahoo.com</a>; <a href="mailto:tomorio@run.edu.ng">tomorio@run.edu.ng</a></td>
</tr>
</tbody>
</table>
Strategic Advisory Group of Experts (SAGE)
Terms of reference

Functions

SAGE serves as the principal advisory group to the World Health Organization (WHO) for development of policy related to vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization and linkages between immunization and other health interventions. The mandate of SAGE 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.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of the Global Immunization Vision and Strategy (GIVS);
2. major issues and challenges to be addressed with respect to achieving the goals of GIVS;
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 GIVS 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, and 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, including the Chairperson, shall be appointed to serve for an initial term of three years. Such three-year terms may only be renewed once.

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 interest 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 agreement(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 the 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 twice annually. 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 in exceptional situations 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 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 participations will be expected from all SAGE members throughout the year, including participation in SAGE working groups, video and telephone conferences as well as 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 further translated and posted on the IVB Departmental website.
DECLAREATION OF INTERESTS FOR WHO EXPERTS

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

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

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

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

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

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

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

Name: 
Institution: 
Email: 

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

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

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

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

<table>
<thead>
<tr>
<th>1a Employment</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b Consulting, including service as a technical or other advisor</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**RESEARCH SUPPORT**

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

| 2a Research support, including grants, collaborations, sponsorships, and other funding | Yes | No |
| 2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) | Yes | No |
| Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work? | Yes | No |

**INVESTMENT INTERESTS**

*Do you have current investments (valued at more than US $10 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.*

| 3a Stocks, bonds, stock options, other securities (e.g., short sales) | Yes | No |
| 3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) | Yes | No |

**INTELLECTUAL PROPERTY**

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

| 4a Patents, trademarks, or copyrights (including pending applications) | Yes | No |
| 4b Proprietary know-how in a substance, technology or process | Yes | No |

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

| 5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? | Yes | No |
| 5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? | Yes | No |

**ADDITIONAL INFORMATION**

| 6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor’s confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? | Yes | No |
| 6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? | Yes | No |
| 6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? | Yes | No |
| 6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? | Yes | No |
| 6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? | Yes | No |
7. **TOBACCO OR TOBACCO PRODUCTS** (answer without regard to relevance to the subject of the meeting or work)
Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Nos. 1 - 4:</th>
<th>Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.</th>
<th>Name of company, organization, or institution</th>
<th>Belongs to you, a family member, employer, research unit or other?</th>
<th>Amount of income or value of interest (if not disclosed, is assumed to be significant)</th>
<th>Current interest (or year ceased)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Nos. 5-6:</th>
<th>Describe the subject, specific circumstances, parties involved, time frame and other relevant details</th>
</tr>
</thead>
</table>

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

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

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

Date: ________________    Signature________________________________
CONFIDENTIALITY UNDERTAKING

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

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

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

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

5. The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that the Information:
   
   (a) was known to him/her prior to any disclosure to him/her by the institution or individual or WHO;
   
   (b) was in the public domain at the time of disclosure by the institution or individual;
   
   (c) becomes part of the public domain through no fault of the Undersigned; or
   
   (d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality to the institution, individual or WHO.

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

Date:…………………………………….…
Signature…………………………………….
Name………………………………………
(print or type)
Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups

Working Group Purpose and decision to establish SAGE Working Groups

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

These Working Groups are established on a time limited basis in exceptional situations 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 charge 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 Groups should not exceed 10 members and will be adjusted based on the need for expertise and representation.

A public call for nomination of 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 DG. 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 allows 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 2 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 eDOI. 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.
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
• Jon Abramson
• Art Reingold (Joined the Working Group after the SAGE meeting in November 2010)
• Claire-Anne Siegrist

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

2. SAGE Working Group on rubella vaccines (established March 2010)

Terms of Reference
The Working Group will be asked to propose necessary updating of WHO recommended vaccination strategies (as stated in the 2000 rubella vaccine position paper) for use of rubella vaccines according to the disease control goal for rubella and congenital rubella syndrome (CRS). Further, the Working Group will identify information gaps, guide the work required to address the information gaps, and review the evidence in preparation for a SAGE review of the updated vaccination strategies.

The specific questions to be addressed:
1. What are the possible goals for CRS and rubella control and what are the most appropriate vaccination strategies to achieve these goals?
2. What is the minimum required immunization coverage that should be achieved and maintained to ensure that the introduction of a rubella containing vaccine does not increase the risk of CRS?

The approach to address these questions may include:
1. Review the burden of CRS according to country development status
2. Review country experience with introduction and use of rubella vaccines (in countries with information that allows a robust analysis)
3. Mathematical modelling to explore different scenarios (model needs to be fully dynamic given the characteristics of rubella and the impact of the vaccine on disease)
4. Cost-effectiveness analysis of different approaches, in particular in low and low-middle income countries (as per WHO guidelines)

Composition
SAGE Members
- Helen Rees, Chair
- Jon Abramson
- Hyam Bashour
- Malik Peiris
- Oyewale Tomori

Experts
- Liliane Grangeot-Keros, Antoine Béclère Hospital, France
- Kari Johansen, European Centre for Disease Prevention and Control, Sweden
- Karen Lewis-Bell, Ministry of Health, Jamaica
- Paba Palihawadana, Ministry of Health, Sri Lanka
- Susan Reef, Centres for Disease Control, USA
- Emilia Vynnycky, Health Protection Agency, UK
- Aiqiang Xu, Shandong Center for Disease Control and Prevention, China

WHO Secretariat
- Alya Dabbagh
- Peter Strebel

3. SAGE Working Group on hepatitis A vaccine (established March 2010)

Terms of Reference
The Working Group will be asked to review the evidence with respect to the following questions/issues and to propose to SAGE recommendations, including the need to update recommendations stated in the current (2000) hepatitis A vaccine position paper:
1. Review data regarding the global prevalence and burden of disease caused by hepatitis A virus infection.
2. Review position paper recommendations regarding when countries should consider introduction of hepatitis A vaccine.
3. Review issues related to establishment of regional or global hepatitis A control goals.
4. Outline aspects of a comprehensive strategy for hepatitis A control.
5. Review issues related to hepatitis A surveillance.
6. Identify additional critical issues that need to be considered in updating, referencing and providing evidence grading for the current hepatitis A vaccine position paper.

Composition
SAGE Members
- Art Reingold, Chair
- Xiaofeng Liang

Experts
- Jeffrey Mphahlele, University of Limpopo, South Africa
- John W. Ward, Centers for Disease Control and Prevention, USA
- Marta Vaccino, National Institute of Epidemiology, Argentina
- Andrew Hall, London School of Hygiene and Tropical Medicine, UK
- Daniel Shouval, Hadassah Hebrew University Hospital, Israel

WHO Secretariat
- Steven Wiersma

Updated: 17 March 2011
4. SAGE Working Group on meningococcal vaccines (established March 2010)

Terms of Reference
The Working Group is expected to review the evidence and prepare for a SAGE review, the necessary changes to be made to update the current meningitis position paper. The new position paper should make recommendation on the use of existing and upcoming conjugate vaccines including meningitis B, tetravalent meningitis ACWY, meningitis A and other and give updates on use of meningococcal polysaccharides vaccine.

The specific questions to be addressed:
1. Review data for recommendations regarding use of vaccines in outbreak settings
2. Review data to make recommendations on conjugate vaccine meningitis C and meningitis ACWY
3. Make recommendations on the use of conjugate vaccine meningitis A
4. Gather data on meningitis B Vaccine efficacy, safety and effectiveness in outbreaks
5. Review and make recommendation of the use of 1/5 fractioned dose of meningococcal polysaccharides vaccine in case of shortage of meningococcal polysaccharides vaccines.

Composition
SAGE Members
- Jon Abramson, Chair
- Zulfiqar Ahmed Bhutta
- David Durrheim
- Juhani Eskola

Experts
- Florence Fermon, Médecins Sans Frontière, France
- Keith Klugman, Emory University, US / National Institute for Communicable Diseases, South Africa
- Nancy Messonnier, Centres for Disease Control, USA
- Mary Ramsay, Health Protection Agency, UK
- Samba Sow, Centre National d’Appui à la Lutte Contre la Maladie, Mali
- Shao Zhujun, Institute for Communicable Disease Control and Prevention, People’s Republic of China

WHO Secretariat
- Carole Tevi-Benissan
- Stéphane Hugonnet

5. SAGE working group on inactivated polio vaccine (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.

Composition
SAGE Members
- Elizabeth Miller, Chair
- Hyam Bashour
- Peter Figueroa

Experts
- Walter Dowdle, Task Force, USA
- Nick Grassly, Imperial College, UK
- Jacob John, Christian Medical College, India
- Antoine Kabore, HIV/AIDS, WHO/AFRO, Burkina Faso
- Francis Nkrumah, University of Ghana Medical School, Ghana
- Walter Orenstein, Bill and Melinda Gates Foundation, USA
- Kimberley Thompson, Kids Risk Project, Harvard School of Public Health, USA

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

6. SAGE Working Group on measles (established September 2006)

Terms of Reference
1. Review experience with and make recommendations for adapting current immunization strategies
2. Identify the key information gaps to be addressed before a decision can be made about the next global measles control goal (i.e., beyond 2010)

Composition
SAGE Members
- Hyam Bashour, Chair
- David Durrheim

Experts
- Steve Cochi, Centers for Disease Control and Prevention, USA
- Ed Hoekstra, UNICEF, USA
- Robert Hall, WHO WPRO Technical Advisory Group on Immunization, Monash University, Australia
- Peter Ndumbe, WHO AFRO Task Force on Immunization, Buea University, Cameroon
- Sudath Peiris, Ministry of Health, Sri Lanka
- Jose Ignacio Santos, General Director, Hospital Infantil de Mexico, Mexico

WHO Secretariat
- Peter Strebel
- Alya Dabbagh
- Tracey Goodman

Updated: 17 March 2011
7. SAGE Working Group on vaccination in humanitarian emergencies (in process of establishment March 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 over the last 10 years 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.
## List of Participants

### SAGE member

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution/Address</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Jon Abramson</td>
<td>Professor and Chair</td>
<td>Wake Forest University Baptist Medical Center</td>
<td>tel: +1 336-716-2512 email: <a href="mailto:jabrams@wfubmc.edu">jabrams@wfubmc.edu</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical Center Blvd. 27157 Winston-Salem, NC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>United States of America</td>
<td></td>
</tr>
<tr>
<td>Professor Narendra Kumar Arora</td>
<td>Executive Director</td>
<td>The INCLEN Trust International</td>
<td>tel: +91-11-47730000 fax: +91-11-4773001 email: <a href="mailto:nkarora@inclentrust.org">nkarora@inclentrust.org</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F-1/5, Second Floor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Okhla Industrial Area, Phase I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>110020 Delhi, Delhi India</td>
<td></td>
</tr>
<tr>
<td>Professor Hyam Bashour (Vice-Chair SAGE)</td>
<td>Professor</td>
<td>Faculty of Medicine, Damascus University</td>
<td>tel: +963 11 6618328 email: <a href="mailto:hbashour@scs-net.org">hbashour@scs-net.org</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Al Mazzeh Highway</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9241 Damascus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syrian Arab Republic</td>
<td></td>
</tr>
<tr>
<td>Professor Zulfiqar Bhutta</td>
<td></td>
<td>The Aga Khan University</td>
<td>tel: +92 21 493 9202 email: <a href="mailto:zulfiqar.bhatta@aku.edu">zulfiqar.bhatta@aku.edu</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P.O. Box 3500, Stadium Road</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>74800 Karachi</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pakistan</td>
<td></td>
</tr>
<tr>
<td>Professor David Durrheim</td>
<td></td>
<td>University of Newcastle</td>
<td>tel: +61-2-49246395 email: <a href="mailto:david.durrheim@newcastle.edu.au">david.durrheim@newcastle.edu.au</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Haynes Avenue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2282 Eleebana, NSW Australia</td>
<td></td>
</tr>
<tr>
<td>Professor Juhani Eskola</td>
<td>Deputy Director General</td>
<td>National Institute for Health and Welfare (THL)</td>
<td>tel: +358 206106006 email: <a href="mailto:juhani.eskola@thl.fi">juhani.eskola@thl.fi</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mannerheimintie 166</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI-00270 Helsinki</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finland</td>
<td></td>
</tr>
<tr>
<td>Professor Peter Figueroa</td>
<td></td>
<td>University of the West Indies</td>
<td>tel: +876-970-6542 email: <a href="mailto:peter.figueroa10@gmail.com">peter.figueroa10@gmail.com</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gibralter Camp Road, Mona</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kingston 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jamaica</td>
<td></td>
</tr>
<tr>
<td>Dr. Xiaofeng Liang</td>
<td>Director</td>
<td>Chinese Center for Disease Control and Prevention</td>
<td>tel: +86-10-63176737 13501080273 email: <a href="mailto:liangxf@hotmail.com">liangxf@hotmail.com</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>27# Nanwei RD, Xuanwu district</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100050 Beijing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The People's Republic of China</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Title</td>
<td>Institution</td>
<td>Address</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Professor Elizabeth Miller</td>
<td>Consultant Epidemiologist</td>
<td>Health Protection Agency, Centre for Infections</td>
<td>61 Colindale Avenue, Colindale, NW9 5EQ London, United Kingdom of Great Britain and Northern Ireland</td>
</tr>
<tr>
<td>Professor Helen Rees (Chair SAGE)</td>
<td>Executive Director</td>
<td>Wits Institute, Hugh Solomon Building, Corner Esselen and Klein Streets, Hillbrow, 2038 Johannesburg, Gauteng, South Africa</td>
<td>tel: +27 11 358 5344, fax: +27 86 639 4305, email: <a href="mailto:hrees@rhru.co.za">hrees@rhru.co.za</a></td>
</tr>
<tr>
<td>Professor Arthur Reingold</td>
<td>Professor</td>
<td>University of California, 101 Haviland Hall, School of Public Health, University of California, 94720 Berkeley, CA, United States of America</td>
<td>tel: +1 510 642 0327, email: <a href="mailto:reingold@berkeley.edu">reingold@berkeley.edu</a></td>
</tr>
<tr>
<td>Professor Claire-Anne Siegrist</td>
<td>University of Geneva</td>
<td>CMU, 1 rue Michel-Servet, 1211 Geneva 4, Switzerland</td>
<td>tel: +41 22 379 5778, fax: +41 22 379 58 01, email: <a href="mailto:claire-anne.siegrist@unige.ch">claire-anne.siegrist@unige.ch</a></td>
</tr>
<tr>
<td>Dr Piyanit Tharmaphornpilas</td>
<td>Senior Medical Advisor</td>
<td>Ministry of Public Health, Muang, Nonthaburi, 11000, 11000 Nonthaburi, Thailand</td>
<td>tel: +66 225 903 196, fax: +66 225 903 196, email: <a href="mailto:piyanit@live.com">piyanit@live.com</a></td>
</tr>
<tr>
<td>Professor Oyewale Tomori</td>
<td>Vice Chancellor</td>
<td>Redeemer's University, KM 46 Lagos-Ibadan Express Road, 3005 Redemption City, Ogun, Nigeria</td>
<td>tel: +234 1 7913890, email: <a href="mailto:oyewaletomori@yahoo.com">oyewaletomori@yahoo.com</a></td>
</tr>
<tr>
<td>Chair of Regional Technical Advisory Groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Robert Hall</td>
<td>Senior Research Fellow</td>
<td>Monash University, 99 Commercial Rd, 3004 Melbourne, Victoria, Australia</td>
<td>tel: +61 3 9903 0452, email: <a href="mailto:robert.hall@monash.edu">robert.hall@monash.edu</a></td>
</tr>
<tr>
<td>Professor Lalitha Mendis</td>
<td>President</td>
<td>Sri Lanka Medical Council, 31, Norris Canal Road, Colombo 10, 10 Colombo, Sri Lanka</td>
<td>tel: +94(0)777 323 716, email: <a href="mailto:sirikotha@yahoo.com">sirikotha@yahoo.com</a></td>
</tr>
<tr>
<td>Dr Ali Jafffer Mohamed</td>
<td>Advisor - Health Affairs &amp; Supervising Directorate General</td>
<td>Ministry of Health, Al Khawair, Muscat, Oman</td>
<td>tel: +968-99335681, email: <a href="mailto:dg-ha@moh.gov.om">dg-ha@moh.gov.om</a></td>
</tr>
<tr>
<td>Name</td>
<td>Title</td>
<td>Organization</td>
<td>Address</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dr Peter Ndumbe</td>
<td></td>
<td>University of Buea</td>
<td>Molyko PO Box 63 South West Province Buea Cameroon</td>
</tr>
<tr>
<td>Dr Ciro de Quadros</td>
<td>Executive Vice-President</td>
<td>Sabin Vaccine Institute</td>
<td>2000 Pennsylvania Ave., NW, Suite 7100 20006 Washington, DC, District of Columbia United States of America</td>
</tr>
<tr>
<td>Professor Pierre van Damme</td>
<td>Professor, Faculty of Medicine</td>
<td>University of Antwerp</td>
<td>Campus Drie Eiken Universiteitsplein 1 2610 Antwerpen Belgium</td>
</tr>
<tr>
<td>Dr Shelley Deeks (Chair IPAC)</td>
<td>Associate Director</td>
<td>Ontario Agency for Health Protection and Promotion</td>
<td>480 University Avenue, Suite 300 M5G 1V2 Toronto, Ontario Canada</td>
</tr>
<tr>
<td>Dr Elwyn Griffiths (Chair ECBS)</td>
<td>Director General</td>
<td>Health Canada</td>
<td>HPFB Building #7 (Locator 0702E) 200 Tunney's Pasture K1A 0K9 Ottawa, Ontario Canada</td>
</tr>
<tr>
<td>Dr Alan Hinman (Chair QUIVER)</td>
<td>Senior Public Health Scientist</td>
<td>Task Force for Global Health</td>
<td>325 Swanton Way 30030 Decatur, Georgia United States of America</td>
</tr>
<tr>
<td>Professor Peter Smith (Chair GACVS)</td>
<td>Professor</td>
<td>London School of Hygiene &amp; Tropical Medicine Keppel St WC1 E7HT London United Kingdom of Great Britain and Northern Ireland</td>
<td></td>
</tr>
<tr>
<td>Dr Marianne A Riise Bergsaker</td>
<td>Senior Medical Officer</td>
<td>Norwegian Institute of Public Health Løvisenbergt 6/</td>
<td>P.O. Box 4404 Nydalen 0403 Oslo Norway</td>
</tr>
<tr>
<td>Mr Daniel Berman</td>
<td>Deputy Director</td>
<td>Médecins Sans Frontières</td>
<td>Rue de Lausanne 78 P.O. Box 116 1211 Genève 21 Switzerland</td>
</tr>
</tbody>
</table>

**Chair of other Immunization Advisory Committees**

**Official representative from governmental or non-governmental organizations**
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Address</th>
<th>Phone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr John Boslego</td>
<td>Director</td>
<td>PATH, 455 Massachusetts Avenue, NW</td>
<td>+1-202-822-0033</td>
<td><a href="mailto:jboslego@path.org">jboslego@path.org</a></td>
</tr>
<tr>
<td>Dr Brent Burkholder</td>
<td>Director/Medical Officer</td>
<td>Centers for Disease Control and Prevention</td>
<td>1.404.639.8252</td>
<td><a href="mailto:btb0@cdc.gov">btb0@cdc.gov</a></td>
</tr>
<tr>
<td>Dr John Clemens</td>
<td>Director General</td>
<td>International Vaccine Institute</td>
<td>+82 2 881 1101</td>
<td><a href="mailto:jclemens@ivi.int">jclemens@ivi.int</a></td>
</tr>
<tr>
<td>Dr Shalini Desai</td>
<td>Medical Specialist</td>
<td>Public Health Agency of Canada</td>
<td>+416-952-2238</td>
<td><a href="mailto:shalini.desai@phac-aspc.gc.ca">shalini.desai@phac-aspc.gc.ca</a></td>
</tr>
<tr>
<td>Mrs Fermon Florence</td>
<td>Leader vaccination international working group</td>
<td>MSF, 8 rue Saint Sabin</td>
<td>+33 1 40 21 28 59</td>
<td><a href="mailto:ffermon@msf.org">ffermon@msf.org</a></td>
</tr>
<tr>
<td>Dr Tesfamicael Ghebrehiwet</td>
<td>Consultant, Nursing &amp; Health Policy</td>
<td>International Council of Nurses 3, Place Jean-Marteau</td>
<td>+41 22 908 0100</td>
<td><a href="mailto:tesfa@icn.ch">tesfa@icn.ch</a></td>
</tr>
<tr>
<td>Dr Jesse Goodman</td>
<td>Chief Scientist and Deputy Commissioner for Science and Public Health</td>
<td>US FDA/HHS, 10903 New Hampshire Avenue, 20993 Silver Spring, MD</td>
<td>+1 301-796-4880</td>
<td><a href="mailto:jesse.goodman@fda.hhs.gov">jesse.goodman@fda.hhs.gov</a></td>
</tr>
<tr>
<td>Dr Brigitte Keller-Stanislawski</td>
<td>Head</td>
<td>Paul-Ehrlich-Institut, Paul-Ehrlich-Strasse 51-59 Langen, Germany</td>
<td>+49 6103 771010</td>
<td><a href="mailto:kelbr@pei.de">kelbr@pei.de</a></td>
</tr>
<tr>
<td>Dr Daniel Koch</td>
<td>Federal Office of Public Health</td>
<td>Schwarztorstrasse 96, 3007 Berne</td>
<td>+41 31 322 7112</td>
<td><a href="mailto:daniel.koch@bag.admin.ch">daniel.koch@bag.admin.ch</a></td>
</tr>
<tr>
<td>Dr Steve Landry</td>
<td>Program Manager</td>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>+1 206-619-9540</td>
<td><a href="mailto:steve.landry@gatesfoundation.org">steve.landry@gatesfoundation.org</a></td>
</tr>
<tr>
<td>Name</td>
<td>Position/Role</td>
<td>Organization/Institution</td>
<td>Address/Location</td>
<td>Contact Details</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Ms Susan McKinney</td>
<td>Senior Technical Advisor for Immunization</td>
<td>USAID</td>
<td>1300 Pennsylvania Ave, NW 20523 Washington, DC United States of America</td>
<td>tel: +1 202 712 0614 email: <a href="mailto:smckinney@usaid.gov">smckinney@usaid.gov</a></td>
</tr>
<tr>
<td>Dr Erin McLean</td>
<td>Manager, Nutrition and Immunization</td>
<td>Canadian International Development Agency</td>
<td>200 Promenade du Portage K1A 0G4 Gatineau, QC Canada</td>
<td>tel: +1 819 953 4446 email: <a href="mailto:erin.mclean@acdi-cida.gc.ca">erin.mclean@acdi-cida.gc.ca</a></td>
</tr>
<tr>
<td>Professor André Meheus</td>
<td>Network for Education and Support in Immunisation (NESI)</td>
<td>University of Antwerpen</td>
<td>Campus Drie Eiken Universiteitsplein 1 2610 Antwerpen Belgium</td>
<td>tel: +32 3 265 2515 email: <a href="mailto:andre.meheus@ua.ac.be">andre.meheus@ua.ac.be</a></td>
</tr>
<tr>
<td>Dr Mark Miller</td>
<td>Director</td>
<td>Fogarty International Center/DIEPS</td>
<td>16 Center Drive, MSC 6705, Bldg. 16, Room 202B 20892 Bethesda, MD United States of America</td>
<td>tel: +1 301-496-0815 fax: +1 301-496-8496 email: <a href="mailto:millemar@mail.nih.gov">millemar@mail.nih.gov</a></td>
</tr>
<tr>
<td>Dr Violaine Mitchell</td>
<td>Senior Program Officer</td>
<td>Bill and Melinda Gates Foundation</td>
<td>PO Box 23350 98102-3706 Seattle, WA United States of America</td>
<td>tel: +1 (206) 709-3100 email: <a href="mailto:violaine.mitchell@gatesfoundation.org">violaine.mitchell@gatesfoundation.org</a></td>
</tr>
<tr>
<td>Dr Judith Mueller</td>
<td>Medical Epidemiologist</td>
<td>Agence de Médecine Préventive (AMP)</td>
<td>at the Institut Pasteur 25-28 rue du Dr Roux Cedex 15 75724 Paris France</td>
<td>tel: +33-153868936 email: <a href="mailto:jmueller@aamp.org">jmueller@aamp.org</a></td>
</tr>
<tr>
<td>Dr Pieter Neels</td>
<td>FAGG/EMA/CHMP</td>
<td>Victor Hortaplein 40/40 1060 Brussels</td>
<td>Belgium</td>
<td>tel: +32 25 24 8176 email: <a href="mailto:pieter.neels@fagg.be">pieter.neels@fagg.be</a></td>
</tr>
<tr>
<td>Ms Bee Leng Sally Soh</td>
<td>Senior Regulatory Specialist</td>
<td>Health Sciences Authority</td>
<td>11 Biopolis Way #11-03 Helios 138667 Singapore Singapore</td>
<td>tel: 65-6304-5448 fax: 65-64789069 email: <a href="mailto:sally_soh@hsa.gov.sg">sally_soh@hsa.gov.sg</a></td>
</tr>
<tr>
<td>Dr Jane Schaller</td>
<td>Executive Director</td>
<td>International Pediatric Association</td>
<td>1-3 Rue Chantepoulet P.O. Box 1726 1211 Geneva Switzerland</td>
<td>tel: +41 22 732 26 07 email: <a href="mailto:jSchaller@cw.bc.ca">jSchaller@cw.bc.ca</a></td>
</tr>
<tr>
<td>Dr Kamel Senouci</td>
<td>Program Director</td>
<td>Agence de Médecine Préventive (AMP)</td>
<td>c/o Institut Pasteur 25-28 rue du Docteur Roux 75724 Paris Cedex 15 France</td>
<td>tel: +33153868923 fax: +33153868939 email: <a href="mailto:ksenouci@aamp.org">ksenouci@aamp.org</a></td>
</tr>
<tr>
<td>Name</td>
<td>Title/Position</td>
<td>Address</td>
<td>Telephone</td>
<td>Email Address</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Ms Sarah Shin</td>
<td>Agence de Médecine Préventive</td>
<td>AMP à l'Institut Pasteur / 25-28 rue du Dr Roux 75724 Paris 75724 Paris cedex 15 France</td>
<td>tel: +33 (0)6 49 19 63 83 email: <a href="mailto:sshin@aamp.org">sshin@aamp.org</a></td>
<td></td>
</tr>
<tr>
<td>Ms Meredith Shirey</td>
<td>Contracts Manager</td>
<td>UNICEF Plads, Freeport 2100 Copenhagen 2100 Copenhagen Denmark</td>
<td>tel: +45 3527 3033      email: <a href="mailto:mshirey@unicef.org">mshirey@unicef.org</a></td>
<td></td>
</tr>
<tr>
<td>Dr Leila Srour</td>
<td>International Pediatric Association</td>
<td>1-3 Rue Chantepoulet P.O. Box 1726 1211 Geneva Switzerland</td>
<td>tel: +41 22 732 26 07 email: <a href="mailto:leila@butterflychildren.org">leila@butterflychildren.org</a></td>
<td></td>
</tr>
<tr>
<td>Dr Joe Vandelaer</td>
<td>UNICEF</td>
<td>3 United Nations Plaza 10017 New York, NY United States of America</td>
<td>tel: +1-212-326-7612    email: <a href="mailto:jvandelaer@unicef.org">jvandelaer@unicef.org</a></td>
<td></td>
</tr>
<tr>
<td>Dr John Wecker</td>
<td>Director, Vaccine Access and Delivery</td>
<td>PATH Bât. Avant Centre - 13 Chemin du Levant 01210 Ferney Voltaire France</td>
<td>tel: +33 450 28 29 76 email: <a href="mailto:jwecker@path.org">jwecker@path.org</a></td>
<td></td>
</tr>
<tr>
<td>Dr Tee Wee Wong</td>
<td>Regulatory Consultant</td>
<td>Health Sciences Authority, Singapore 11 Biopolis Way, #11-03 Helios Singapore 138667 Singapore 138667 Singapore</td>
<td>tel: +65 6866 3411 email: <a href="mailto:wong_tee_wei@hsa.gov.sg">wong_tee_wei@hsa.gov.sg</a></td>
<td></td>
</tr>
<tr>
<td>Dr Alfred da Silva</td>
<td>Executive Director</td>
<td>Agence de Médecine Préventive (AMP) A l'Institut Pasteur 25-28 rue du Dr Roux 75724 Paris cedex 15 France</td>
<td>tel: +33 (0)1 53 86 89 20 fax: +33(0)1 53 86 89 39 email: <a href="mailto:ads@aamp.org">ads@aamp.org</a></td>
<td></td>
</tr>
<tr>
<td>Dr Syed Asad Ali</td>
<td>The Aga Khan University</td>
<td>P.O. Box 3500 Stadium Road Karachi Pakistan</td>
<td>tel: +092 308 2227852   email: <a href="mailto:asad.ali@aku.edu">asad.ali@aku.edu</a></td>
<td></td>
</tr>
<tr>
<td>Professor Bjarne Bjorvatn</td>
<td>Consultant</td>
<td>Moland 4994 Akland Norway</td>
<td>tel: +47 37 03 38 49 email: <a href="mailto:Bjarne.Bjorvatn@cih.uib.no">Bjarne.Bjorvatn@cih.uib.no</a></td>
<td></td>
</tr>
<tr>
<td>Professor Ray Borrow</td>
<td>Consultant Clinical Scientist</td>
<td>Health Protection Agency Clinical Sciences Building 2 Manchester Royal Infirmary Oxford Road M13 9WZ Manchester United Kingdom of Great Britain and Northern Ireland</td>
<td>tel: +44 161 276 6791 fax: +44 161 276 6792 email: <a href="mailto:ray.borrow@hpa.org.uk">ray.borrow@hpa.org.uk</a></td>
<td></td>
</tr>
</tbody>
</table>

**Other participants**

- **Dr Syed Asad Ali**
  - The Aga Khan University
  - P.O. Box 3500
  - Stadium Road
  - Karachi
  - Pakistan
  - tel: +092 308 2227852
  - email: asad.ali@aku.edu

- **Professor Bjarne Bjorvatn**
  - Consultant
  - Moland
  - 4994 Akland
  - Norway
  - tel: +47 37 03 38 49
  - email: Bjarne.Bjorvatn@cih.uib.no

- **Professor Ray Borrow**
  - Consultant Clinical Scientist
  - Health Protection Agency
  - Clinical Sciences Building 2
  - Manchester Royal Infirmary
  - Oxford Road
  - M13 9WZ Manchester
  - United Kingdom of Great Britain and Northern Ireland
  - tel: +44 161 276 6791
  - fax: +44 161 276 6792
  - email: ray.borrow@hpa.org.uk
<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Position</th>
<th>Address</th>
<th>Phone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sir Liam Donaldson</td>
<td>(By telephone connection)</td>
<td>Department of Health&lt;br&gt;79 Whitehall&lt;br&gt;SW1 2NS London&lt;br&gt;United Kingdom of Great Britain and Northern Ireland</td>
<td>+44 207 210 5152</td>
<td><a href="mailto:liam.donaldson@dh.gsi.gov.uk">liam.donaldson@dh.gsi.gov.uk</a></td>
</tr>
<tr>
<td>Dr Harvey Fineberg</td>
<td>(By telephone connection)</td>
<td>Institute of Medicine&lt;br&gt;2101 Constitution Avenue N.W.&lt;br&gt;20418-0006 Washington&lt;br&gt;United States of America</td>
<td>+1 202-334-3300</td>
<td><a href="mailto:fineberg@nas.edu">fineberg@nas.edu</a></td>
</tr>
<tr>
<td>Professor Herwig Kollaritsch</td>
<td>Associate Professor&lt;br&gt;Medical University of Vienna&lt;br_KINDERSPITALGASSE 15&lt;br&gt;1090 Vienna&lt;br&gt;Austria</td>
<td>tel: +436641623321</td>
<td>email: <a href="mailto:herwig.kollaritsch@meduniwien.ac.at">herwig.kollaritsch@meduniwien.ac.at</a></td>
<td></td>
</tr>
<tr>
<td>Dr Justin Lessler</td>
<td>Johns Hopkins Bloomberg School of Public Health</td>
<td>615 N Wolfe St, E6545&lt;br&gt;21224 Baltimore, MD&lt;br&gt;United States of America</td>
<td>+1 410-955-3551</td>
<td><a href="mailto:jlessler@jhsp.edu">jlessler@jhsp.edu</a></td>
</tr>
<tr>
<td>Dr Brian Maskery</td>
<td>International Vaccine Institute&lt;br&gt;SNU Research Park, San 4-8 Nakseoungdae-dong, Kwanak-gu, Seoul, Korea, 151-919&lt;br&gt;Seoul&lt;br&gt;Republic of Korea</td>
<td>tel: +82 2881 1295</td>
<td>email: <a href="mailto:bmaskery@ivi.int">bmaskery@ivi.int</a></td>
<td></td>
</tr>
<tr>
<td>Dr Nancy Messonnier</td>
<td>Center for Disease Control and Prevention</td>
<td>1600 Clifton Road NE&lt;br&gt;30333 Atlanta, Georgia&lt;br&gt;United States of America</td>
<td>+1 404-639-4734</td>
<td><a href="mailto:NMessonnier@cdc.gov">NMessonnier@cdc.gov</a></td>
</tr>
<tr>
<td>Dr Jessica Metcalf</td>
<td>Dept of Zoology, Oxford University&lt;br&gt;South Parks Road, Tinbergen Building, OX1 3PS&lt;br&gt;Oxford&lt;br&gt;United Kingdom of Great Britain and Northern Ireland</td>
<td>tel: +44 (0)186 528 1235</td>
<td>email: <a href="mailto:cmetcalf@princeton.edu">cmetcalf@princeton.edu</a></td>
<td></td>
</tr>
<tr>
<td>Dr Mary Ramsay</td>
<td>Head&lt;br&gt;Health Protection Agency</td>
<td>61 Colindale Avenue&lt;br&gt;NW9 5EQ London&lt;br&gt;United Kingdom of Great Britain and Northern Ireland</td>
<td>+44 208 327 7085</td>
<td><a href="mailto:mary.ramsay@hpa.org.uk">mary.ramsay@hpa.org.uk</a></td>
</tr>
<tr>
<td>Dr Susan Reef</td>
<td>Medical Officer&lt;br&gt;CDC&lt;br&gt;MS E-05&lt;br&gt;1600 Clifton Rd., NE&lt;br&gt;30333 Atlanta, Georgia&lt;br&gt;United States of America</td>
<td>tel: +1-404639-8982</td>
<td>email: <a href="mailto:sreef@cdc.gov">sreef@cdc.gov</a></td>
<td></td>
</tr>
<tr>
<td>Professor Sow Samba Ousmane</td>
<td>Director General&lt;br&gt;Center for Vaccine Development Mali&lt;br&gt;Dijocoroni Para Bamako MALI&lt;br&gt;BP 251 Bamako, Bamako&lt;br&gt;Mali</td>
<td>tel: +223 20 23 60 31</td>
<td>email: <a href="mailto:ssow@medicine.umaryland.edu">ssow@medicine.umaryland.edu</a></td>
<td></td>
</tr>
<tr>
<td>Dr Jochen Süß</td>
<td>Head&lt;br&gt;Friedrich-Loeffler-Institute&lt;br&gt;Naumburger Strasse 96a&lt;br&gt;07743 Jena&lt;br&gt;Germany</td>
<td>tel: +49 364 1804 2248</td>
<td>email: <a href="mailto:jochen.suess@fli.bund.de">jochen.suess@fli.bund.de</a></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Position</td>
<td>Organization</td>
<td>Address</td>
<td>Phone Numbers</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
| Dr Emilia Vynnycky           | Health Protection Agency           | 61 Colindale Avenue                              | Colindale                                                             | tel: +44 (0) 208 327 7439  
  email: emilia.vynnycky@hpa.org.uk |                       |
| Mrs Atika Abelin              | Industry representative            | sanofi pasteur                                  | 2 avenue Pont Pasteur  
  69367 Lyon Cedex 7  
  France                                                            | tel: +33 4 37 37 78 82  
  fax: +33 4 37 37 72 02  
  email: atika.abelin@sanofipasteur.com |                       |
| Dr Joan Benson                | Industry representative            | Merck & Co. Inc.                                | 770 Sumneytown Pike  
  P.O. Box 4  
  19486 West Point, PA  
  United States of America                                           | tel: +1 215 652 1815  
  email: joan_benson@merck.com |                       |
| Mr Toon Digneffe              | Industry representative            | Baxter World Trade sprl                         | 2-4 Boulevard d’Angleterre  
  Braine l’Alleud  
  1420 Brussels  
  Belgium                                                          | tel: +32 238 68672  
  email: toon_digneffe@baxter.com |                       |
| Dr Norbert Hehme              | Industry representative            | GSK Biologicals                                 | Zirkusstrasse 40  
  01069 Dresden  
  Germany                                                           | tel: +49 351 4561 5104  
  fax: +49 351 4561 5321  
  email: norbert.w.hehme@gskbio.com |                       |
| Dr Akira Homma (President DCVMN) | Industry representative         | Bio-Manguinhos / Fiocruz                        | Avenida Brasil, 4365  
  Manguinhos  
  21040-360 Rio de Janeiro, Rio de Janeiro  
  Brazil                                                            | tel: +55 21 3882-7200  
  fax: +55 21 3882-7176  
  email: akira@bio.fiocruz.br |                       |
| Dr Alexander Kiktenko         | Industry representative            | Deputy Director on Quality                      | Federal State Unitary Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences  
  P.O. Institute of Poliomyelitis, 27th km of Kiev Highway,  
  Leninsky District  
  142782 Moscow, Moscow Region  
  Russian Federation                                                   | tel: +7 495 439 9341  
  fax: +7 495 439 9321  
  email: sue_polio@chumakovs.ru |                       |
| Dr Ryoko Krause               | Industry representative            | Director                                        | International Federation of Pharmaceutical Manufacturers & Associations  
  15 chemin Louis-Dunant, P.O. Box 195  
  1211 Geneva 20  
  Switzerland                                                       | tel: +41 22 338 3212  
  email: r.krause@ifpma.org |                       |
| Dr Barbara Kuter              | Industry representative            | Executive Director                              | Merck & Co. Inc.  
  770 Sumneytown Pike  
  19486 West Point, Pennsylvania  
  United States of America                                           | tel: +1 215 652 4090  
  email: Barbara_Kuter@merck.com |                       |
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Address</th>
<th>Contact Information</th>
</tr>
</thead>
</table>
| Dr Andrew Malkin             | Head of Division                  | Federal State Unitary Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences | tel: +7 495 546 7840  
fax: +7 495 439 9321  
email: andrew.malkin@chumakovs.ru |
| Mrs Eunice Miranda           |                                   | GlaxoSmithKline Biologicals                  | tel: +32 1085 8754  
email: eunice.miranda@gskbio.com |
| Ms Tamara Music              | Policy Analyst                    | International Federation of Pharmaceutical Manufacturers & Associations | tel: +41 22 338 3200  
email: t.music@ifpma.org |
| Mrs Valerie Oriol Mathieu    | Governmental Affairs and Public Health Director | Crucell  
Rehhagstrasse 79  
3018 BERN  
Switzerland | tel: +41 (0)31 980 66 32  
email: valerie.oriolmathieu@crucell.com |
| Dr Olga Popova               | Sr Director Govt. Affairs & Public Health | Crucell  
Rehhagstrasse 79  
3018 Bern  
Switzerland | tel: +41-31-9806316  
fax: +41-31-9806472  
email: olga.popova@crucell.com |
| Dr Alexandra Sinyugina       | Head of Division                  | Federal State Unitary Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences | tel: +7 495 439 9065  
fax: +7 495 439 9321  
email: a.sinyugina@chumakovs.ru |
| Mrs Kathleen Vandendael      | Director International Relation   | GSK Biologicals  
GlaxoSmithKline Biologicals  
Site de Wavre-Nord/W35  
Noire Epine  
Avenue Fleming, 20  
Wavre  
Belgium | tel: +3210853455  
email: kathleen.m.vandendael@gskbio.com |
| Dr Michael Watson            | Vice President                    | sanofi pasteur  
2 Ave Pont Pasteur  
69367 Lyon Cedix 7  
France | tel: +33 437 37 51 32  
email: michael.watson@sanofipasteur.com |
<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Position</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Nihal Abeysinghe</td>
<td>WHO Regional Office for South-East Asia (SEARO)</td>
<td>SE/IVD Immunization and Vaccine Development</td>
<td>+91 11 23370804</td>
<td><a href="mailto:abeysinghen@searo.who.int">abeysinghen@searo.who.int</a></td>
</tr>
<tr>
<td>Dr Maria Teresa Aguado de Ros</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals, RPD</td>
<td>+41 22 791 2644</td>
<td><a href="mailto:aguadom@who.int">aguadom@who.int</a></td>
</tr>
<tr>
<td>Dr Raymond Bruce J. Aylward</td>
<td>World Health Organization</td>
<td>Polio Eradication Initiative</td>
<td>+41 22 79 14419</td>
<td><a href="mailto:aylwardb@who.int">aylwardb@who.int</a></td>
</tr>
<tr>
<td>Dr Kaushik Banerjee</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 13293</td>
<td><a href="mailto:banerjeek@who.int">banerjeek@who.int</a></td>
</tr>
<tr>
<td>Dr Adwoa Desma Bentsi-Enchill</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/QSS</td>
<td>+41 22 79 11154</td>
<td><a href="mailto:bentsienchilla@who.int">bentsienchilla@who.int</a></td>
</tr>
<tr>
<td>Mrs Alison Ruth Brunier</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals</td>
<td>+41 22 79 14468</td>
<td><a href="mailto:bruniera@who.int">bruniera@who.int</a></td>
</tr>
<tr>
<td>Dr Venkatraman Chandra-Mouli</td>
<td>World Health Organization</td>
<td>Child and Adolescent Health/Adolescent Health and Development</td>
<td>+41 22 79 14814</td>
<td><a href="mailto:chandramouliv@who.int">chandramouliv@who.int</a></td>
</tr>
<tr>
<td>Dr Thomas Cherian</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 14460</td>
<td><a href="mailto:cheriant@who.int">cheriant@who.int</a></td>
</tr>
<tr>
<td>Dr Nora Dellepiane de Rey Tolve</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/QSS</td>
<td>+41 22 79 14788</td>
<td><a href="mailto:dellepianen@who.int">dellepianen@who.int</a></td>
</tr>
<tr>
<td>Dr Modibo Dicko</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 14895</td>
<td><a href="mailto:dickomo@who.int">dickomo@who.int</a></td>
</tr>
<tr>
<td>Dr Philippe Duclos</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals</td>
<td>+41 22 79 14527</td>
<td><a href="mailto:duclosp@who.int">duclosp@who.int</a></td>
</tr>
<tr>
<td>Dr Rudi Eggers</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 15051</td>
<td><a href="mailto:eggersrr@who.int">eggersrr@who.int</a></td>
</tr>
<tr>
<td>Mr David Alexander Featherstone</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 14405</td>
<td><a href="mailto:featherstoned@who.int">featherstoned@who.int</a></td>
</tr>
<tr>
<td>Dr Olivier Fontaine</td>
<td>World Health Organization</td>
<td>Child and Adolescent Health/Newborn and Child Health and Development</td>
<td>+41 22 79 12894</td>
<td><a href="mailto:fontaineo@who.int">fontaineo@who.int</a></td>
</tr>
<tr>
<td>Ms Tracey S. Goodman</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/EPI</td>
<td>+41 22 79 12947</td>
<td><a href="mailto:goodmant@who.int">goodmant@who.int</a></td>
</tr>
<tr>
<td>Ms He Guo</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals (IVB)</td>
<td>+41 22 79 12337</td>
<td><a href="mailto:guoh@who.int">guoh@who.int</a></td>
</tr>
<tr>
<td>Dr Ana Maria Henao Restrepo</td>
<td>World Health Organization</td>
<td>Immunization, Vaccines and Biologicals/Initiative for Vaccine Research</td>
<td>+41 22 79 13402</td>
<td><a href="mailto:henaorestrepoa@who.int">henaorestrepoa@who.int</a></td>
</tr>
<tr>
<td>Name</td>
<td>Organization</td>
<td>Telefax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Joachim Maria Hombach</td>
<td>World Health Organization</td>
<td>+41 22 79 14531</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ms Lidija Namisa Kamara</td>
<td>World Health Organization</td>
<td>+41 22 79 12145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Carsten Frithjof Mantel</td>
<td>World Health Organization</td>
<td>+41 22 79 13830</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Rebecca Martin</td>
<td>Regional Office for Europe (EURO)</td>
<td>45 3917 1216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Ezzeddine Mohsni</td>
<td>Regional Office for the Eastern Mediterranean (EMRO)</td>
<td>+202 2276 5267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Pem Namgyal</td>
<td>World Health Organization</td>
<td>+41 22 79 2431</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Maria Purificacion Neira</td>
<td>World Health Organization Protection of the Human Environment (PHE)</td>
<td>+41 22 79 15526</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Sergio Andrade Nishioka</td>
<td>World Health Organization</td>
<td>+41 22 79 15579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Deo Nshimirimana</td>
<td>Regional Office for Africa (AFRO) IVD Programme Manager</td>
<td>+724139203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Jean-Marie Okwo-Bele</td>
<td>World Health Organization</td>
<td>+41 22 79 12779</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Marie-Pierre Preziosi</td>
<td>World Health Organization Immunization, Vaccines and Biologicals / IVR</td>
<td>+41 22 79 13744</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Cuauhtemoc Ruiz Matus</td>
<td>Regional Office for the Americas (AMRO)</td>
<td>+3 2 528 9745</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Julia Schmitz</td>
<td>World Health Organization Initiative for Vaccine Research (IVR)</td>
<td>+41 22 79 13047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs Caroline E. Scudamore</td>
<td>World Health Organization</td>
<td>+41 22 79 12337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr David Sniadack</td>
<td>Regional Office for the Western Pacific (WPRO)</td>
<td>+1 22 791 12337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Peter Strebel</td>
<td>World Health Organization</td>
<td>+41 22 791 1338</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Siu Lun (John) Tam</td>
<td>World Health Organization</td>
<td>+41 22 79 14231</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Nadia Teleb</td>
<td>Regional Office for the Eastern Mediterranean (EMRO) Vaccine Preventable Diseases and Immunization</td>
<td>+20105710228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Organization</td>
<td>Contact Details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Mable Carol Tevi Benissan</td>
<td>World Health Organization</td>
<td>tel: +41 22 79 12499 email: <a href="mailto:tevibenissanc@who.int">tevibenissanc@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Susan Annemarie Wang</td>
<td>World Health Organization</td>
<td>tel: +41 22 79 11606 email: <a href="mailto:wangsu@who.int">wangsu@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr David Wood</td>
<td>World Health Organization</td>
<td>tel: +41 22 791 4050 email: <a href="mailto:woodd@who.int">woodd@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Patrick Louis F. Zuber</td>
<td>World Health Organization</td>
<td>tel: +41 22 79 11521 email: <a href="mailto:zuberp@who.int">zuberp@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Jan Frans Jozef van Erps</td>
<td>World Health Organization</td>
<td>tel: +41 22 79 15867 email: <a href="mailto:vanerpsj@who.int">vanerpsj@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Severin von Xylander</td>
<td>World Health Organization</td>
<td>tel: +41 22 79 12684 email: <a href="mailto:xylanders@who.int">xylanders@who.int</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>FULL FORM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPE</td>
<td>Advisory Committee on Polio Eradication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADIP</td>
<td>Accelerated Development and Introduction Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse events following immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFI</td>
<td>Audit and finance committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP</td>
<td>Acute flaccid paralysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFR</td>
<td>Acute fever and rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHU</td>
<td>Air-handling unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMC</td>
<td>Advanced Market Commitment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>Antenatal care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>Assessment reports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVI</td>
<td>Accelerated Vaccine Introduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIW</td>
<td>African Immunization Week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARDA</td>
<td>Biomedical Advanced Research and Development Authority</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIC</td>
<td>Brazil, Russia, India, and China</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRV</td>
<td>Bovine Reassortment Vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSL-2</td>
<td>Biological Safety Level-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT</td>
<td>Coalition Against Typhoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBAW</td>
<td>Child bearing age women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFR</td>
<td>Case-fatality rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>Child Health Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medical Products for Human Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMYP</td>
<td>Comprehensive multi-year plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>Congenital rubella syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSO</td>
<td>Civil society organization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC</td>
<td>Controlled Temperature Chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTD</td>
<td>Common Technical Document</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRC</td>
<td>Democratic Republic of Congo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEVAC</td>
<td>Diarrhoeal and Enteric Vaccines Advisory Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DoV</td>
<td>Decade of Vaccines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria-tetanus-pertussis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV</td>
<td>Dengue virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Executive Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Control and Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIW</td>
<td>European Immunization Week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>Emerging Manufacturer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP</td>
<td>Expert Resource Panel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESAVEI</td>
<td>Events supposedly attributable to vaccination or immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETAGE</td>
<td>European Technical Advisory Group of Experts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUVAC.NET</td>
<td>European Surveillance Community Network for Vaccine Preventable Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVM</td>
<td>Effective Vaccine Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVSM</td>
<td>Effective Vaccine Store Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EW</td>
<td>European immunization week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZI</td>
<td>Egon Zehnder International</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRR</td>
<td>Financial Resource Requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GADI</td>
<td>Global Adjuvant Development Initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAP</td>
<td>Global Action Plan for Laboratory Containment of Polioviruses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIDEON</td>
<td>Global disease and epidemiology network</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIM</td>
<td>Global Immunization Meeting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIVS</td>
<td>Global Immunization Vision and Strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLO/VQ</td>
<td>Global Learning Opportunities for Vaccine Development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMC</td>
<td>Geometric mean antibody concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric mean titres</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNI</td>
<td>Gross national income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPEI</td>
<td>Global Polio Eradication Initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1N1</td>
<td>Pandemic influenza A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5N1</td>
<td>Avian influenza A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepB</td>
<td>Hepatitis B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>Haemagglutination inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human immunodeficiency virus/acquired immunodeficiency syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPAI</td>
<td>Highly pathogenic avian influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSFP</td>
<td>Health Systems Funding Platform</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSS</td>
<td>Health system strengthening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAC</td>
<td>Independent Assessment Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>Invasive bacterial disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBRD</td>
<td>International Bank for Reconstruction and Development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFIFm</td>
<td>International Finance Facility for Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHR</td>
<td>International Health Regulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>Immunization monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMB</td>
<td>Independent Monitoring Board</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMD</td>
<td>Invasive meningococcal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INS</td>
<td>Injection safety support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAC</td>
<td>Immunization Practices Advisory Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive pneumococcal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPR</td>
<td>Intellectual Property Rights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td>Inactivated Polio Vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>Independent Review Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRIS</td>
<td>Incentives for Routine Immunization Strengthening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>Immunization Services Support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITAG</td>
<td>Immunization Technical Advisory Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITD</td>
<td>Intratypic differentiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>Immunization vaccination and biologicals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVI</td>
<td>International Vaccine Initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JE</td>
<td>Japanese Encephalitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JEV</td>
<td>Japanese encephalitis virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JRF</td>
<td>Joint Reporting Form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KFDV</td>
<td>Kyasanur Forest disease virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPI</td>
<td>Key Performance Indicators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>Live-attenuated influenza vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMIC</td>
<td>Low-income and middle-income countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>Lipooligosaccharide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSP</td>
<td>Lot summary protocols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>Marketing authorization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>Maternal and child health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>Measles containing vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>Meningitis conjugate vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Developments Goals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDVP</td>
<td>Multi-dose vial policy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MECACAR</td>
<td>Mediterranean and Caucasian countries and central Asian republics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MICS</td>
<td>Multiple Indicator Cluster Survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCC</td>
<td>Meningocccal C conjugate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>Measles-mumps-rubella</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNC</td>
<td>Multinational companies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNT</td>
<td>Maternal and neonatal tetanus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNTE</td>
<td>Maternal and neonatal tetanus elimination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>Measles-rubella</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVP</td>
<td>Meningitis Vaccine Project</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCC</td>
<td>National Certification Commission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCL</td>
<td>National control laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NID</td>
<td>National Immunization Day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIS</td>
<td>Newly Independent States of the former Soviet Union</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NML</td>
<td>National measles lab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPEV</td>
<td>Non-polio enterovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>Neonatal tetanus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>Neutralizing antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUVI</td>
<td>New and Under-utilized Vaccines Implementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVC</td>
<td>National Validation Committees</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVI</td>
<td>Netherlands Vaccine Institute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVT</td>
<td>Non-vaccine serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVS</td>
<td>New and underused vaccine support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCV</td>
<td>Oral cholera vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM</td>
<td>Otitis media</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMCL</td>
<td>Official Medicine Control Laboratories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMV</td>
<td>Outer membrane visicles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OOS</td>
<td>Out of specification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPA</td>
<td>Opsonophagocytosis assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPV (m, b, t)</td>
<td>Oral polio vaccine (monovalent, bivalent, trivalent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV (1, 2)</td>
<td>Porcine circovirus (Type 1, Type 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDP</td>
<td>Product Development Partnership</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIC</td>
<td>Pacific Island Countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIRI</td>
<td>Periodic Intensification of Routine Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POC</td>
<td>Point of Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POW</td>
<td>Powassan virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNI</td>
<td>National Immunization Program (Brazil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPC</td>
<td>Programme and Policy Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>Position paper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRC</td>
<td>Polio Research Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSF</td>
<td>Product summary file</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSUR</td>
<td>Programmatic suitability of vaccines for prequalification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QS</td>
<td>Quality system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUIVER</td>
<td>Quantitative Immunization and Vaccines Related Research</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RC</td>
<td>Regional Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>Regional Certification Commission for Poliomyelitis Eradication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>Randomized controlled trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCV</td>
<td>Rubella containing vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>Regional Director</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RED</td>
<td>Reaching every district strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>Revolving Fund</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLL</td>
<td>Regional Reference Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTAG</td>
<td>Regional Technical Advisory Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAM</td>
<td>Surveillance, Monitoring and Evaluation Team</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIA</td>
<td>Supplementary Immunization Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBA</td>
<td>Serum bactericidal antibody</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SII</td>
<td>Serum Institute of India</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIVAC</td>
<td>Supporting National Independent Immunization and Vaccine Advisory Committees initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAG</td>
<td>Technical Advisory Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP</td>
<td>Transparency and Accountability Policy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBE</td>
<td>Tick-borne encephalitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBEV</td>
<td>Tick-borne encephalitis virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDI</td>
<td>Targeted Diseases and Immunization Team</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TESSy</td>
<td>The European Surveillance System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFI</td>
<td>Task Force on Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIVs</td>
<td>Trivalent inactivated influenza vaccines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLAC</td>
<td>Technologies and Logistics Advisory Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPP</td>
<td>Target Product Profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSAP</td>
<td>Typhoid Fever Surveillance Program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible spongiform encephalopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus Toxoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNIL</td>
<td>University of Lausanne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAT</td>
<td>Vaccine-associated serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Event Reporting System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDPV</td>
<td>Vaccine-derived poliovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cVDPV</td>
<td>Circulating vaccine-derived poliovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iVDPV</td>
<td>Vaccine-derived poliovirus isolated from immunodeficient patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIPS</td>
<td>Vi polysaccharide vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISI</td>
<td>Vaccine Identification Standards Initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIVA</td>
<td>Vi-based Vaccines for Asia Initiative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMA</td>
<td>Vaccine Management Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPD</td>
<td>Vaccine-preventable diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>Vaccine Serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVM</td>
<td>Vaccine vial monitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WB</td>
<td>World Bank</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC-rBS</td>
<td>Whole cell-recombinant B subunit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCBA</td>
<td>Women of childbearing age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WER</td>
<td>Weekly Epidemiological Record</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WG</td>
<td>Working Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WNV</td>
<td>West-Nile virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WPV</td>
<td>Wild poliovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YFV</td>
<td>Yellow fever virus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010 – summary, conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on Immunization1 met on 9–11 November 2010 in Geneva, Switzerland.2

Report from WHO Department of Immunization, Vaccines and Biologicals

Recent licensure of the meningococcal A conjugate vaccine MenAfriVac allowed pilot campaigns to be launched successfully in Burkina Faso, Mali and Niger; coverage exceeded 90% in all targeted districts, and nationwide campaigns in these countries will begin in December 2010. SAGE encouraged WHO to draw global attention to this achievement. SAGE also noted that more clarity was needed on recommendations for vaccinating subpopulations (such as pregnant and lactating women) because they should not be denied vaccines if no specific concerns or contraindications exist.

Pneumococcal conjugate vaccination is being expanded to additional countries with support from the GAVI Alliance. There is evidence of nonvaccine serotype replacement in areas where the vaccine has been used, although changes in nonvaccine serotypes vary according to incidence before the vaccine was introduced, surveillance methods, vaccine dose and schedules, the use of antibiotics and patterns of antimicrobial resistance. Changes in serotype distribution have also been seen in countries that have not introduced pneumococcal conjugate vaccines. Related data were reviewed during a recent consultation.3 The results of a systematic review of published and unpublished data on se-

1 On trouvera de plus amples informations sur le Groupe stratégique consultatif d’experts (SAGE) à l’adresse suivante: http://www.who.int/immunization/sage/fr/index.html

Reunion du Groupe strategique consultatif d’experts sur la vaccination, novembre 2010 – resumé, conclusions et recommandations

Le Groupe stratégique consultatif d’experts (SAGE) sur la vaccination1 s’est réuni du 9 au 11 novembre 2010 à Genève, (Suisse).2

Rapport du Département Vaccination, vaccins et produits biologiques

L’autorisation de mise sur le marché récemment accordée au vaccin antîménongococcique A conjugué MenAfriVac a permis de lancer des campagnes pilotes avec succès au Burkina Faso, au Mali et au Niger; la couverture a dépassé 90% dans tous les districts ciblés, et des campagnes nationales démarreront dans ces pays en décembre 2010. Le SAGE a encouragé l’OMS à attirer l’attention du monde sur cette réalisation. Il a également noté que les recommandations relatives à la vaccination des sous-populations (telles que les femmes enceintes ou qui allaient) avaient besoin d’être clarifiées, celles-ci ne devant pas se voir refuser le vaccin si aucune préoccupation ni contre-indication particulières n’existent.

La vaccination par le vaccin antîpnuemococcique conjugué est étendue à d’autres pays avec le soutien de l’Alliance GAVI. Il y a des signes de remplacement des sérotypes non vaccinaux dans les zones où le vaccin a été utilisé, même si les changements observés au niveau des sérotypes non vaccinaux montrent des variations en fonction de l’incidence de la maladie avant l’introduction du vaccin, des méthodes de surveillance, des doses et des calendriers d’administration, du recours aux antibiotiques et des caractéristiques de la résistance antimicrobienne. On a également observé des modifications de la distribution des sérotypes dans les pays qui n’ont pas introduit les vaccins antîpnuemococciques conjugués. Les données à ce sujet ont été examinées au cours d’une consultation récente.3 Les résultats d’un examen systématique des
rototype replacement will be presented to SAGE in November 2011.

In 2009, global coverage with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) reached 82%, short of the 90% coverage goal of the Global Immunization Vision and Strategy (GIVS). A total of 97 countries have not reached 80% coverage of DTP3 in all districts. SAGE emphasized that national coverage figures may conceal inequities, and that accurate data from the subnational level are essential for identifying marginalized, under-immunized groups.

Global coverage with 3 doses of Haemophilus influenzae type b vaccine (Hib) is only 38% because many countries, including large countries such as India and Nigeria, have not yet introduced the vaccine. The need to develop specific strategies for working with large countries to implement recommended vaccine policies was highlighted.

SAGE was updated on developments occurring as a result of the initiation of the Decade of Vaccines. In January 2010, Bill and Melinda Gates pledged US$ 10 billion for this initiative which builds on the lessons learnt from and the goals of the Global Immunization Vision and Strategy. At the World Health Assembly (WHA) in May 2010, the Director-General affirmed WHO’s commitment to work with partners to develop a framework for the Decade of Vaccines. This framework includes the following 4 areas of work: (i) strengthening public support for the use and financing of vaccines, (ii) expanding the reach of delivery programmes, (iii) maintaining a strong research and development pipeline, and (iv) exploring strategies to ensure global access to sufficient supplies of affordable vaccines. An action plan for the Decade of Vaccines will be finalized by the end of 2012, and SAGE expressed interest in contributing to the development of the plan. SAGE emphasized the need for thorough and early engagement with regions and countries. SAGE emphasized that health-care systems can be strengthened by implementing vaccination programmes and that this focus should be incorporated into one of the areas of work; SAGE also pointed out that investing in surveillance should be incorporated into one of the areas of work.

The use of vaccines during humanitarian crises will be discussed at a forthcoming SAGE meeting.

Report from the GAVI Alliance

The mission of the GAVI Alliance remains the same for 2011–2015. It is underpinned by 4 strategic goals, including shaping vaccine markets, and the mission is supported by the Alliance’s engagement in advocacy and communication, public policy, and monitoring and evaluation. The new business plan is performance-based, and payments are linked to deliverables.

In December 2010, the GAVI Alliance Board will be presented with a performance-based policy that builds on the Immunization Systems Strengthening policy with a focus on providing support to countries where routine coverage of DTP3 is ≤70%. The Board will also be presented with a simplified cofinancing policy. The majority of countries eligible for funding from the Alliance will be required to make modest co-payments. Countries will no longer be eligible for support once they surpass the eligibility threshold of >US$ 1500 gross national income données relatives au remplacement des sérotypes, publiées ou non, seront présentés au SAGE en novembre 2011.

En 2009, la couverture mondiale des 3 doses de vaccin anti-diphtherie-tétanos-anti-pertuisseux (DTP3) a atteint 82%, soit une valeur en deçà de l’objectif de couverture de 90% fixé par l’Initiative «La vaccination dans le monde: vision et stratégie». Quatre-vingt-dix-sept pays au total n’ont pas atteint une couverture de 80% dans l’ensemble des districts. Le SAGE a souligné le fait que les chiffres nationaux de la couverture vaccinale peuvent cacher des inégalités et qu’il est essentiel de disposer de données précises provenant de l’échelon infranational pour identifier des groupes marginalisés et sous-vaccinés.

La couverture mondiale par les 3 doses de vaccin anti-Haemophilus influenzae type b (Hib) n’est que de 38% parce que de nombreux pays, notamment de grands pays comme l’Inde et le Nigeria, n’ont pas encore introduit ce vaccin. La nécessité d’élaborer des stratégies spécifiques de collaboration avec les grands pays afin de mettre en œuvre les politiques vaccinales recommandées a été soulignée.

Le SAGE a été informé des développements survenus à la suite du lancement de la Décennie des vaccins. En janvier 2010, Bill et Melinda Gates ont promis US$ 10 milliards à cette initiative qui s’appuie sur les enseignements tirés de l’Initiative «La vaccination dans le monde: vision et stratégie» et sur les objectifs de cette dernière. Lors de l’Assemblée mondiale de la Santé de mai 2010, le Directeur général a affirmé la détermination de l’OMS à élaborer avec ses partenaires un cadre de travail pour la Décennie des vaccins. Ce cadre comprend les 4 domaines d’activité suivants: i) le renforcement du soutien public en faveur de l’utilisation et du financement des vaccins; ii) l’extension de la portée des programmes d’administration; iii) le maintien d’une solide filière de recherche et développement; et iv) l’exploration de stratégies visant à assurer l’accès à un approvisionnement suffisant en vaccins d’un prix abordable partout dans le monde. Un plan d’action pour la Décennie des vaccins sera finalisé d’ici la fin 2012 et le SAGE a indiqué qu’il souhaiterait participer à son élaboration. Il a souligné la nécessité d’un engagement total et précoce avec les Régions et les pays. Il a rappelé que les systèmes de soins de santé peuvent être renforcés par la mise en œuvre des programmes de vaccination et que cet aspect devrait être incorporé dans l’un des domaines d’activité; il a également fait valoir que le fait d’investir dans la surveillance devrait également être incorporé dans l’un des domaines d’activité.

L’utilisation des vaccins au cours des crises humanitaires sera évoquée lors d’une prochaine réunion du SAGE.

Rapport de l’Alliance GAVI

La mission de l’Alliance GAVI reste la même pour 2011-2015. Elle est fondée sur 4 objectifs stratégiques, notamment sur la détermination de ce que seront les marchés pour le vaccin, et est soutenue par l’engagement de l’Alliance dans des activités de sensibilisation et de communication, de politique publique, de suivi et d’évaluation. Le nouveau plan d’activité est fondé sur les résultats, et les paiements sont liés aux résultats attendus.

En décembre 2010, le Conseil de l’Alliance a été saisi de la politique fondée sur les résultats qui s’appuie sur la politique de renforcement des systèmes de vaccination mise en place aux pays dans lesquels la couverture systématique du DTC3 est ≤70%. Il a également été saisi de la politique simplifiée de cofinancement. La majorité des pays pouvant prétendre à un financement de l’Alliance devront apporter une contribution financière modeste. Ils ne pourront plus recevoir de soutien dès qu’ils dépasseront le seuil de >US$ 1500 de revenu national brut par habitant; ils devront assumer le coût total de leurs vaccins d’ici 2016. Il existe une
per capita; these countries will be expected to assume the full cost of their vaccines by 2016.

Following the launch of the Advanced Market Commit-
ment for pneumococcal vaccine, 4 manufacturers have
registered, and 2 are already producing the vaccine. The
maximum Advanced Market Commitment price is
US$ 3.50 per dose. The Alliance’s supply strategy is being
revised and will be brought to SAGE for discussion.

The GAVI Alliance still faces a significant funding chal-
lenge. However, the October Call for Action and Re-
sources meeting yielded positive results and further
pledges are expected at the June 2011 donor pledging
meeting.

Regional reports

Region of the Americas
The Region of the Americas is preparing a plan of ac-
tion to enhance existing surveillance for timely detec-
tion of poliovirus importation and to reduce the risk
of spread by increasing coverage with oral poliovirus
vaccine (OPV) in high-risk districts. The region has
eliminated measles, and has not had a confirmed case
of rubella reported for the past 20 months.

The annual immunization week, an initiative first
launched in the Region, has catalysed similar synchro-
nized activities in other Regions; in 2011 it is expected
that all Regions except South-East Asia will participate.

The Region of the Americas responded to the challenges
posed by the pandemic influenza A(H1N1) 2009 virus
by successfully deploying pandemic vaccine and is now
rolling out pneumococcal conjugate vaccine, rotavirus
vaccine and human papillomavirus vaccine. SAGE noted
that countries in the Region had difficulty in convincing
pregnant women to accept the vaccine despite the high
morbidity and mortality seen in that group.

The importance has been recognized of ensuring uni-
versally high coverage with routine immunizations to
sustain the gains made by immunization programmes
in order to benefit fully from new vaccines, and to pro-
tect entire families, including adolescents and the el-
derly. Closely monitoring district-level coverage, con-
ducting evaluations of national immunization pro-
grammes, and using immunization weeks to raise
awareness of the value of immunization have proven
effective in this regard. Immunization programmes
have also been strengthened by improving assessments
of vaccine safety, ensuring resources are available for
evidence-based decision-making, and documenting the
introduction of new vaccines. The national govern-
ments of the Region, through the Directing Council of
the Pan American Health Organization, resolved that
national immunization programmes are a public good,
and supported the regional strategy for immunization
and the Revolving Fund for Vaccine Procurement.

The January 2010 earthquake in Haiti rendered >1.2 mil-

lon people homeless and caused >220 000 deaths. Haiti
has the weakest immunization system in the Region.
Thus, a post-disaster vaccination plan has been devel-
oped and vaccination will be conducted in phases. Vac-
cination initially targeted people who had been injured or
hospitalized; those in temporary settlements and camps
were targeted next, followed by people in af-
fected communities. Finally, full immunization services
will be re-established.

proposition d’analyse de l’espace budgétaire des pays qui ne béné-
ficieront bientôt plus du soutien de l’Alliance.

Suite au lancement de l’Engagement de marché préalable pour
le vaccin antipneumococcique, 4 fabricants se sont inscrits et
2 d’entre eux produisent déjà le vaccin. Le prix maximum fixé
pour l’Engagement de marché préalable est de US$ 3,50 par
dose. La stratégie d’approvisionnement de l’Alliance est en
cours de révision et sera présentée au SAGE pour examen.

L’Alliance GAVI fait encore face à des problèmes de financement
importants. Cependant, la réunion d’octobre d’appel à l’action
et à la mobilisation de ressources a donné des résultats positifs
et plusieurs promesses de dons supplémentaires sont attendues
lors de la réunion des annonces des donateurs de juin 2011.

Rapports régionaux

Région des Amériques
La Région des Amériques prépare un plan d’action visant à
renforcer la surveillance existante pour détecter en temps utile
les importations de poliovirus et réduire les risques de propa-
gation en augmentant la couverture du vaccin antirotavirus
oral (VPO) dans les districts à haut risque. La Région a
éliminé la rougeole et aucun cas confirmé de rubéole n’y a été
notifié au cours des 20 derniers mois.

La semaine annuelle de la vaccination, une initiative lancée pour
la première fois dans cette Région, a catalysé des activités synchro-
nisées comparables dans d’autres Régions; en 2011, on espère que
toutes les Régions sauf celle de l’Asie du Sud-Est y participeront.

La Région des Amériques a répondu aux problèmes posés par le
virus de la grippe pandémique A (H1N1) 2009 en déployant avec
succès le vaccin antigrrippique pandémique et elle s’occupe à présent
de déployer le vaccin antipneumococcique conjugué, le vaccin
antirotavirus et le vaccin antipapillomavirus humain. Le SAGE a
pris note de ce que les pays de la Région avaient des difficultés
de convaincre les femmes enceintes d’accepter le vaccin malgré
la morbidité et la mortalité élevées observées dans ce groupe.

On a reconnu l’importance d’une couverture universellement
elevée des vaccinations systématiques pour maintenir les avan-
cées obtenues par les programmes de vaccination de façon à
profiter pleinement des nouveaux vaccins et à protéger des
familles entières, notamment les adolescents et les personnes
âgées. Un suivi étroit de la couverture à l’échelle du district,
des évaluations des programmes nationaux de vaccination et le
recours à des semaines de la vaccination pour mieux faire
connaître les vaccins se sont avérés efficaces à cet égard. Les
programmes de vaccination ont également été renforcés par
l’amélioration de l’évaluation de l’innocuité des vaccins, la mise
da disposition de ressources pour une prise de décision reposant
sur des bases factuelles et par la documentation de l’introduc-
tion des nouveaux vaccins. Les gouvernements nationaux de la
Région, par l’intermédiaire du Conseil directeur de l’Organisa-
tion panaméricaine de la Santé, ont décidé que les programmes
nationaux de vaccination constituaient un bien public et ont
soutenu la stratégie régionale de vaccination et le Fonds renou-
velable pour l’achat des vaccins.

Le tremblement de terre de janvier 2010 en Haïti a fait
>1,2 million de sans-abri et provoqué >220 000 décès. Haïti a
le système de vaccination le plus faible de la Région. Ainsi, on
a élaboré un plan de vaccination postcatastrophe qui se dérou-
lera par phases. Initialement ciblée sur les personnes qui ont
été blessées ou hospitalisées, puis sur les structures et camps
temporaires, la vaccination ciblera ensuite personnes des
communautés touchées. Enfin, des services complets de vacci-
nation seront réimplantés.
The cholera outbreak, with 8000 reported cases and 544 deaths as of 8 November 2010, resulted in a regional review which concluded that vaccination would be of limited benefit and that efforts should focus on improving water and sanitation, and on case-management. SAGE noted with concern the high case-fatality ratio observed during this outbreak. SAGE also noted that considering the reality of such outbreaks and its recommendations on cholera vaccination, a role for vaccination should be considered to help contain outbreaks at an early stage.

SAGE applauded the success of the Region's immunization programmes, and noted the leadership provided by the regional office, the strong commitment of national governments (through their own programmes and 99% of funding provided by countries in Latin America and the Caribbean) and the commitment to equity of access through the adoption of a rights-based approach to immunization.

SAGE supported the promotion of national immunization programmes within the primary health-care framework.

SAGE encouraged the Regional Office to formally document the factors contributing to countries' ownership of the programmes and the successful delivery of immunizations and to share these with other regions.

**European Region**

The outbreaks of imported poliomyelitis and of measles in countries reporting high coverage of routine immunizations have highlighted deficiencies in immunization programmes that need to be addressed if disease eradication, elimination and control goals are to be met.

An outbreak of poliomyelitis in Tajikistan caused by imported type-1 wild poliovirus was recognized in early 2010. In 2009, reported coverage with 3 doses of OPV was 93%, however household surveys found lower coverage. Supplementary immunization activities (SIAs) were recommended for the border areas of Tajikistan in 2009 but were postponed because of funding constraints and conflicting priorities. The Regional Office assisted Tajikistan in implementing 4 rounds of SIAs with monovalent type-1 OPV and 2 rounds with trivalent OPV to stop the outbreak and prevent spread to neighbouring countries.

As of 5 November 2010, an outbreak of measles in Bulgaria during 2009–2010 had resulted in 24 137 reported cases and 25 deaths; most cases occurred among the Roma population. Reported national coverage of the first dose of measles vaccine in 2009 was 96.1%; reported coverage of the second dose was 92.8%. The primary reasons identified for the outbreak were lower immunization coverage than reported, inaccurate census, and segments of the population being missed by immunization services. The Regional Office has identified surveillance solutions that can be used by countries to estimate coverage more accurately; these solutions include: sera surveys; population-based surveys of coverage; triangulation of information with other sources, such as vaccine procurement services; and improved management of vital statistics. Because vaccination behaviour (that is, whether a person decides to be vaccinated) is determined by a range of factors, including opportunity, ability and motive, the Regional Office will profile countries and tailor responses based on their specific mix of factors.

La flambée de choléra, avec 8000 cas notifiés et 544 décès au 8 novembre 2010, a entraîné un examen régional qui a conclu que la vaccination présenterait un intérêt limité et qu’il fallait mettre l’accent sur l’amélioration de la qualité de l’eau et de l’assainissement et sur la prise en charge des cas. Le SAGE a noté avec préoccupation le taux de létalité élevé observé au cours de cette flambée. Il a également noté qu’étant donné la réalité de ces flambées et les recommandations qu’il a formulées sur la vaccination anticho- lérique, il faudrait songer au rôle que pourrait jouer la vaccination pour aider à contenir précocement les flambées.

Le SAGE s’est félicité du succès remporté par les programmes de vaccination de la Région et a pris bonne note de la direction assurée par le Bureau régional, de l’engagement sans faille des gouvernements nationaux (qui se sont appropriés les programmes et où 99% du financement sont assurés par les pays en Amérique latine et dans les Caraïbes) et de l’engagement en faveur de l’égalité d’accès par l’adoption d’une approche fondée sur le droit à la vaccination.

Le SAGE a soutenu la promotion des programmes nationaux de vaccination dans le cadre des soins de santé primaires. Il a encouragé la Région à établir l’existence de facteurs favorisant l’adhésion des pays aux programmes et le succès de l’administration des vaccins, et l’a incitée à partager son expérience avec d’autres Régions.

**Région européenne**

Les flambées de poliomyélite importée et de rougeole dans des pays faisant état d’une couverture élevée des vaccinations systématiques ont souligné les carences des programmes de vaccination auxquelles il faut remédier si l’on veut réussir à atteindre les objectifs de lutte, d’élimination et d’éradication des maladies.

Une flambée de poliomyélite survenue au Tadjikistan due à un poliovirus sauvage de type 1 importé a été identifiée au début 2010. En 2009, la couverture par les 3 doses de VPO était de 93% selon les rapports, mais des enquêtes dans les ménages ont permis de constater qu’elle était plus faible. Des activités de vaccination supplémentaire (AVS) ont été recommandées en 2009 pour les zones frontalières du Tadjikistan mais remises à plus tard en raison de difficultés financières et de priorités contradictoires.

Le Bureau régional a assisté le Tadjikistan dans la mise en œuvre de 4 tournées d’AVS au moyen du VPO monovalent contre le type 1, et de 2 tournées au moyen du VPO trivalent pour mettre fin à la flambée et prévenir une propagation aux pays voisins.

Au 5 novembre 2010, une flambée de rougeole ayant sévi en Bulgarie en 2009-2010 avait provoqué 24 137 cas notifiés et 25 décès; la plupart des cas se sont produits dans la population rom. La couverture nationale de la première dose de vaccin antirougeoleux rapportée en 2009 était de 96,1%; celle de la deuxième dose de 92,8%. Les principales raisons de la flambée ont été une couverture vaccinale inférieure à celle rapportée, un recensement inexact et des segments entiers de la population qui ont été manqués par les services de vaccination. Le Bureau régional a déterminé les solutions que les pays peuvent mettre en œuvre en matière de surveillance pour estimer de façon plus exacte la couverture; parmi elles figurent les enquêtes sérologiques, les enquêtes de couverture en population, la triangulation des informations avec d’autres sources, par exemple les services d’achat de vaccins, et une meilleure gestion des statistiques de l’état civil. Parce qu’en matière de vaccination le comportement (c’est-à-dire le fait qu’une personne décide de se faire vacciner ou non) est déterminé par toute une série de facteurs, dont la possibilité de le faire, l’aptitude à le faire et la motivation pour cela, le Bureau régional établira le profil des pays et adaptera les réponses à apporter en fonction de leurs combinaisons de facteurs spécifiques.
The declining uptake of measles vaccine in several western European countries threatens the elimination goal. Misperceptions about the usefulness and safety of the vaccine in the community and among health professionals must be corrected by effectively providing accurate information on the risks and benefits of immunization. In 2010, the Regional Committee for Europe renewed its commitment to eliminating measles and rubella but moved the target year from 2010 to 2015. The Regional Office has been requested to provide leadership and strategic direction, establish a regional verification commission and work with countries to strengthen routine immunization programmes, particularly for vulnerable groups; the Regional Office has also been asked to use the European immunization week as a platform for increasing public awareness of the benefits of immunization and countering the false messages put forth by antivaccination movements.

SAGE welcomed regional plans to address surveillance gaps, and encouraged the region to document and share its experiences in country profiling, tailoring responses and using novel communication strategies to effect behaviour change.

Western Pacific Region

In the Western Pacific Region the 2003 resolution by the Regional Committee emphasized that eliminating measles and controlling hepatitis B should be the pillars of efforts made to strengthen national immunization programmes. The Regional Committee's 2010 resolution reaffirmed the targeted disease goals and the need to strengthen routine immunization services. Regional progress towards meeting the goals mandated by the Regional Committee and the role of the goals in strengthening routine immunization systems and improving child health were reviewed. SIAs have been used to improve all aspects of routine immunization programmes, including forecasting the need for supplies and logistics, management, microplanning, social mobilization and programme communication, supervision, monitoring, surveillance of adverse events following immunization, data management, resource mobilization and partnership development.

SIAs conducted in 30 countries and areas during the past decade have led to a substantial decline in the incidence of measles. From 2008 to 2009, the incidence of measles cases declined by 58%, and further decreases are expected following national SIAs conducted in 2010 and planned for 2011. There have been consistent increases in regional coverage of the first dose of measles vaccine administered through routine programmes; this coverage reached 93% in 2009; and 76% of all districts achieved ≥90% coverage of DTP3. Altogether, 30/37 countries or areas have added rubella vaccine to measles vaccine in their national immunization programmes; and efforts to eliminate measles are being used to control rubella in highly endemic countries where measles-rubella vaccine will be administered during upcoming SIAs.

To reduce the seroprevalence of hepatitis B surface antigen among children aged 5 years to <2%, at least 65% coverage with a birth dose of hepatitis B vaccine and 85% coverage with 3 doses are required. A total of 27 countries and areas will achieve this 2012 goal, but 9 will not and these countries require integrated plan-

Le recours moins fréquent au vaccin antirougeoleux dans plusieurs pays d’Europe occidentale menace l’objectif d’élimi-

Releve epidémiologique hebdomadaire, no 1-2, 7 janvier 2011

Le SAGE a accueilli avec satisfaction les plans régionaux visant à combler les lacunes de la surveillance et encouragé la Région à renforcer son expression, sa mobilisation et sa capacité d’adaptation des réponses, et d’utilisation de nouvelles stratégies de communication pour parvenir à un changement de comportement et à la partager.

Région du Pacifique occidental

Dans cette Région, la résolution adoptée en 2003 par le Comité régional mettait l’accent sur le fait que l’élision de la rougeole et la lutte contre l’hépatite B devaient être le fondement des efforts consentis pour renforcer les programmes nationaux de vaccination. La résolution adoptée en 2010 par le Comité régional a réaf-

méré les objectifs à atteindre pour les maladies cibles et la nécessi-

té de renforcer les services de vaccination systématique. Les progrès réalisés au niveau régional en vue d’atteindre les objectifs fixés par le Comité régional et le rôle qu’ils jouent dans le renfor-
cement des systèmes de vaccination systématique et l’amélioration de la santé de l’enfant ont été examinés. Des AVS ont été menées afin d’améliorer tous les aspects des programmes de vaccination systématique, à savoir: la prévision des besoins en matière d’ap-

provisionnement et de logistique, la gestion, la microplanification, la mobilisation sociale et la communication du programme, la supervision, le suivi, la surveillance des manifestations postvaccina-

les indésirables, la gestion des données, la mobilisation de resours et le développement des partenariats.

Les AVS menées dans 30 pays et territoires au cours de la derniè-

dernière décennie ont conduit à une baisse non négligeable de l’incidence de la rougeole. Entre 2008 et 2009, l’incidence de la rougeole a baissé de 58%, et des baisses supplémentaires sont attendues suite aux AVS menées au niveau national en 2010 et prévues pour 2011. On a observé une augmentation régulière de la couverture régionale de la première dose de vaccin anti-

rougeoleux administrée par les programmes de vaccination systématique; elle a atteint 93% en 2009; par ailleurs, 76% de l’ensemble des districts ont atteint une couverture du DTC3 ≥90%. En tout, 30 pays ou territoires sur 37 ont ajouté le vaccin antirougeoleux au vaccin antirougeoleux dans leurs programmes nationaux de vaccination; et les efforts visant à éliminer la rougeole sont utilisés pour lutter contre la rubéole dans les pays de forte endémie où le vaccin antirougeoleux-antirougeoleux sera administré au cours des AVS à venir.

Pour réduire à <2% la séroprévalence de l’antigène de surface du virus de l’hépatite B chez les enfants âgés de 5 ans, il faut une couverture d’au moins 65% de la dose de vaccin anti-hépatite B administrée à la naissance et une couverture de 85% des 3 doses de ce vaccin. Au total, 27 pays et territoires atteindront cet objec-
tif fixé pour 2012, mais 9 n’y parviendront pas et ces pays ont
ning with maternal and child health programmes to increase coverage of the birth dose of the hepatitis B vaccine.

All but 5 countries have eliminated maternal and neonatal tetanus.

In addition to the role that polio eradication may have in strengthening routine immunization services and case-based surveillance before certification, sustaining polio-free status despite the increased threat of importation requires countries and areas to bolster their routine immunization programmes and the performance of their surveillance systems.

The Western Pacific Region was the first Region to deploy vaccines against the pandemic (H1N1) 2009 virus donated by WHO, and 14/17 eligible countries received donated vaccine by March 2010. Vaccine use varied considerably among countries, reaching 100% of the targeted population in Tuvalu and Vanuatu but only 28% in the Philippines. Experience with SIAs was useful in delivering pandemic influenza vaccines.

Evidence suggests that focusing on targeted diseases has not hindered the introduction of new vaccines, since 30 countries and areas have include Hib vaccine in their routine schedules, and this is the only region in which all low-income countries have introduced Hib vaccine.

SAGE noted the positive impact of SIAs on routine immunization in the Region but considers that the impact of SIAs in other Regions requires further study.

Reports from other advisory committees

At its October 2010 meeting, the WHO Expert Committee on Biological Standardization adopted new guidance on the independent release of lots of vaccines by national authorities. This guidance emphasizes the need for expertise in testing to reduce the risk of interrupting the vaccine supply through inappropriate testing. The committee adopted a revised prequalification procedure for assessing the acceptability of vaccines for purchase by UN agencies. The revision enhances assistance from eligible national regulatory authorities with collaborative agreements to share information. It ensures improved transparency for determining the programmatic suitability of vaccines for prequalification.

SAGE received an update from the June 2010 meeting of the Global Advisory Committee on Vaccine Safety (GACVS), information was also provided on interim statements on pandemic influenza vaccines and narcolepsy, and on rotavirus vaccines and intussusception.

SAGE was encouraged by the safety assessments of the new meningococcal A conjugate vaccine. The latest data

4 SAGE noted the positive impact of SIAs on routine immunization in the Region but considers that the impact of SIAs in other Regions requires further study.

4 Reports from other advisory committees

At its October 2010 meeting, the WHO Expert Committee on Biological Standardization adopted new guidance on the independent release of lots of vaccines by national authorities. This guidance emphasizes the need for expertise in testing to reduce the risk of interrupting the vaccine supply through inappropriate testing. The committee adopted a revised prequalification procedure for assessing the acceptability of vaccines for purchase by UN agencies. The revision enhances assistance from eligible national regulatory authorities with collaborative agreements to share information. It ensures improved transparency for determining the programmatic suitability of vaccines for prequalification.

SAGE received an update from the June 2010 meeting of the Global Advisory Committee on Vaccine Safety (GACVS), information was also provided on interim statements on pandemic influenza vaccines and narcolepsy, and on rotavirus vaccines and intussusception.

SAGE was encouraged by the safety assessments of the new meningococcal A conjugate vaccine. The latest data

4 SAGE noted the positive impact of SIAs on routine immunization in the Region but considers that the impact of SIAs in other Regions requires further study.

4 Rapports d’autres comités consultatifs

Lors de sa réunion d’octobre 2010, le Comité OMS d’experts de la Standardisation biologique a adopté de nouvelles recommandations relatives à la mise en circulation des lots de vaccins par les autorités nationales de manière indépendante. Ces recommandations soulignent la nécessité de disposer de compétences en matière d’épreuves de laboratoire afin de réduire le risque d’interruption de l’approvisionnement en vaccins du fait d’épreuves inappropriées. Le Comité a adopté une procédure révisée de présélection afin d’évaluer l’acceptabilité des vaccins achetés par les institutions des Nations Unies. Cette révision renforce l’assistance apportée par les autorités nationales de réglementation habilitées à le faire grâce à des accords de collaboration pour partager l’information. Elle garantit une meilleure transparence de la détermination des vaccins convenant sur le plan programmatique et pouvant être qualifiés.

Le SAGE a été informé des éléments nouveaux apparus lors de la réunion du Comité consultatif mondial de Sécurité vaccinale (GACVS) de juin 2010. Il a également été tenu au courant des déclarations provisoires sur les vaccins antigrippes pandémique et la narcolepsie, ainsi que sur les vaccins antirétrovirus et l’invagination.

Le SAGE a jugé encourageantes les évaluations de l’innocuité du nouveau vaccin antiméningocoque A conjugué. Les
from clinical trials provide further reassurance of its safety. SAGE concurred with the GACVS guidance on the need for careful postmarketing surveillance in order to: confirm the safety profile of the vaccine in subgroups such as pregnant women; better understand immunogenicity and whether a booster dose is needed; the effect on carriage; whether there are interactions with other vaccines; and whether serogroup replacement occurs.

SAGE noted that data on the safety of pandemic (H1N1) 2009 virus vaccine were reassuring, and there have been no new demonstrated safety concerns. Recent studies into other purported signals, including laboratory evidence. Les investigations progress, and several regulatory agencies are carefully reviewing the data. SAGE strongly supported the implementation of collaborative agreements between WHO and the main national regulatory authorities to facilitate rapid exchange of safety information.

SAGE noted the preliminary observation of an increased risk of intussusception shortly after the first dose of rotavirus vaccination in some populations.

SAGE received an update on the June and November 2010 meetings of the WHO Immunization Practices Advisory Committee (IPAC) which replaces the Technologies and Logistics Advisory Committee. The new committee will focus on operationalizing SAGE’s policy decisions, and receive operational challenges from regions and countries for consideration and advice.

SAGE was presented with a report from the October 2010 meeting of the Quantitative Immunization and Vaccine-Related Search (QUIVER) Advisory Committee. The different approaches to estimating childhood mortality require harmonization as well as comprehensible methods for describing uncertainties and differences. Progress has been made on providing different modelling groups with common datasets to assess differences among models and identify the principal factors causing the differences in order to enhance the transparency of the models.

SAGE noted the need to obtain recent field data on age-specific incidence and age-specific death: case ratios, particularly for low-income and middle-income countries.

**Seasonal and pandemic influenza**

SAGE received an update on pandemic (H1N1) 2009 vaccine pharmacovigilance and deployment. A continuing review of global data conducted by GACVS has found an excellent safety profile. Study results have demonstrated high effectiveness and a good match between vaccine antigen and the circulating pandemic (H1N1) 2009 influenza virus. Pledges for vaccine donations were made quickly to WHO, although there were delays between the pledge and the fulfillment of commitment. In addition, there were delays from commitment to deployment owing to vaccine availability, the requirement for letters of intent and agreement, and a vaccine deployment plan. WHO deployed 78 million doses, most of which went to the African Region, the South-East Asia Region and the Eastern Mediterranean Region. WHO is reviewing ways to shorten timelines to expedite the availability of vaccine. Eleven vaccines were prequal-

SAGE notées les plus récentes des essais cliniques rassurent encore sur son innocuité. Le SAGE souscrit aux recommandations du GACVS relatives à la nécessité d’une surveillance postcommercialisation attentive afin de: confirmer le profil d’innocuité de ce vaccin dans des sous-groupes tels que les femmes enceintes; de mieux comprendre l’immunogénicité de ce dernier et de savoir si un rappel est nécessaire; quels sont les effets sur le portage de la bactérie et s’il y a des interactions avec d’autres vaccins ou s’il se produit un remplacement du sérogroupe.

Le SAGE a pris note de ce que les données relatives à l’innocuité du vaccin antigrippé pandémique A (H1N1) 2009 étaient rassurantes et qu’aucune nouvelle préoccupation à ce sujet n’a été mise en évidence. Les autres affaires, dont notamment la narcolepsie, sont en cours et plusieurs organismes de réglementation examinent soigneusement les données. Le SAGE a fortement appuyé la mise en œuvre d’accords de collaboration entre l’OMS et les principales autorités nationales de réglementation; et enfin, faciliter l’échange rapide des informations relatives à l’innocuité.

Le SAGE a pris note de l’observation préliminaire faisant état d’un risque accru d’invagination intestinale peu après la première dose de vaccin antirotavirus dans certaines populations.

Le SAGE a été informé des différents éléments des réunions du Comité consultatif sur les pratiques vaccinales (IPAC) de l’OMS, qui remplace le Comité consultatif sur les Technologies et la Logistique, qui ont eu lieu en juin et en novembre 2010. Ce nouveau Comité axera ses efforts sur le fait de rendre opérationnelles les décisions du SAGE et sera informé par les Régions et les pays des problèmes opérationnels qu’ils rencontrent afin de les étudier et de donner un avis.

Le rapport de la réunion d’octobre 2010 du Comité consultatif sur la Vaccination quantitative et la Recherche liée aux Vaccins (QUIVER) a été présenté au SAGE. Les différentes approches adoptées pour estimer la mortalité de l’enfant doivent être harmonisées, de même que les méthodes permettant d’expliquer les incertitudes et différences observées. Des progrès ont été accomplis pour fournir aux différents groupes de modélisation des séries de données communes afin d’évaluer les différences entre modèles et de repartir les principaux facteurs à l’origine de ces différences, de façon à renforcer la transparence des modèles.

Le SAGE a pris note de la nécessité d’obtenir des données de terrain récentes sur l’incidence et le taux de letalité par âge, en particulier dans les pays à revenu faible ou intermédiaire.

**Grippe saisonnière et grippe pandémique**

Le SAGE a été informé des derniers éléments relatifs au déploiement du vaccin contre la grippe pandémique A (H1N1) 2009 et à la pharmacovigilance. L’examen continu des données mondiales mené par le GACVS a permis de constater que ce vaccin avait un excellent profil d’innocuité. Les résultats d’étude ont mis en évidence sa grande efficacité et une bonne correspondance entre l’antigène vaccinal et le virus pandémique (H1N1) 2009 circulant. Des promesses de dons de vaccin ont été rapidement faites à l’OMS, mais il y a eu des retards entre la promesse et sa mise en œuvre effective. De plus, des retards ont été constatés entre les engagements pris et le déploiement des vaccins en raison de la non-disponibilité de ces derniers, de la nécessité d’avoir des lettres d’intention et d’accord, ainsi qu’un plan de déploiement du vaccin. L’OMS a mobilisé 78 millions de doses de ce vaccin, dont la plupart ont été distribuées dans les Régions africaine, de l’Asie du Sud-Est et de la Méditerranée orientale. Elle examine actuellement les moyens permettant de raccourcir les délais afin

---


SAGE requested that WHO report on the utilization of deployed vaccine, including by risk group, once data collection has been completed. SAGE also noted the variability of influenza seasons in different regions and the challenges this poses to prioritizing the distribution of vaccines.

SAGE expressed support for the review of lessons learnt from pandemic (H1N1) 2009 vaccination activities that WHO is undertaking, and encouraged WHO to carefully consider factors that caused delays and ways to improve coordination among WHO, its Regions, and Member States. SAGE commended WHO on the rapid prequalification of pandemic (H1N1) 2009 vaccines.

The SAGE working group on H5N1 vaccines reported on a review of 2 previous SAGE recommendations made regarding (i) the vaccination of people who may have contact with infected animals during the interpandemic period and (ii) the purpose and size of the H5N1 vaccine stockpile. SAGE found insufficient new evidence on disease risk to warrant making any change to the original recommendations about target groups, including the recommendation that licensed H5N1 vaccine may be made available to persons in potential contact with highly pathogenic avian influenza. However, SAGE noted additional evidence of a good safety profile, and should data demonstrate a higher risk to subpopulations, the recommendation may be revisited.

SAGE further recommended that vaccine pledges for the WHO pandemic (H1N1) 2009 vaccine stockpile should be used to allow low-income and middle-income countries to immunize essential personnel at the onset of a pandemic. SAGE expressed a need for more information about the shelf-life and other characteristics of pandemic influenza vaccines before making additional recommendations about options for the constitution of the stockpile. These issues and other questions about pandemic influenza vaccines will be addressed by SAGE’s working group on influenza vaccines and immunization.

SAGE received a report from its working group on influenza vaccines and immunization, which is tasked with: preparing an evidence-based review of WHO’s recommendations on the use of seasonal influenza vaccine, with a particular focus on low-income and middle-income countries; identifying essential evidence gaps that would hinder the updating of recommendations on the use of influenza vaccines; recommending coverage goals for seasonal influenza vaccination; and providing advice about pandemic vaccine preparedness. At its first meeting in October the many challenges facing influenza-vaccine programmes and policy development were identified, particularly the sparse data on the burden of disease in many countries, which makes cost-effectiveness analyses and priority-setting difficult. Other challenges include the scale of influenza-vaccine programmes and manufacturing capacity, limitations of global surveillance and laboratory capacity, the difficulty of prioritizing target groups and the variability of

de garantir une mise à disposition rapide des vaccins. Onze vaccins ont été préselectionnés rapidement grâce aux procédures accélérées qui prévoyaient d’obtenir l’assistance des autorités de réglementation dans un certain nombre de pays et de recruter du personnel supplémentaire de façon que la préselection d’autres produits ne soit pas retardée.

Le SAGE a demandé que l’OMS rende compte de l’utilisation des vaccins ainsi déployés, notamment par groupe à risque, une fois la collecte des données achevée. Il a également pris note de la variabilité des saisons grippales dans les différentes Régions et des difficultés que cela entraîne pour établir les priorités en matière de distribution des vaccins.

Il a exprimé son appui à l’examen des enseignements tirés des activités de vaccination contre la grippe pandémique A (H1N1) 2009 entrepris par l’OMS et a encouragé cette dernière à étudier soigneusement les facteurs ayant engendré des retards et les moyens permettant d’améliorer la coordination entre l’OMS, ses Régions et ses États Membres. Le SAGE a félicité l’OMS pour la préélection rapide des vaccins contre la grippe pandémique A (H1N1) 2009.

Le groupe de travail du SAGE sur les vaccins H5N1 a fait état d’un examen de 2 recommandations faites précédemment par le SAGE concernant i) la vaccination des personnes qui ont pu être en contact avec des animaux infectés au cours de la période interpandémique et ii) le but poursuivi par le fait de constituer un stock de vaccins anti-H5N1 et la taille de ce dernier. Le SAGE n’a pas trouvé suffisamment de nouveaux éléments sur le risque de maladie pour justifier d’apporter un changement quelconque aux recommandations originelles concernant les groupes cibles, notamment celle selon laquelle les vaccins anti-H5N1 homologués pourraient être mis à la disposition des personnes potentiellement en contact avec la grippe aviaire hautement pathogène. Toutefois, le SAGE a pris note des données supplémentaires en faveur d’un bon profil d’innocuité du vaccin et a indiqué qu’au cas où des données mettraient en évidence un risque plus élevé pour certaines sous-populations, cette recommandation pourrait être réexaminée.

Le SAGE a recommandé en outre que les promesses de vaccins en vue de constituer un stock contre la grippe pandémique A (H1N1) 2009 devraient servir à vacciner le personnel essentiel des pays à revenu faible ou intermédiaire dès le début d’une pandémie. Il a exprimé le besoin d’obtenir davantage d’informations sur la durée d’utilisation et les autres caractéristiques des vaccins contre la grippe pandémique avant de formuler des recommandations supplémentaires concernant la constitution de ce stock. Le groupe de travail du SAGE sur les vaccins et la vaccination contre la grippe traitera de ces questions et d’autres relatives aux vaccins antigrippaux.

Le SAGE a reçu un rapport de son groupe de travail sur les vaccins et la vaccination contre la grippe, qui s’efforce de préparer un examen des recommandations de l’OMS relatives à l’utilisation du vaccin contre la grippe saisonnière reposant sur les bases factuelles, en s’intéressant plus particulièrement aux pays à revenu faible ou intermédiaire; de recenser les principales lacunes dans les données qui empêcheraient la mise à jour des recommandations relatives à l’utilisation des vaccins antigrippaux; de recommander des objectifs de couverture pour la vaccination contre la grippe saisonnière; et de formuler un avis sur le volet vaccin de la préparation à une pandémie. Lors de sa première réunion en octobre, les nombreuses difficultés auxquelles sont confrontés les programmes et l’élaboration des politiques de vaccination antigrippale ont été répertoriées, en particulier la rareté des données relatives à la charge de morbidité de la grippe dans de nombreux pays, qui rend difficiles les analyses de coût/efficacité et l’établissement des priorités. Parmi les autres difficultés, on peut citer l’étendue des programmes de vaccination antigrippale et la capacité de fabrication des
transmission in different regions and settings. SAGE supported the conceptual matrix proposed by the working group that focuses on key issues (disease burden, vaccine performance and cost-effectiveness, and operational issues) and target populations (children, elderly people, pregnant women and other high-risk groups). Health-care workers' resistance to receiving influenza vaccine was highlighted as an important area for consideration. SAGE recommended that the working group develop a research agenda.

**Polio eradication**

SAGE received an update on the Global Polio Eradication Initiative's strategic plan for 2010–2012, the United States Centers for Disease Control and Prevention's most recent quarterly risk assessment on polio surveillance and SIAs, and a report from SAGE's working group on inactivated poliovirus vaccine (IPV).

SAGE concluded that considerable progress had been made towards eradicating polio since its last meeting, noting that 14/15 outbreaks with onset in 2009 appeared to have stopped, 2/4 countries where transmission had been re-established had not reported cases for >6 months (Chad, southern Sudan), and 2/4 polio-endemic countries had had a >90% year-on-year decline in cases (India, Nigeria).

However, SAGE noted with deep concern that some countries had either missed their relevant milestone in the new plan or were at very high risk for doing so. Most notably, the outbreak in Kenya and Uganda in 2009 appears to have continued beyond mid-2010; Angola and the Democratic Republic of Congo where transmission has been re-established are unlikely to stop polio transmission by the end of 2010; and Pakistan was the only endemic country that had failed to reduce the number of cases compared with the same period in 2009. SAGE was also concerned by the large outbreak that had occurred in Central Asia during the first half of 2010 as well as the evolving outbreak in the Republic of Congo. These events highlight the importance of strengthening capacities for surveillance and response in areas where there has been recent transmission and in areas where the risk of importation is highest.

SAGE emphasized the importance of strengthening surveillance in critical areas at the subnational level to facilitate the early detection of and effective response to importations of wild poliovirus.

SAGE strongly supported the role of the Independent Monitoring Board established in October 2010 to monitor the progress of the strategic plan, but noted that its most critical contribution will be to suggest urgent plans for corrective action in close coordination with ministries of health and country-level and regional-level technical advisory groups. Noting this role, SAGE strongly recommended that the Independent Monitoring Board should meet as soon as possible. SAGE noted that corrective action plans should strengthen both the implementation of the polio eradication strategy as well as routine immunization services.

SAGE identified the US$ 810 million financing gap through the end of 2012 as one of the greatest risks for vaccines, the limits of the surveillance mondiale et de la capacité de laboratoire, la difficulté à établir des priorités parmi les groupes cibles et la variabilité de la transmission dans les différents contextes et Régions. Le SAGE a soutenu la matrice conceptuelle proposée par le groupe de travail qui est axée sur les questions essentielles (charge de morbidité, efficacité et coût/efficacité du vaccin, et problèmes opérationnels) et les populations cibles (enfants, personnes âgées, femmes enceintes et autres groupes à haut risque). Le refus du personnel de soins de santé de se faire vacciner contre la grippe est apparu comme une question importante à examiner. Le SAGE a recommandé que le groupe de travail élabore un agenda de recherche.

**Éradication de la poliomyélite**


Il a conclu que des progrès considérables avaient été accomplis en vue de l’éradication de la poliomyélite depuis sa dernière réunion, constatant que 14 flambées sur les 15 s’étant déclarées en 2009 semblaient avoir été interrompues, que 2 pays sur les 4 dans lesquels la transmission avait été rétablie n’avaient pas rapporté de cas depuis >6 mois (Tchad, Sud-Soudan) et que 2 pays d’endémie de la poliomyélite sur 4 avaient enregistré une diminution de >90% des cas d’une année sur l’autre (Inde, Nigéria).

Cependant, le SAGE a noté avec une profonde inquiétude que certains pays n’avaient pas atteint les étapes importantes du nouveau plan ou risquaient fortement de les manquer. Sont à noter particulièrement les éléments suivants: la flambée survenue au Kenya et en Ouganda en 2009 semble s’être poursuivie au-delà du premier semestre 2010; l’Angola et la République démocratique du Congo où la transmission a été rétablie ont peu de chances d’interrompre d’ici la fin 2010; enfin, le Pakistan est le seul pays d’endémie qui n’a pas réussi à réduire le nombre de cas par rapport à la même période en 2009. Le SAGE s’est également inquiété de la grande flambée survenue en Asie centrale au cours du premier semestre 2010, ainsi que de la flambée en cours en République du Congo. Ces événements soulignent l’importance qu’il y a à renforcer les moyens de surveillance et de riposte dans les zones où il y a eu une transmission récente et dans celles où le risque d’importation est le plus élevé.

Le SAGE a souligné l’importance d’un renforcement de la surveillance dans les zones critiques au niveau infranational afin de faciliter la détection précoces des cas et la riposte efficace en cas d’importation de poliovirus sauvage.

Le SAGE a fermement soutenu le rôle joué par le Conseil de surveillance indépendant créé en octobre 2010 afin de suivre la progression du plan stratégique, mais a constaté que la contribution la plus essentielle de ce dernier sera de proposer des plans d’urgence pour des mesures correctives en coordination étroite avec les ministères de la santé et avec les groupes consultatifs techniques des pays et des Régions. Prenant acte de ce rôle, le SAGE recommande vivement que le Conseil de surveillance indépendant de la mise en œuvre se réunisse dès que possible. Il constate également que ces plans d’action révisés devraient profiter aussi bien à la mise en œuvre de la Stratégie d’éradication de la poliomyélite qu’aux services de vaccination systématique.

Le SAGE a déterminé que l’un des plus grands risques menaçant le succès de l’Initiative mondiale d’éradication de la poliomyélite...
the success of the Global Polio Eradication Initiative and noted that the lack of sustainable financing threatens established and promised gains in the field of immunization overall.

SAGE noted that the first remit of the IPV working group had been completed with the publication of the WHO position paper on the routine use of OPV and IPV. Although it had been anticipated that the working group’s second aim – making recommendations on post-eradication policies for IPV – would be presented to SAGE in April 2011, SAGE decided to extend this timeline by 12 months. This extension will allow the working group to benefit from considering additional data expected from field trials of IPV efficacy in Cuba and India that will become available in 2011, a planned state-of-the-art meeting on vaccine-derived polioviruses, further mathematical modelling of post-eradication risks, and continuing IPV development projects.

SAGE expanded the working group’s remit by requesting it to assess whether, in view of the apparent eradication of type-2 wild poliovirus and the preponderance of circulating type-2 vaccine-derived polioviruses in recent years, trivalent OPV should be replaced with bivalent OPV for routine vaccination. SAGE requested that the working group report on this by November 2011.

Feasibility of measles eradication

SAGE reviewed the report and recommendations from the July 2010 Global Technical Consultation to Assess the Feasibility of Measles Eradication. Measles has been eliminated in the Region of the Americas since 2002, and 4 of the remaining 5 Regions have established a target date for the elimination of measles: it is to be eliminated in the Eastern Mediterranean Region by 2010, in the Western Pacific Region by 2012, in the European Region by 2015 and in the African Region by 2020. In 2009, the Regional Committee for South-East Asia passed a resolution urging Member States to move towards eliminating measles. In May 2010, the WHA endorsed the following measles control targets for 2015 as milestones towards measles eradication: increasing measles immunization coverage to >90% nationally and >80% in every district; reporting an incidence of <5 cases/1 000 000 population; and reducing measles mortality by 95% compared with 2000 levels.

Remarkable progress has made been in reducing deaths from measles worldwide. From 2000 to 2008, an estimated 4.3 million additional deaths among children were averted as a result of increases in coverage of routine immunizations and implementation of measles SIAs. However, since 2009, the African Region has experienced outbreaks affecting 28 countries, and there have been >200 000 reported cases. These outbreaks highlight the fragility of the gains. There is a growing risk that the critical contribution of the reduction in measles mortality to achieving Millennium Development Goal 4 (approximately 25% of the overall reduction in child mortality) will be lost because of declining political and financial commitments to measles control and the competition for resources from other immunization and public-health initiatives.

SAGE noted the results of recent studies showing the overall positive impact that activities to eliminate mea-

Faisabilité de l’éradication de la rougeole


Des progrès remarquables ont été réalisés pour réduire les décès par rougeole partout dans le monde. Entre 2000 et 2008, selon les estimations, 4,3 millions de décès supplémentaires ont été évités chez les enfants par suite de l’augmentation de la couverture des vaccinations systématiques et de la mise en œuvre d’AVS antirougeoleuses. Toutefois, depuis 2009, des flambées ont sévi dans 28 pays de la Région africaine et plus de 200 000 cas ont été notifiés. Ces flambées soulignent la fragilité des succès remportés. Il existe un risque grandissant que soient réduits à néant tous les efforts consentis pour réduire la mortalité par rougeole afin d’atteindre l’objectif 4 du Millénaire pour le développement (environ 25% de réduction en tout en ce qui concerne la mortalité chez les enfants), du fait de la diminution des engagements politiques et financiers en faveur de la lutte antirougeoleuse et de la compétition existant avec d’autres initiatives de vaccination et de santé publique pour la répartition des ressources.

Le SAGE a pris note des résultats des études récentes montrant, d’une part, les efforts généraux positifs que les activités visant
les have on immunization systems, and the predictions from 2 independent modelling groups that measles eradication would be highly cost effective across all countries’ income groups as well as cost-saving and life-saving in countries that have already eliminated measles. Considering these findings and the comprehensive review of evidence establishing the biological and technical feasibility of measles eradication, SAGE concluded that measles can and should be eradicated. A goal for measles eradication should be established with a proposed target date based on measurable progress made towards existing goals and targets. The eradication of measles represents unique disease control and developmental opportunities, and 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 noted the substantial challenges to achieving the 2015 global targets and regional goals for elimination, including: weak immunization systems; the highly infectious nature of measles; populations that are inaccessible due to conflict; the increasing refusal of immunization by some populations; the changing epidemiology of measles which has led to increased transmission among adolescents and adults; the need to provide catch-up measles vaccination to >130 million children in India; and the gaps in human and financial resources at the country, regional and global levels. In addition, there is an urgent need for operational research to address the barriers to achieving current targets and confirm the operational feasibility of eradication in the most challenging settings.

Recognizing these challenges, SAGE strongly encouraged countries and the global community to enhance their efforts to fully implement and accelerate the expansion of proven strategies for measles immunization and surveillance. In addition, SAGE welcomed the news that India has begun implementing eradication and provide a second opportunity for measles immunization. SAGE also encouraged the South- East Asia Region to establish a target date for achieving measles elimination. SAGE requested that progress towards meeting the 2015 global targets and regional elimination goals be monitored. SAGE proposed that the demonstration of sufficient achievements towards measles elimination be made as a basis for establishing a target date for measles eradication, and requested frequent updates on the progress.

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.

SAGE noted the real threat of losing momentum in the fight against measles and recommended enhancing advocacy efforts to highlight the importance of measles control to achieving overall child-health goals; these efforts should emphasize that further reduction in measles mortality and measles eradication rank among the “best buys” in public health. A greater commitment of à éliminer la rougeole ont sur les systèmes de vaccination et, de l’autre, les prévisions de 2 groupes de modélisation indépendants indiquant que l’éradication de cette maladie aurait un très bon coût/efficacité dans tous les groupes de revenus des pays et permettrait de sauver des vies et des dépenses dans les pays qui ont déjà éliminé la rougeole. Au vu de ces résultats et de l’examen complet des données établissant la faisabilité biologique et technique de l’éradication de la rougeole, le SAGE a conclu qu’il pouvait et devait être éradiquée. Il convient d’établir un objectif d’éradication de la rougeole avec une date butoir proposée sur la base des progrès mesurables accomplis en vue de ces objectifs. L’éradication de la rougeole représente une occasion sans précédent de lutter contre la maladie et d’accélérer le développement et doit être menée dans le contexte d’un renforcement des programmes de vaccination systématique. En outre, l’efficacité de l’utilisation des vaccins associés antirougeoleux-antirubéoleux et de la surveillance intégrée de la fièvre et des éruptions cutanées offre la possibilité pour les activités d’éradication de la rougeole d’accélérer la lutte contre la rougeole et la prévention du syndrome rubéole congénitale.

Le SAGE a pris note des difficultés importantes auxquelles on va se heurer pour atteindre les cibles mondiales et objectifs régionaux d’élimination de 2015, notamment de la faiblesse des systèmes de vaccination; de la nature hautement infectieuse de la rougeole; des populations inaccessibles en raison de conflits; du refus croissant de la vaccination de certaines populations; de l’évolution de l’épidémiologie de la rougeole qui a conduit à une transmission accrue parmi les adolescents et les adultes; de la nécessité de fournir une vaccination antirougeoleuse de rattrapage à plus de 130 millions d’enfants en Inde; et des déficiences en ressources humaines et financières aux niveaux national, régional et mondial. En outre, il est urgent de mener des recherches opérationnelles pour venir à bout des obstacles empêchant d’atteindre les cibles actuelles et confirmer la faisabilité opérationnelle de l’éradication dans les situations les plus difficiles.

Reconnaissant toutes ces difficultés, le SAGE a vivement encouragé les pays et la communauté mondiale à renforcer leurs efforts pour mettre en œuvre pleinement et accélérer l’extension des stratégies avérées de vaccination et de surveillance de la rougeole. En outre, il a accentué avec satisfaction les nouveaux résultats indiquant que l’Inde avait commencé à mettre en œuvre des stratégies pour fournir une deuxième possibilité de vaccination antirougeoleuse. Il a également encouragé la Région de l’Asie du Sud-Est à fixer une date butoir pour parvenir à l’élimination de la rougeole. Il a demandé que les progrès accomplis en vue d’atteindre les cibles mondiales et les objectifs régionaux d’élimination fixés pour 2015 soient suivis. Il a proposé de faire la preuve de suffisamment de réalisations en vue de l’élimination de la rougeole avant de fixer une date butoir pour l’éradication de cette maladie et a demandé à être fréquemment tenu au courant des progrès accomplis.

Le SAGE a demandé que les groupes de travail sur la rougeole et la rubéole soient fusionnés et suivent les progrès accomplis, supervisent le programme de recherche nécessaire pour l’éradication et rendent compte régulièrement au SAGE. Ce groupe de travail doit être en relation avec le QUIVER et le Comité consultatif sur les pratiques vaccinales (IPAC) afin de faire face aux problèmes quantitatifs qui se posent ainsi qu’à ceux liés aux pratiques vaccinales.

Le SAGE a pris note de la menace réelle qui existe de perdre l’élan de la lutte antirougeoleuse et a recommandé de renforcer les efforts de sensibilisation afin de souligner l’importance de la lutte antirougeoleuse pour atteindre les objectifs généraux en matière de santé de l’enfant; ces efforts doivent insister sur le fait qu’une baisse de la mortalité rougeoleuse et l’éradication de cette maladie offrent le meilleur rapport qualité-prix qui soit
resources needs to be made by high-burden countries and their local and international partners to counter the threat of resurgence and achieve existing global and regional goals. The initiation of the Decade of Vaccines represents a unique opportunity for prioritizing the expansion of resources to support countries’ efforts towards achieving the 2015 global measles control targets and regional elimination goals.

**Typhoid vaccines: feedback on regional implementation of SAGE recommendations**

Most developed countries recommend typhoid vaccine to travellers visiting high-risk areas. Despite resource limitations, several areas where the disease is endemic have initiated typhoid vaccination programmes, including (i) Delhi state in India, where children aged 2–5 years were successfully vaccinated; (ii) Fiji, which initiated a mass campaign targeting 70 000 children and adults in high-risk areas and has plans to introduce a routine school-based programme in 2011; and (iii) Sri Lanka, which is restarting its programme to vaccinate high-risk groups. Although many countries have expressed interest in introducing typhoid vaccines, progress on the use of these vaccines has been slow due to a lack of local surveillance of the burden of disease, commitment of resources to support countries introducing the vaccines, a simple and affordable diagnostic tool, and prequalified vaccines.

SAGE was briefed on 2 new initiatives: (i) The Typhoid Surveillance in Sub-Saharan Africa Project, managed by the International Vaccine Institute, has been established to help generate standardized data on enteric fever-related illnesses and deaths in sub-Saharan Africa; data will be collected through a network of sentinel surveillance sites. (ii) The establishment of the Coalition Against Typhoid, overseen by the Sabin Vaccine Institute, is a broad coalition of parties working to expedite evidence-based decisions on typhoid vaccination.

SAGE reiterated the importance of its 2007 recommendations and expressed concern over the slow progress of vaccine introduction, emphasizing that it need not wait for detailed local surveillance. SAGE called on partners to support the improvement of surveillance systems and the development of appropriate and affordable tools to diagnose typhoid. SAGE stressed the importance of timely WHO prequalification of typhoid vaccines to improve access by developing countries to these vaccines.

Recognizing that typhoid and cholera are prevalent in similar conditions and populations, SAGE highlighted opportunities to link prevention and control efforts for these diseases, which will complement broader goals of improving living conditions, sanitation and access to safe water. Synergies with the delivery of other vaccines for enteric diseases should be identified. Although paratyphoid disease does not have the same high mortality rate as typhoid, it is often mistaken for typhoid; thus, if this problem is not addressed the population in countries using typhoid vaccine may conclude that the vaccine is not effective. The Decade of Vaccines provides an opportunity to make further improvements to typhoid vaccines.

**Vaccins antityphoidiques: rétro-information sur la mise en œuvre régionale des recommandations du SAGE**

La plupart des pays développés recommandent la vaccination antityphoïdique aux voyageurs se rendant dans des zones à haut risque. Malgré la restriction des ressources, plusieurs zones dans lesquelles cette maladie est endémique ont lancé des programmes de vaccination antityphoïdique, notamment: i) l’État de Delhi en Inde, où les enfants âgés de 2 à 5 ans ont été vaccinés avec succès; ii) Fidji, qui a lancé une campagne de masse ciblant 70 000 enfants et adultes dans les zones à haut risque et prévoit d’introduire un programme de vaccination systématique en milieu scolaire en 2011; et iii) le Sri Lanka qui a redémarré son programme de vaccination des groupes à haut risque. Bien que de nombreux pays aient fait part de leur intérêt pour l’introduction des vaccins antityphoïdiques, les progrès enregistrés en matière d’utilisation de ces vaccins ont été lents en raison de l’absence de différentes composantes: surveillance locale de la charge de morbidité de cette maladie, mobilisation des ressources pour soutenir les pays introduisant ces vaccins, outil diagnostique simple et d’un coût abordable, et vaccins présélectionnés.

Le SAGE a été informé de 2 nouvelles initiatives. La première, le Projet de surveillance de la typhoïde en Afrique subsaharienne, dirigée par l’International Vaccine Institute a été créée pour permettre d’obtenir des données standardisées sur les maladies et les décès liés aux fièvres entériques en Afrique subsaharienne; les données seront recueillies à travers un réseau de sites sentinelles de surveillance. La deuxième initiative, à savoir la création de la Coalition contre la typhoïde, supervisée par le Sabin Vaccine Institute est une vaste coalition de parties prenantes s’efforçant d’accélérer les décisions relatives à la vaccination antityphoïdique reposant sur des bases factuelles.

Le SAGE a réaffirmé l’importance de ses recommandations de 2007 et fait part de ses préoccupations concernant la lenteur de l’introduction du vaccin, soulignant qu’il n’était pas nécessaire d’attendre les résultats d’une surveillance locale détaillée pour l’introduire. Il a demandé aux partenaires de soutenir l’amélioration des systèmes de surveillance et la mise au point d’outils appropriés et d’un coût abordable pour le diagnostic de la typhoïde. Le SAGE a souligné l’importance d’une présélection en temps utile des vaccins antityphoïdiques par l’OMS pour améliorer l’accès des pays en développement à ces vaccins.

Reconnaissant que la typhoïde et le choléra sont des maladies que l’on rencontre fréquemment dans les mêmes populations et dans des conditions similaires, le SAGE a souligné la possibilité de relier les efforts de prévention et de lutte contre ces maladies, qui viendraient compléter ceux déployés en vue des objectifs plus généraux d’amélioration des conditions de vie, de l’assainissement et de l’accès à l’eau potable. Il faudra déterminer les synergies à mettre en œuvre pour l’administration d’autres vaccins contre les maladies entériques. Bien que la paratyphoïde n’ait pas le taux de mortalité élevé de la typhoïde, on la confond souvent avec cette dernière; ainsi, si l’on ne résout pas ce problème, la population des pays utilisant le vaccin antityphoïdique risque d’en conclure qu’il n’est pas effi-

---

9 See No. 1, 2008, pp. 1–16.

10 Voir N° 1, 2008, pp. 1-16.
phoid vaccines, including developing a combined typhoid and paratyphoid vaccine, and improving diagnostic tools.

**Optimizing immunization schedules**

SAGE received an update on the Optimizing Immunization Schedules project, which aims to develop a standard tool to review evidence supporting immunization schedules and their appropriateness in different epidemiological settings. The project entails: (i) reviewing local epidemiological data; (ii) conducting systematic reviews of the effectiveness of different vaccination schedules; (iii) modelling the impact and cost-effectiveness of immunization schedules in different epidemiological scenarios; and (iv) conducting evidence-based assessments of the trade-offs made by selecting a particular schedule in the context of local operational and health-system realities. It has been proposed that the project’s outcomes be shared with country-level and regional policy-makers using the Internet. The example of pneumococcal conjugate vaccines was used to illustrate the proposed process for optimizing immunization schedules at country level.

SAGE recognized that optimizing schedules for new vaccines could reduce cost and streamline their integration with other vaccines, and that the proposed approach had the potential to inform schedule optimization. There may also be value in reviewing traditional vaccine schedules. SAGE acknowledged that several countries are introducing vaccines using schedules that differ from WHO recommendations. While SAGE concluded that models were a legitimate tool for assessing various schedules in different epidemiological contexts and identifying research questions, it was noted that caution should be exercised in weighing the relevance of estimates from modelling against evidence from trials and observational studies and should take account of existing regulatory guidance.

SAGE supported the use of various epidemiological scenarios for evaluating well characterized schedules relevant to multiple countries. SAGE requested that the models reflect operational realities – for example, delays in vaccine administration – and noted that gains from alternative schedules should be substantial and justified by strong evidence before a new schedule is introduced.

SAGE agreed that information-sharing is critical and that a web site might facilitate this but urged that it be designed to ensure its relevance to country-level policy-makers by providing the key programmatic implications of the schedules being evaluated along with clear evidence-based guidance. In addition, SAGE recommended that WHO provide support to country-level policy-makers on the rational use of analyses generated by the tool.

SAGE encouraged WHO to complete the project promptly, noting that a small investment could lead to major public-health gains by achieving the most efficient use of vaccines in different epidemiological contexts. SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.

La Décennie des vaccins offre une occasion d’améliorer encore les vaccins antityphoïdiens, notamment de mettre au point un vaccin associé antityphoïdique-antiparatyphoïdique, et d’améliorer les outils diagnostiques.

**Optimisation des calendriers vaccinaux**

Le SAGE a établi un cadre au cours du projet d’optimisation des calendriers vaccinaux, qui vise à élaborer un instrument standard permettant d’analyser les données établissant les calendriers vaccinaux et la pertinence de ces derniers dans les différentes situations épidémio-logiques. Ce projet suppose: i) d’examiner les données épidémiologiques locales; ii) d’effectuer des examens systématiques de l’efficacité des différents calendriers vaccinaux; iii) de modéliser les effets et le coût/efficacité des calendriers vaccinaux dans différents scénarios épidémiologiques; et iv) d’effectuer des évaluations reposant sur des bases factuelles des arbitrages effectués en choisissant un calendrier particulier dans le contexte des réalités opérationnelles et sanitaires locales. Il a été proposé de partager les résultats du projet avec les responsables de l’élaboration des politiques nationales et régionales au moyen de l’Internet. On s’est servi de l’exemple des vaccins antipneumococciques conjugués pour illustrer le processus proposé d’optimisation des calendriers vaccinaux dans les pays.

Le SAGE a reconnu que l’optimisation des calendriers pour les nouveaux vaccins permettrait de réduire les coûts et de rationaliser leur intégration avec d’autres vaccins et que l’approche proposée pouvait inspirer une telle optimisation. Il serait peut-être également intéressant d’examiner les calendriers des vaccins traditionnels. Le SAGE a reconnu que plusieurs pays introduisaient des vaccins avec des calendriers d’administration différents de ceux recommandés par l’OMS. Si le SAGE s’accorde à penser que les modèles sont un instrument légitime pour évaluer divers calendriers dans divers contextes épidémiologiques et recenser les questions posées à la recherche, il a noté que la prudence était de rigueur lorsqu’il s’agit d’évaluer la pertinence des estimations des modèles au regard des données des essais et des études d’observation et qu’il faut tenir compte des avis de la réglementation existante.

Le SAGE a appuyé le recours à divers scénarios épidémiologiques pour évaluer les calendriers bien caractérisés s’appliquant à de nombreux pays. Il a demandé que les modèles reflètent les réalités opérationnelles – par exemple les retards dans l’administration des vaccins – et a noté que les avantages présentés par des calendriers alternatifs devaient être importants et justifiés par des données solides avant de songer à les introduire.

Le SAGE a convenu que le partage de l’information était essentiel et qu’un site Web pourrait faciliter un tel échange, mais a instamment demandé qu’on le conçoive de façon à garantir sa pertinence pour les responsables de l’élaboration des politiques dans les pays, en indiquant les principales conséquences programmatiques des calendriers évalués et en les accompagnant de recommandations claires reposant sur des bases factuelles. En outre, il a recommandé que l’OMS apporte un soutien aux responsables de l’élaboration des politiques dans les pays s’agissant de l’usage rationnel des analyses générées par cet outil.

Le SAGE a encouragé l’OMS à mener rapidement ce projet à bien notant qu’un petit investissement pourrait conduire à des gains importants pour la santé publique, faisant le meilleur usage possible des vaccins dans les différents contextes épidémiologiques. Le SAGE a demandé une évaluation critique d’autres calendriers d’administration du vaccin antipneumococcique conjugué, du vaccin antirotavirus et du vaccin anti-Hib en 2011.
Lower-middle-income countries: sustainable adoption and financing for new vaccines

In April 2008, SAGE requested further investigation into the financial challenges facing lower-middle-income countries in order to identify actionable activities for countries and their partners. In the same year, the WHA requested that WHO collaborate with partners, donors and vaccine producers to mobilize resources to support low-income and middle-income countries to increase the supply of affordable, quality vaccines.

WHO and its partners have thus developed a plan of action for introducing new vaccines that considers the context and needs of lower-middle-income countries. With the support of the Bill & Melinda Gates Foundation, WHO initiated a study of the adoption of new vaccines by lower-middle-income countries not eligible for support from the GAVI Alliance, or that were graduating from the Alliance’s support; the study sought to understand constraints on countries’ adoption of new vaccines and recommend solutions. The study by the Results for Development Institute analysed quantitative and qualitative data collected from 15 countries, information from interviews with experts on global immunization programmes and interviews with vaccine manufacturers.

Costs, budgets and price-related issues were of high importance to lower-middle-income countries. Decision-makers in these countries assume that they have to pay for vaccines without external support and they are therefore concerned about getting value for money. While these countries valued local epidemiological evidence, they invested little in gathering high-quality data. There is limited intercountry collaboration on epidemiological studies. Lower-middle-income countries lack the robust information needed to facilitate vaccine procurement, especially information about prices, the availability of vaccines, procurement options and market dynamics. The decision on whether to adopt new vaccines is made at senior political levels and is not always evidence-based. These countries have established or emerging national immunization technical advisory groups that have growing importance in decision-making. Many lower-to-middle-income countries graduating from support from the GAVI Alliance are uncertain about sustaining financing. These diverse challenges demand individualized approaches. Recommendations have been formulated at global, regional and national levels, and priorities have been identified.10

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 supported the high-priority study’s recommendations, many of which have utility beyond lower-middle-income countries.

SAGE noted that price continues to be a major barrier preventing the introduction of new vaccines in these countries. SAGE emphasized the need for advocacy at national, regional and global levels to support equitable access to new vaccines.

SAGE endorsed the WHO activities in gathering epidemiological and vaccine-related data at regional and country levels, and encouraged WHO to assist countries

---


---

Pays à revenu intermédiaire de la tranche inférieure: adoption et financement durable des nouveaux vaccins

En avril 2008, le SAGE a demandé une étude approfondie des difficultés financières rencontrées par les pays à revenu faible ou intermédiaire, de façon à déterminer quelles étaient les activités à engager par les pays et leurs partenaires. Cette même année, l’Assemblée mondiale de la Santé a demandé que l’OMS collabore avec les partenaires, donateurs et producteurs de vaccins afin de mobiliser des ressources pour permettre aux pays à revenu faible ou intermédiaire d’augmenter leur approvisionnement en vaccins de qualité et d’un prix abordable.

L’OMS et ses partenaires ont ainsi élaboré un plan d’action pour l’introduction de nouveaux vaccins, qui prend en compte le contexte et les besoins des pays à revenu intermédiaire de la tranche inférieure. Avec l’aide de la Fondation Bill & Melinda Gates, elle a engagé une étude sur l’adoption des nouveaux vaccins par les pays à revenu intermédiaire de la tranche inférieure, qui ne remplissent pas les conditions voulues pour bénéficier du soutien de l’Alliance GAVI ou qui n’en bénéficient plus; l’étude a cherché à comprendre les problèmes que rencontrent les pays pour adopter de nouveaux vaccins et à recommander des solutions. Par ailleurs, pour son étude, le Results for Development Institute a analysé les données quantitatives et qualitatives recueillies dans 15 pays, ainsi que les informations tirées d’entretiens avec des experts des programmes mondiaux de vaccination et avec des fabricants de vaccin.

Les questions de coût, de budget et de prix revêtent une importance élevée pour les pays à revenu intermédiaire de la tranche inférieure. Dans ces pays, les décideurs partent du principe qu’ils doivent acheter des vaccins sans aucun soutien extérieur et veulent donc un bon rapport qualité/prix. Si ces pays ont accordé de l’importance aux données épidémiologiques locales, ils ont peu investi dans le fait de collecter des données de qualité. La collaboration interpays est limitée en matière d’études épidémiologiques. Les pays à revenu intermédiaire de la tranche inférieure manquent des informations solides nécessaires pour faciliter l’achat des vaccins, surtout s’agissant des prix, de la disponibilité des vaccins, des possibilités d’achat et de la dynamique du marché. La décision d’adopter ou non les nouveaux vaccins est prise par des instances politiques supérieures et ne repose pas toujours sur des bases factuelles. Ces pays ont déjà ou sont en train de mettre en place des groupes consultatifs techniques nationaux sur la vaccination qui ont une importance croissante dans la prise de décision. Bon nombre des pays à revenu intermédiaire de la tranche inférieure qui ne peuvent plus bénéficier du soutien de l’Alliance GAVI ne savent pas très bien s’ils vont pouvoir financer durablement les vaccins. Ces divers problèmes demandent des stratégies individualisées. Des recommandations ont été formulées à l’échelle mondiale, régionale et nationale, et des priorités ont été désagéées.

Notant le grand nombre de ménages pauvres dans les pays à revenu intermédiaire de la tranche inférieure et la nécessité pour ceux-ci d’avoir un accès équitable à des vaccins peu coûteux, le SAGE a soutenu les recommandations hautement prioritaires de l’étude, dont beaucoup sont applicables à d’autres pays que ceux à revenu faible ou intermédiaire.

Le SAGE a constaté que les prix continuent d’être un obstacle majeur à l’introduction de nouveaux vaccins dans ces pays. Il a souligné la nécessité d’une sensibilisation accrue aux niveaux national, régional et mondial en faveur d’un accès équitable aux nouveaux vaccins.

Il a approuvé les activités de l’OMS visant à rassembler des données épidémiologiques et liées aux vaccins à l’échelon régional et dans les pays, et a encouragé l’OMS à apporter un soutien...
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.

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.

**Accessibility of affordable vaccines: gaps and WHO’s role in supporting emerging manufacturers**

SAGE received a landscape analysis of WHO’s role in supporting emerging vaccine manufacturers. While emerging manufacturers produce >50% of vaccines in the global market, they supply a minority of vaccines purchased by the GAVI Alliance. Reasons for this include emerging manufacturers’ vaccine portfolios and concerns over the security of their supplies. Although multiple suppliers are necessary for vaccine prices to fall, this alone is insufficient to bring about a decrease in prices. SAGE reviewed 4 methods used by WHO to support manufacturers: (i) engage in a partnership to develop new products, (ii) provide direct support to manufacturers, and (iii) provide support through a technology hub that includes (a) transferring technology for vaccine production to the clinical-lot stage or (b) transferring technology for a precompetitive research and development platform. Case studies were presented to demonstrate the use of these approaches for the Meningitis Vaccine Project, the development of pandemic influenza vaccines, the Sabin inactivated poliovirus vaccine project, and the Global Adjuvant Development Initiative.

Presentations emphasized the role that national immunization technical advisory groups have in developing country-specific vaccine recommendations. Prequalification is critical. It was noted that domestic vaccine production should not be carried out by all countries because it is a risky and complex endeavor. Partnerships have been central to the successful development of vaccines in Brazil, where the public sector covers 95% of the market. Collaboration between Brazilian manufacturers and international manufacturers has facilitated local research and development, and technology-transfer agreements.

The successful transfer of technology may take a number of years as has been demonstrated by the production of cholera vaccine facilitated by the International Vaccine Institute. Six manufacturers of rotavirus vaccine may soon enter the market following the transfer of public intellectual property to emerging manufacturers. This transfer followed public financing for research and development, the provision of technical assistance and the sharing of costs for clinical development and trials. The importance of sustainable vaccine demand was emphasized.

WHO is currently developing guidelines for technology transfer and more rapid appraisal of new vaccines. WHO also promotes the development of correlates of protection to facilitate comparative assessments. These activities accelerate the development of vaccines and reduce barriers that prevent manufacturers from entering the market. WHO’s investment should be weighed against potential public-health benefits.

aux pays afin qu’ils se servent des données de pays voisins et de leur Région lors de la prise de décision. Il a reconnu que cela nécessitait de renforcer les bureaux de l’OMS dans les pays à revenu intermédiaire de la tranche inférieure.

Le SAGE a demandé à l’OMS de faciliter la création d’un partenariat entre toutes les parties prenantes concernées afin de se pencher sur les systèmes d’achats groupés, un établissement des prix échelonnés, une plus grande transparence dans la fixation des prix, et de s’intéresser au rôle que pourraient avoir l’UNICEF, l’Organisation panaméricaine de la Santé et les fondations dans l’assistance prête à ces pays pour l’achat et le financement des vaccins.

**Accessibility de vaccins d’un prix abordable: lacunes et rôle de l’OMS pour soutenir les nouveaux fabricants**

Un tour d’horizon du rôle joué par l’OMS dans le soutien aux nouveaux fabricants de vaccins a été présenté au SAGE. Si ces derniers produisent >50% des vaccins du marché mondial, ils fournissent une minorité de ceux achetés par l’Alliance GAVI. La raison en est imputable à la gamme de vaccins proposés par ces nouveaux fabricants et aux préoccupations liées à la sécurité de leurs approvisionnements. S’il est nécessaire qu’il y ait de nombreux fournisseurs pour que les prix des vaccins baissent, cette seule condition est insuffisante pour faire baisser les prix. Le SAGE a examiné 4 méthodes utilisées par l’OMS pour soutenir les fabricants: i) s’engager dans un partenariat pour développer de nouveaux produits; ii) fournir un soutien direct aux fabricants; iii) fournir un soutien par l’intermédiaire d’un plateau technologique comprenant a) le transfert de technologie pour la production de vaccin jusqu’au stade du lot clinique ou b) le transfert de technologie pour constituer une base de recherche et développement «pré compétitif». Des études de cas ont été présentées pour montrer comment ces approches avaient été utilisées pour le projet de vaccin contre la méningite, le développement des vaccins contre la grippe pandémique, le projet de vaccin antipoliomyélitique inactivé Sabin et la Global Adjuvant Development Initiative.

Les exposés ont souligné le rôle que jouent les groupes consultatifs techniques nationaux sur la vaccination dans l’élaboration des recommandations relatives aux vaccins propres à chaque pays. La préqualification est essentielle. Il a été noté que la production domestique de vaccin ne doit pas être mise en œuvre par tous les pays car il s’agit d’une entreprise risquée et complexe. Les partenariats ont été au cœur de la réussite du développement des vaccins au Brésil, où le secteur public couvre 95% du marché. La collaboration entre les fabricants brésiliens et les fabricants internationaux a facilité la recherche et le développement locaux, ainsi que les accords de transfert de technologie.

Pour être un succès, le transfert de technologie peut prendre un certain nombre d’années comme cela a été démontré pour la production du vaccin anticholérique facilitée par l’International Vaccine Institute. Six fabricants de vaccin antirétrovirus pourraient bientôt entrer sur le marché du fait du transfert de propriété intellectuelle publique aux nouveaux fabricants. Ce transfert a fait suite au financement public de la recherche et du développement, à la fourniture d’une assistance technique, et au partage des coûts du développement et des essais cliniques. On a souligné l’importance d’une demande durable en vaccins.

L’OMS élabore actuellement des lignes directrices pour le transfert de technologie et pour l’évaluation plus rapide des nouveaux vaccins. Elle met également en avant le développement d’indicateurs de la protection afin de faciliter les évaluations comparatives. Ces activités accélèrent la mise au point des vaccins et lévent les obstacles qui empêchent les fabricants d’entrer sur le marché. L’investissement de l’OMS doit être mis en balance avec les bienfaits potentiels pour la santé publique.
Noting the complexity of transferring technology and developing vaccines, and the potentially high costs and risks, as well as several examples of successful WHO involvement in such projects, SAGE concluded that support for emerging manufacturers is one element that could increase access to affordable vaccines. SAGE reinforced the need for WHO to focus its efforts on core activities, such as prequalifying vaccines, strengthening national regulatory authorities, developing target product profiles, building capacity, and strengthening systems in areas related to vaccine supply, demand, financing and delivery.

Recognizing that there will continue to be gaps and opportunities which WHO is uniquely positioned to address, SAGE recommended that WHO monitor them and develop a systematic process to respond to these needs in collaboration with key partners.

SAGE recognized that consideration of these issues is at an early stage, and suggested that a more developed perspective be presented at a future SAGE meeting.

The epidemiology of unimmunized children and gender-related issues

SAGE was presented with follow-up information on the epidemiology of unimmunized children. This included plans, both in India and Nigeria, to develop and pilot-test tools to enhance coverage in areas where routine immunization coverage remains low. This was followed by presentations related to gender and immunization that included a quantitative analysis of data from 166 Demographic and Health Surveys from 67 countries; this was complemented by a systematic review of qualitative data on gender and immunization using case studies from a few countries, and a study by PATH on the utility and feasibility of collecting data on routine immunization disaggregated by sex. SAGE commended the follow-up work on the epidemiology of unimmunized children and requested that WHO quickly roll out tools so that other countries can address low coverage.

SAGE noted that there is no evidence to suggest a significant difference between the coverage of routine immunization in boys and girls at the global level. However, there are some countries where such differences have been reported at the subnational level. The routine collection of data disaggregated by sex at the global level is thus not the most appropriate approach to use in order to determine whether coverage is equitable among boys and girls, but local surveys clearly provide valid data that can be used to address local barriers to immunization, including gender. SAGE also noted that in some settings the low status of women prevents them from accessing immunization services for their children.

SAGE emphasized the importance of implementing strategies such as Reach Every District to enhance overall coverage and reduce differences in immunization coverage among boys and girls and other inequities where these exist. 

Notant la complexité du transfert de technologie et de la mise au point des vaccins, ainsi que les coûts et les risques potentiellement élevés qui leur sont associés, et considérant plusieurs exemples positifs de la participation de l’OMS à des projets de ce type, le SAGE a conclu que le soutien aux nouveaux fabricants constituait un élément qui pourrait accroître l’accès à des vaccins d’un prix abordable. Il a réaffirmé la nécessité pour l’OMS de concentrer ses efforts sur des activités de base telles que la présélection des vaccins, le renforcement des autorités de réglementation nationales, le développement de profils de produits cibles, le renforcement des capacités, et le renforcement des systèmes dans les domaines liés à l’approvisionnement, à la demande, au financement et à la fourniture de vaccins.

Reconnaissant qu’il continuera d’y avoir des lacunes et des occasions que seule l’OMS – et par la position qu’elle occupe – est en mesure de pouvoir combler ou saisir, le SAGE a recommandé que l’Organisation, en collaboration avec des partenaires importants, les suive et élabore un processus systématique permettant d’y faire face.

Le SAGE a reconnu que l’étude de ces questions en est à un stade précoce et a proposé qu’on lui en présente un panorama plus détaillé lors d’une de ses futures réunions.

Épidémiologie de la non-vaccination des enfants et questions de parité entre les sexes

Une étude de suivi sur l’épidémiologie de la non-vaccination des enfants a été présentée au SAGE. Elle comportait des plans, en Inde et au Nigeria, visant à élaborer et à tester des outils permettant de renforcer la couverture dans les zones où la vaccination systématique reste faible. Cette étude a été suivie de présentations sur la vaccination et la parité entre les sexes comportant une analyse quantitative des données de 166 enquêtes démographiques et sanitaires réalisées dans 67 pays; un examen systématique des données qualitatives relatives à la sexospécificité de la vaccination au moyen d’études de cas provenant de quelques pays et une étude du PATH sur l’utilité et la faisabilité de la collecte des données sur la vaccination systématique ventilées selon le sexe sont venus compléter le tableau.

Le SAGE a fait l’éloge du travail de suivi sur l’épidémiologie de la non-vaccination des enfants et demandé que l’OMS présente rapidement des outils pour que d’autres pays puissent s’attaquer à l’insuffisance de la couverture.

Le SAGE a pris note de ce que rien ne permet de penser qu’il y ait une différence significative entre la couverture vaccinale des garçons et celle des filles à l’échelle mondiale. Toutefois, il existe des pays dans lesquels des différences de ce type ont été rapportées à l’échelle infranationale. La collecte systématique de données ventilées par sexe au niveau mondial n’est donc pas l’approche la plus appropriée à utiliser pour déterminer si la couverture est équitablement répartie entre garçons et filles, mais il est clair que des enquêtes locales peuvent fournir des données valables qui peuvent être utilisées pour s’attaquer aux obstacles locaux que rencontre la vaccination, notamment aux différences liées au sexe. Le SAGE a également pris note de ce que, dans certaines situations, le faible statut social accordé aux femmes les empêche d’avoir accès aux services de vaccination pour leurs enfants.

Le SAGE a souligné l’importance de la mise en œuvre de stratégies comme celle visant à atteindre chaque district, pour renforcer la couverture vaccinale générale et réduire les différences observées entre garçons et filles dans cette couverture et les autres inégalités, là où elles existent. 

---

The purpose of the tracking sheet is to monitor the work of the WHO Secretariat on the implementation of SAGE recommendations. The sheet consists of a consolidated set of recommendations from previous SAGE meetings that require further action by the Secretariat. The monitoring of progress is conducted by the WHO Department of Immunization, Vaccines and Biologicals. The Department uses the tracking sheet, located online, as a working tool and updates it regularly. Items completed some time ago have been archived and do not show in this document but are available on request.

Recommendations intended for countries are not included in the tracking sheet but are reflected in WHO vaccine position papers. The implementation of such recommendations is monitored through the UNICEF/WHO Joint Reporting Form.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations/Action item</th>
<th>Category</th>
<th>Meeting Date</th>
<th>Status</th>
<th>Comments and Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>SAGE recommended that new approaches, such as periodic intensification of routine immunization, be carefully evaluated prospectively to determine their effectiveness and cost-effectiveness.</td>
<td>Action</td>
<td>Apr 2009</td>
<td>Ongoing</td>
<td>Ongoing work with Immunization Basics to document country experiences has continued. 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 being prepared). Identification of a third country for case-study is underway.</td>
</tr>
<tr>
<td>General</td>
<td>SAGE recommended that ways to improve curricula for medical personnel should be explored.</td>
<td>Action</td>
<td>Nov 2008</td>
<td>Ongoing</td>
<td>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).</td>
</tr>
<tr>
<td>General</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>The WHO European Region inaugurated its Immunization Communication Working Group in December 2010. At this meeting, the toolkit to profile and tailor responses was presented and feedback from members was provided. The toolkit is in its final phases of being documented and this will be shared by the end of 2011 with SAGE. The toolkit will be piloted in Bulgaria and one other country in 2011 - work to begin in May 2011. At the European Union Hungary Presidency, the Regional Office presented the toolkit and best practices compendium with the EU countries. It was well received and many countries are interested in implementing.</td>
</tr>
<tr>
<td>General</td>
<td>SAGE encouraged AMRO to formally document the factors contributing to countries’ ownership of the programmes and the successful delivery of immunizations and to share these with other regions.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Most of the lessons learned have been documented in our Immunization Newsletter, available at: <a href="http://new.paho.org/hq/index.php?option=com_content&amp;task=view&amp;id=3130&amp;Itemid=3504&amp;lang=en">http://new.paho.org/hq/index.php?option=com_content&amp;task=view&amp;id=3130&amp;Itemid=3504&amp;lang=en</a> PAHO will soon have an e-book of this Newsletter with a thematic index to facilitate article searches.</td>
</tr>
</tbody>
</table>

1. The Expanded Program on Immunization (EPI) has been in place for over 30 years
2. Vaccines are considered a public good in the Americas
3. Immunization topics have been presented in most of PAHO’s Directing Council meetings:
   (3a) Strengthening immunization programs
   (3b) Disease elimination goals
   (3c) Sustainability of immunization programs
   (3d) Vaccination Week in the Americas (VWA)
4. Several countries/territories have legislation regarding immunization; two other countries are in the process of passing such laws. These laws go from making vaccination mandatory to securing budget lines for vaccine purchase or ensuring the functioning of the immunization program.
5. PAHO’s Revolving Fund for vaccine purchase belongs to the countries of the Americas and it is the preferred mechanism to procure vaccines and immunization supplies of assured quality and at the lowest price in the market
6. Several presidents, first ladies and other political figures have participated in vaccination activities and endorsed vaccination campaigns. They often participate in VWA launching events.
7. There is a culture of vaccination among health care workers, parents, and communities
8. The immunization program makes an effort to engage professional societies, such as medical and nurse associations
9. Vaccination Week in the Americas has served to keep vaccines in the public agenda
<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations/Action item</th>
<th>Category</th>
<th>Meeting Date</th>
<th>Status</th>
<th>Comments and Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers</td>
<td>SAGE recommended that WHO monitor gaps and opportunities and develop a systematic process to respond to these needs in collaboration with key partners.</td>
<td>Pending</td>
<td>Nov 2010</td>
<td>Pending</td>
<td>This is in part being addressed through the general discussions on the process of technology transfers that are taking place under the leadership of the Innovation, Evidence, Information and Research Cluster and through the bilateral meetings with members from the DCVMN. This will also be discussed in the context of WHO’s contribution to the DoV work stream on global access.</td>
</tr>
<tr>
<td>Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers</td>
<td>SAGE suggested that a more developed perspective be presented at a future SAGE meeting on accessibility of affordable vaccines.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Pending</td>
<td>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. Proposed to organize regular meetings with vaccine industry representatives on this topic and in particular with members of the Developing Countries Vaccine Manufacturer’s Network (DCVMN). A general discussion is being proposed for the annual meeting of the DCVMN. 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 &amp; Associations (IFPMA). General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster.</td>
</tr>
<tr>
<td>Categorization of vaccine-preventable diseases</td>
<td>SAGE requested exercise to be completed in a timely manner. Final disease prioritization results to be submitted for peer-review and provided to SAGE members for their review.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>Regional level exercise could not be completed due to drop out of collaborators and loss of data. Reprogramming to publish global data ongoing - draft will be provided to SAGE members in Q2 2011.</td>
</tr>
<tr>
<td>Childhood mortality</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>Cholera</td>
<td>Prepare a business case for oral cholera vaccines to provide critical information for donors regarding the potential demand for cholera vaccines, the costs and cost-effectiveness of cholera vaccination to meet this demand, possible funding sources, and the funding gap.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Completed</td>
<td>WHO was not in a position to undertake this task but encouraged other institutions to move forward. The International Vaccine Institute (IVI) has prepared a draft investment case and they may make it available upon request for SAGE or other groups interested in investing efforts on cholera control and prevention.</td>
</tr>
<tr>
<td>Decade of Vaccines</td>
<td>SAGE expressed interest in contributing to the development of the action plan for the Decade of Vaccines. SAGE emphasized the need for thorough and early engagement with regions and countries. SAGE emphasized that healthcare systems can be strengthened by implementing vaccination programmes and that this focus should be incorporated into one of the areas of work; SAGE also pointed out that investing in surveillance should be incorporated into one of the areas of work.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>SAGE will be updated on the progress to date on the Decade of Vaccines (DoV) collaborative effort and more specifically on the processes and timelines for the development of the DoV Delivery workstream by WHO and UNICEF. The updates will include the proposed focus areas under Delivery, consultation processes, and further plans for regional and country engagement in the process. The Director's report will also include an overall status report on the DoV Collaboration and status of the other workstreams of Research &amp; Development, Global Access and Public and Political Support.</td>
</tr>
<tr>
<td>Feasibility of measles eradication</td>
<td>SAGE requested that progress towards meeting the 2015 global targets and regional elimination goals be monitored.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Current monitoring activities include the annual WHO/UNICEF estimates of measles vaccination coverage, monthly reporting and feedback of measles surveillance data (see WHO/HQ website), and updating the model to estimate the global burden of measles based on recommendations from QUIVER.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>-------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Feasibility of measles eradication</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Pending</td>
<td>Pending completion of rubella discussion at April 2011 SAGE meeting.</td>
</tr>
<tr>
<td>Financing</td>
<td>SAGE identified the need to support countries that become ineligible and lower middle income countries through pooled procurement.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>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 (IPMA&amp;DVMMN). The study began in November 2009 and was completed in March 2011. Finding and preliminary conclusions and recommendations will be presented to the SAGE in November 2010 - 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 and develop transition plans.</td>
</tr>
<tr>
<td>Financing</td>
<td>SAGE requests that WHO conduct further situation analysis of financial challenges for low or middle-income countries and consultation with countries concerned &amp; partners to distil issues to more actionable activities.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>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 NUVE 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 NUVE 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, ...).</td>
</tr>
<tr>
<td>GRADing and review of evidence</td>
<td>SAGE also supported the development of a paper describing SAGE’s approach to reviewing evidence when issuing recommendations. The proposed partnership among SAGE and other immunization advisory committees to enhance the GRADE approach was encouraged.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>Active collaboration has been started with the US ACIP, the Global Advisory Committee on Vaccine Safety, the German STIKO, the European CDC, and other national advisory committees on immunization for further collaboration and consensus building. An international workshop on procedures for the development of evidence-based recommendations for immunization was organized on 22-23 November 2010 by the Robert Koch Institute. This meeting brought together a number of well functioning national technical advisory groups on immunization. A draft methodological paper will be presented to SAGE at its April 2011 meeting.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>GRADing and review of evidence</strong></td>
<td>SAGE encouraged the grading discussion group to develop a communication strategy to mitigate any potentially deleterious effects of a narrowly applied GRADE approach used to evaluate immunization strategies. SAGE also encouraged the group to suggest appropriate adjustments to the process – for example, by applying criteria to increase or decrease the quality-of-evidence score when taking into account broader population effects – with a possible longer term goal of recommending fundamental improvements to the approach.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>A draft document on proposed adjustments to GRADE scoring of quality of scientific evidence for vaccines and clarifications on how to apply scoring for vaccines has been developed by the discussion group. This document was discussed with other advisory committees on immunization and the GRADE Working Group. A formal interaction on specific needed adjustments to GRADE took place at the 13-14 January 2011 meeting of the GRADE Working Group. This resulted in some adjustments to the GRADE evidence scoring scheme that allow to better accommodate vaccine related issues. This is reflected in the draft related paper presented to SAGE at the April 2011 SAGE meeting. This together with adjustments in the wording of the conclusions of the GRADE scoring table should greatly contribute to mitigate potential unwanted deleterious effects of the GRADing process.</td>
</tr>
<tr>
<td><strong>HIV - Horizon scanning for R&amp;D of vaccines against HIV, Tuberculosis and Malaria</strong></td>
<td>SAGE requested regular updates on the progress of HIV-vaccine research.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Pending</td>
<td>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 Trial 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 is being developed targeting the national regulatory authorities in countries where this type of trials are being planned in the coming years.</td>
</tr>
<tr>
<td><strong>HPV</strong></td>
<td>SAGE urged the completion of ongoing research in HIV-infected individuals, on prolonged (including yearly) intervals between doses, demonstration projects on delivery methods, and cost-effectiveness studies of vaccinating young adolescents and older catch-up populations in low- and medium-income countries. The committee also urged new research on the feasibility and effectiveness of simplified schedules such as dose schedules or infant/young child dosing to assess initial and sustained immunogenicity.</td>
<td>Action</td>
<td>Apr 2007</td>
<td>Ongoing</td>
<td>A study on cost and financing issues for HPV vaccine adoption in developing countries was carried out by PATH and the report is available. HVAC, the AC for HPV vaccines met in April 2010 to review and discuss new clinical data available. Of potential importance to SAGE were the updates related to a) cross-protection against oncogenic HPV genotypes not included in the vaccine, b) comparison of 2 vs 3 dose schedules, c) duration of protection induced, d) performance when co-administered with other vaccines, e) use in HIV-infected persons and d) performance an implications of possible use of these vaccines in males. Lessons learnt with the four demonstration projects conducted by PATH in India, Peru, Viet-Nam and Uganda, as well as other accomplishments from WHO partners were also presented and discussed. In respect to the PATH projects, the focus was comparing community-based delivery vs school-based strategies and using the opportunity to answer a number of distinct operational questions, using the opportunities offered by the different country programmatic preferences. A comprehensive HVAC report has been prepared and a shorter version is available. HVAC met for their last time in 2010. Nonetheless, it would appear important for SAGE to be updated at a later date on the outcomes of the above-mentioned studies.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2009</td>
<td>Ongoing</td>
<td>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 &quot;Melbourne Declaration&quot; for advocacy purposes and a monograph documenting the systematic review and best practices from the consultation. Work is in progress to revise JRF (Joint Reporting Form) and associated materials to improve reporting of birth dose. Analysis of timely birth dose data for 2008 shows no significant changes from 2006 analysis and major issue is lack of data quality.</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2008</td>
<td>Ongoing</td>
<td>WHO HQ is drafting a new global viral hepatitis strategy that will likely call for establishing a global time-limited control goal for hepatitis B virus. EMRO is working with Member States to ensure achievement of the Regional Committee goal for HBsAg reduction in vaccinated children. WPRO continues to monitor progress towards achieving 2012 goal—the 2010 WPR TAG recommended actions to ensure achievement of this goal. New staff position developed in WPRO to focus on this issue with donor support. SEARO conducted a regional review of Viral Hepatitis prevention and control in 2010. AFRO is developing a background paper and has developed, under the umbrella of TFI, a hepatitis TAG. The hepatitis TAG met and has developed a comprehensive strategy for viral hepatitis control including a hepatitis B control goal that will be considered by the African Regional Committee in 2012. EURO will consider a regional hepatitis B control goal. PAHO is planning a best practices study in Cuba in early 2011. EMRO developed best practices for conducting serosurveys to support country impact work. These are under external peer for reviewing and would be published in early 2011.</td>
</tr>
<tr>
<td>Hib</td>
<td>Expand new framework for Hib introduction to the fullest extent possible to increase demand for the vaccine and accelerate the lowering of its price.</td>
<td>Action</td>
<td>Nov 2005</td>
<td>Ongoing</td>
<td>The Hib Initiative had conducted regional fora in Africa, Asia, Europe and the Middle East and had devised a strategic plan to assist the poorest countries with decision-making on Hib vaccine introduction including research activities. GAVI has a procurement strategy to which WHO and PATH provide advice through the work on vaccine pre-qualification and demand forecast. A WHO-maintained spreadsheet provides up-to-date information about programmatic elements. There has been an acceleration of the uptake of Hib-containing vaccines as a result of the SAGE recommendation, availability of GAVI funding and improving supply base. By the end of 2010, 172 countries had introduced Hib vaccine or indicated intention to introduce. WHO continues to support UNICEF Supply Division by participating in the Procurement Reference Group for Hib, Hep B, and YF vaccines which provides information upon which tenders are issued. In addition, as part of the Accelerated Vaccine Introduction Initiative, WHO supports work on long-term forecasting to estimate demand for Hib vaccine to ensure vaccine availability.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Immunization safety</td>
<td>SAGE encourages development of simple technological solutions with improved environmental characteristics, and encourages donors to support such work as a priority.</td>
<td>Action</td>
<td>Nov 2007</td>
<td>Ongoing</td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- In the context of the Libreville declaration on Health and Environment in Africa, a workshop in Cameroon in July 2010 has produced a framework for health care waste management.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- A study on the safety to use needle remover has been completed in Bangladesh. This could influence the WHO position on the use of such device and would have an impact on safety but also on the management of waste from injection activities.</td>
</tr>
<tr>
<td></td>
<td>SAGE urged for clarification for activities that could be funded under health system strengthening to incl. injection safety and waste management incl. training and supervision activities.</td>
<td>Action</td>
<td>Nov 2007</td>
<td>Ongoing</td>
<td>WHO through GAVI support is providing technical support to countries to develop and finalize national plans. Some countries have now moved into implementation and the allocation of equipment and trainings such as in Mali are taking place in districts. WHO has also developed a tool to monitor progress in countries. This tool will help to see progress and define country status in health-care waste and prioritize interventions. An assessment on injection safety and waste from immunization activities took place in Rwanda and Gambia in 2009-2010 to assess the country strategy but also to specifically assess the introduction of the PVC7 vaccine in pre-filled glass syringes. Good progress is seen in most GAVI eligible countries and a good number can be seen as model countries. There is still a long way to go. Health-care waste management has a cost and WHO has developed core principles to advocate for the mobilization of resources for health-care waste. Health-care waste is now seen by all as a priority intervention to prevent the transmission of diseases and for safety.</td>
</tr>
<tr>
<td>Immunization schedules</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>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 (<a href="http://www.who.int/immunization/policy/immunization_tables/en/index.html">http://www.who.int/immunization/policy/immunization_tables/en/index.html</a>). This document outlines how countries can use the WHO recommendations to review their national immunization schedules. 2. Not addressed yet. 3. Preliminary discussions with IVR to consider collaborating on a study of missed opportunities in 1-2 countries as part of the IVR EPI Schedules Optimization Project.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Immunization schedules</td>
<td>WHO is encouraged to continue its work to support countries in establishing &amp; strengthening national advisory committees and in efforts to and optimize their immunization schedules.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>Global survey of national technical advisory committees on immunization completed. Several related articles have been published in Health Policy and Vaccine. Results presented at several regional technical advisory group and immunization managers meetings. Data for the Americas summarized by AMR in the immunization newsletter. Ongoing regional initiatives to strengthen establishment and strengthening of national technical advisory groups with regular video-conferences and coordination within WHO. Well established priority of work within the Organization. Collaboration with SIVAC initiative, CDC, Provac and other partners. Supplement of Vaccine with focus on NITAGs published in April, 2010. SIVAC implementing a resource center. Summary Tables of WHO Recommendations for Immunization finalized and published on the WHO web site on 16 January 2009. These are updated on an ongoing basis whenever there is a new policy recommendation.</td>
</tr>
<tr>
<td>Immunization schedules</td>
<td>SAGE encouraged WHO to further address the public health value of immunization strategies optimizing the cost-effectiveness of interventions for populations compared with individuals.</td>
<td>Action</td>
<td>Apr 2007</td>
<td>Ongoing</td>
<td>See related information on public health value of immunization strategies.</td>
</tr>
<tr>
<td>Immunization schedules</td>
<td>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.</td>
<td>Information</td>
<td>Apr 2007</td>
<td>Ongoing</td>
<td>Work in progress. Staff recruited to work on these issues. Presentation of the project at SAGE October 2009 meeting. Update and discussion took place at the November 2010 SAGE meeting.</td>
</tr>
<tr>
<td>Impact of the introduction of new vaccines on immunization and health systems</td>
<td>SAGE requested that WHO assesses how the introduction of new vaccines has helped strengthen immunization and health systems.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>An ad-hoc working group has produced a framework on new vaccines introduction impact on the health and immunization systems, which contains hypotheses on major effects, partly backed by published literature, which was reviewed by SAGE in April 2010.</td>
</tr>
<tr>
<td>Impact of the introduction of new vaccines on immunization and health systems</td>
<td>In relation with the impact of the introduction of new vaccines of immunization and health systems, SAGE encouraged completion of the literature review.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>A published literature review and a grey literature review are scheduled to be completed in March 2011. For other activities on this topic, please see related recommendation re: New vaccine introduction.</td>
</tr>
<tr>
<td>Impact of the introduction of new vaccines on immunization and health systems</td>
<td>SAGE recommended that the 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. In this context SAGE encouraged completion of the literature review.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>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. Ongoing research conducted on this topic is being reviewed with regards to specific vaccines (injectable, oral, targeted at infants and older age groups). The ad-hoc group presently updates the framework based on the data obtained and will draft and pilot-test a guideline to assist country decision makers and EPI managers contemplating the introduction of new vaccines to take account of the effects/impacts on the health system. A presentation to SAGE is foreseen for November 2011.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Impact of the introduction of new vaccines on immunization and health systems</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>The ad hoc working group continues to include a broad range of partner agencies (WHO, UNICEF, WB, CDC, PATH, JSI, LSHTM, JHU) and will seek endorsement of this work at senior levels of partner agencies.</td>
</tr>
<tr>
<td>Influenza</td>
<td>WHO should ensure that there is unrestricted sharing of samples and vaccines strains internationally.</td>
<td>Action</td>
<td>Nov 2006</td>
<td>Ongoing</td>
<td>Under the overarching goal of pandemic influenza preparedness, Member States worked through an intergovernmental process (IGM) to develop a Framework to increase the transparency of the WHO virus sharing system and establish fairer and more equitable mechanisms for the sharing of resulting benefits. The IGM process formally concluded in May 2009. Through WHA resolution 62.10 Member States requested that the Director-General facilitate a transparent process to finalize the remaining elements of the Framework, including the SMTA, and report thereon to the 126th Executive Board. In this connection, the Director-General has invited Member States and regional economic integration organizations to a consultation on 19-20 October 2009. Following discussions at the Executive Board, it was agreed that negotiations between Member States should be conducted by an open-ended working group that convened from 10-12 May 2010. The aim of said working group was to reach agreement on remaining elements under the draft Framework. The Executive Board requested that the Director-General facilitate the process and specified that the outcome of the work of the open-ended working group would be reported to WHA 63. The outcome and report on the technical studies under Resolution WHA63.1 is currently on its final stages of drafting and will be made available to SAGE.</td>
</tr>
<tr>
<td>Influenza</td>
<td>SAGE recommended to the Director-General that WHO should establish mechanisms for ensuring access to pandemic vaccine, should a pandemic be declared by the Director-General, for distribution to developing countries without influenza vaccine production capacity or resources to purchase such vaccines.</td>
<td>Action</td>
<td>Apr 2007</td>
<td>Ongoing</td>
<td>WHO supports developing country manufacturers since 2007 to acquire the capacity to produce influenza vaccines. After the declaration of the 2009 pandemic, 6 of these 11 developing countries have produced clinical lots of A(H1N1) vaccine, 4 have completed or are conducting clinical trials of pandemic vaccine, 3 have registered this vaccine for use in humans. A royalty-free license was negotiated by WHO with Nobilon-Schering-Plough-Merck on the LAIV technology. A Center of Excellence and Training for transfer of technology (technology hub) was established at the Netherland Vaccine Institute, to overcome the lack of a willing technology provider. To help countries protect people from developing severe disease from pandemic influenza H1N1 infection, WHO coordinated the distribution of donated pandemic influenza vaccine to eligible countries. By December 2010, 82 countries from all WHO Regions have submitted their NDVP, vaccine was delivered to 77 countries and over 78 million doses have been donated with syringes and safety boxes.</td>
</tr>
</tbody>
</table>
### Influenza

**SAGE agreed to review available information for it to provide an opinion on:**
1. **use of H5N1 influenza vaccine in the inter-pandemic period.**
2. **use of H5N1 influenza vaccine in high risk groups - incl. vaccine reaching end of shelf life at future meetings.**

**Recommendations:**

**A SAGE WG was established to review the evidence available for developing an opinion for the SAGE to review.** The working group (WG) held several consultations between 3 November 2008 and 19 March 2009, and presented a comprehensive review of available evidence to SAGE in April 2009, for consideration in a potential recommendation.

SAGE endorsed most of the recommendations proposed by the WG, and left a number of issues open for further discussion. Among those:

- WHO will develop guidance to assist countries to carry out a risk assessment in persons known to be in contact with poultry in confirmed active H5N1 outbreak areas, before vaccine may be made available;
- Holders of licensed H5N1 vaccine stockpile are encouraged to gain experience with H5N1 vaccine use, and to build knowledge further on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity in order to inform public health policies.

Moreover, SAGE welcomed a future discussion on the cost-effectiveness of vaccination with H5N1 vaccines in the inter-pandemic period.

Shortly after the SAGE April 2009 meeting, the H1N1 pandemic started, which put on hold most of the activities on H5N1 preparedness.

The SAGE H5N1 WG resumed its work on 15 February 2010 with the intention to update SAGE during its April 2010 meeting on new developments which might impact recommendations formulated in April 2009. The H5N1 WG met on 27 September 2010 and reported to SAGE in November 2010. The WG was terminated after the November 2010 SAGE meeting. SAGE has recommended that any further pandemic vaccine related discussion be included in the ToRs of the SAGE Working Group on influenza vaccines and immunization.

### Influenza

**SAGE recommends WHO continue urgent development of H5N1 stockpile.**

**Action**

**Nov 2007**

**Ongoing**

This project being taken forward by SAGE influenza working group.

**WHO should ensure that the expertise in rapid mobilization for mass immunization is included in influenza preparedness planning.**

**Action**

**Nov 2005**

**Ongoing**

By December 2010, 82 countries from all WHO Regions have submitted their NDVP, vaccine was delivered to 77 countries and over 78 million doses have been donated with syringes and safety boxes at the time of this update. A series of workshops at WHO regional level is being planned by 2011, for reviewing deployment and vaccinations activities, one of the objectives of the workshops is to ensure that the experiences in deployment and vaccination is integrated in the immunization area of preparedness and response plans.

**WHO should pursue its efforts in strengthening the capability in developing countries of health ministries and national regulatory authorities to facilitate the movement of samples and to ensure prompt registration of pandemic vaccines.**

**Action**

**Research**

**Nov 2005**

**Ongoing**

This project being followed-up through ongoing discussion in the Inter-Governmental Working Group.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations/Action item</th>
<th>Category</th>
<th>Meeting Date</th>
<th>Status</th>
<th>Comments and Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2007</td>
<td>Ongoing</td>
<td>The WHO Guidelines stipulate that EPI logistic system should be the template for the rapid delivery of a pandemic influenza vaccine. In 2007 two meetings were convened - 1. Informal consultation on regulatory preparedness for human pandemic influenza vaccines, held in Geneva on 14-15 June 2007 (see <a href="http://webtipreview.who.int/entity/vaccine_research/diseases/influenza/meeting">http://webtipreview.who.int/entity/vaccine_research/diseases/influenza/meeting</a>) and 2. Informal consultation on technical specifications for a (WHO) international H5N1 vaccine stockpile, held in Geneva on 17-18 October 2007 (see <a href="http://who.int/vaccine_research/diseases/influenza/meeting_stockpile">http://who.int/vaccine_research/diseases/influenza/meeting_stockpile</a>). WHO in collaboration with Gates Foundation and Oliver Wyman evaluated different options for logistical design of the WHO international H5N1 vaccine stockpile and associated trade-offs, strategies and mechanisms for funding the stockpile (see <a href="http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf">http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf</a>). SAGE working group on H5N1 vaccine, after evaluating the available evidence, recommended that the size of the stockpile should remain at 50 million doses for rapid containment and 100 million doses for equitable distribution to low and middle income countries to help maintain the services considered most essential. SAGE working group recommended the use of the licensed H5N1 vaccine in different groups during interpandemic period. In addition, the use of stockpiled vaccines before they reach their expiry date may be considered for use (see <a href="http://www.who.int/wer/2009/wer8424.pdf">http://www.who.int/wer/2009/wer8424.pdf</a>). Due to the outbreak of the Pandemic (H1N1) 2009 in April 2009 and the declaration of the pandemic phase VI in June 2009, activities related to the WHO international H5N1 vaccine stockpile were interrupted. The SAGE H5N1 Working Group convened in 27 September 2010 and reviewed the stockpile related SAGE recommendations. This will be discussed during the influenza session in November 2010 SAGE meeting. The responsibility for the SAGE H5N1 stockpile is currently under the Working Group on influenza vaccine and immunization. The Working Group held a meeting on 14-15 February 2011 and discussed the H5N1 stockpile.</td>
</tr>
<tr>
<td>Influenza</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>The new working group on influenza vaccines and immunization was constituted, under the chairmanship of Professor Liz Miller. Its first meeting took place on 11-12 October 2010. An update of the meeting and workplan of the working group has been presented to SAGE in November 2010. A second face-to-face meeting of the Working Group is scheduled for 14-15 February 2011.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>---------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Influenza</td>
<td>WHO should support R&amp;D for pandemic and seasonal vaccines, including alternative and more effective methods of vaccine delivery.</td>
<td>Action</td>
<td>Nov 2005</td>
<td>Ongoing</td>
<td>May 2–3, 2006 consultation intended to produce a global action plan to increase supply of pandemic influenza vaccines. The Global Action Plan (GAP) was developed and presented at the November 2006 SAGE meeting. Update for 2009/2010: 1) Since 2007 eleven developing country vaccine manufacturers, which never produced any licensed influenza vaccine in the past, and two technology transfer “hubs” have received ~40 million USD “seed” grant in total in support of influenza vaccine production capacity building. 2) At the time of this report, as a result of these “seed” grants one seasonal (Indonesia), four pandemic H1N1 vaccines (Rumania, Korea, India) were licensed by National Regulatory Authorities (NRAs), including a live attenuated influenza vaccine (LAIV). More than 25 million of the licensed pandemic vaccines were used during the 2009/10 H1N1 pandemic in Europe, Asia and the Americas. Three additional pandemic H1N1 vaccines reached clinical trial stage (Thailand, Brazil, Indonesia), including an additional LAIV vaccine. 3) The GAP Advisory Group evaluated the three-year progress in May 2010. 4) The 4th meeting on seasonal and pandemic candidate vaccines which potentially elicit broad spectrum and long lasting immune responses was held in November 2009 in collaboration with the Wellcome Trust in London, England. A peer reviewed meeting summary was published in Vaccine. 5) The 6th meeting to evaluate the progress on clinical trials with pandemic prototype vaccines, including pandemic H1N1, was held in Geneva, Switzerland in February 2010. A peer reviewed summary was published in Vaccine. The next clinical trial meeting is planned to be held in early 2011. 6) In 2009 a report was published in the journal Vaccine from a WHO organized workshop, September 2008, Vilamur, Portugal, which addressed the potential role of neuraminidase in influenza vaccination. 7) A novel grant package was secured during the fall of 2010 for continuation of these influenza vaccine production capacity building programmes. In September 2010 a Technical Advisory Group (TAG) reviewed nine applications. Approved contracts expected to be finalized in November 2010. 8) Additional funds were secured for 2011 with possibilities to invite additional vaccine manufacturers from regions still without local influenza vaccine production, such as Central Asia or Sub-saharan Africa.</td>
</tr>
<tr>
<td>Influenza</td>
<td>SAGE recommended that the Influenza Vaccines and Immunization Working Group develop a research agenda.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>This was discussed and listed on an action item at the 14-15th February meeting of the Working Group.</td>
</tr>
<tr>
<td>Influenza</td>
<td>SAGE expressed a need for more information about the shelf-life and other characteristics of pandemic influenza vaccines before making additional recommendations about options for the constitution of the stockpile.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>This project is under consideration by SAGE influenza Working Group.</td>
</tr>
<tr>
<td>Influenza</td>
<td>SAGE requested that WHO report on the utilization of deployed vaccine, including by risk group, once data collection has been completed.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Findings on the utilization of deployed vaccine, including by risk group is expected to be available by next April 2011 once data collection is finished and vaccination coverage figures are conciliated, and a related presentation is scheduled on the April 2011 meeting.</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Interference with the immune response to other vaccinations, number of doses required and the duration of protection need to be assessed.</td>
<td>Action</td>
<td>Apr 2006</td>
<td>Ongoing</td>
<td>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 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 is pending publication). WHO review might be needed once results are available.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action Item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2008</td>
<td>Ongoing</td>
<td>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, which is submitted for publication. Identification of target populations are being discussed in the context of country control strategies. The publication is submitted to bulletin WHO, currently responding to reviewers queries, the manuscript calculates some 66,000 cases/year.</td>
</tr>
<tr>
<td>Lower-middle-income countries: sustainable adoption and financing for new vaccines</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>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.</td>
</tr>
<tr>
<td>Lower-middle-income countries: sustainable adoption and financing for new vaccines</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>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 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 organized in January 2010 a successful brainstorming meeting on vaccine price and vaccine pricing focusing on issues faced by GAVI graduating and middle income countries. A proposal is under discussion with BMGF (Bill and Melinda Gates Foundation) on vaccine price.</td>
</tr>
<tr>
<td>Malaria</td>
<td>SAGE indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur during the evaluation.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>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 <a href="http://www.ncbi.nlm.nih.gov/pubmed/20735271">www.ncbi.nlm.nih.gov/pubmed/20735271</a>). 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 influenzae 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.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Measles mortality reduction</td>
<td>SAGE encouraged a careful analysis of the challenges facing the end stages of polio eradication as part of the work to assess the feasibility of measles eradication.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Completed</td>
<td>A discussion of the challenges facing the polio eradication efforts and how these may apply to measles eradication efforts were held with Director of Global Polio Eradication at the Technical Global Consultation meeting to assess the feasibility of measles eradication (July 2010). It was highlighted that a proof of concept in the most challenging areas (weakest links) should be considered prior to embarking on a measles eradication efforts.</td>
</tr>
<tr>
<td>Measles mortality reduction</td>
<td>Report back to SAGE on the outcome of the January 2010 Executive Board as well as the results of the ongoing studies relating to the impact on health systems and estimated costs of measles eradication.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Completed</td>
<td>The January 2010 EB accepted the report with the proposed 2015 milestones and the report was discussed and the milestones endorsed at the 2010 May WHA. The ongoing studies on the impact of measles eradication on health and immunization systems and the cost and cost effectiveness of measles eradication have been completed. The results were presented at the November 2010 SAGE and the reports of these studies are posted on the SAGE website.</td>
</tr>
<tr>
<td>Measles mortality reduction</td>
<td>Undertake work to prepare for discussions on the feasibility of a global elimination goal.</td>
<td>Action/Agenda item</td>
<td>Apr 2009</td>
<td>Completed</td>
<td>This work has been completed and presented to SAGE at the November 2010 meeting.</td>
</tr>
<tr>
<td>Meningitis</td>
<td>SAGE recommended that the impact of inter-African migration on the occurrence of meningitis should be monitored.</td>
<td>Action</td>
<td>Apr 2009</td>
<td>Ongoing</td>
<td>Following the 3rd international Meningitis Environmental Risk Information Technologies (MERIT) technical meeting held in Niger in November 2009, current efforts of the public health, meteorological and research communities are focused on advancing the development of a decision-support tool for testing prospectively in Niger during the current meningitis epidemic season. The decision-support tool will integrate epidemiological information and knowledge of the environmental and social influences impacting meningitis epidemics across the Meningitis Belt. Close monitoring of the current 2010 epidemic season by several MERIT partners is providing near real-time analyses of the forecasts and changes in environmental conditions associated with meningitis incidence in affected areas. This information was analysed alongside the dynamics of the disease in the context of the decision-making process for the distribution of vaccines, the results of which was reviewed at the end of the epidemic season in May 2010. The surveillance data received from 14 endemic countries reported 22831 cases and 2415 deaths, case fatality rate 10.6%. The number of cases has been lower compared to 2009 epidemic season with the highest reported cases since 1996 with 79296 cases and 4288 deaths. Nigeria was the most affected country with 55747 cases (70% of the total). In addition, The Neisseria meningitidis confirmed cases were 26.5% serogroup A, 0.18% serogroup C, 3.3% X and 43.9% W135. Other meningitis cases were Streptococcus pneumoniae 19.7% and Haemophilus influenzae 2.5%</td>
</tr>
<tr>
<td>Meningococcal A conjugate vaccine</td>
<td>SAGE encouraged WHO to draw global attention to the achievement of the recent licensure of the meningococcal A conjugate vaccine pilot campaigns launched successfully in Burkina Faso, Mali and Niger; with coverage exceeding 90% in all targeted districts.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Meningococcal A conjugate vaccine was successfully launched in Burkina Faso, Mali and Niger through large preventive mass campaigns vaccination in December 2010, targeting the 1-29 years old population, with an unprecedented coverage rate approaching 100%. News of the event was spread across the pages of newspapers all over the world, and broadcast outlets reported the story, reflecting the strong global interest in the promise of this new vaccine against meningitis A.</td>
</tr>
<tr>
<td>Meningococcal A conjugate vaccine</td>
<td>SAGE noted that more clarity was needed on recommendations for vaccinating subpopulations (such as pregnant and lactating women).</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Recommendations for vaccinating pregnant and lactating women were presented to and endorsed by GACVS in December 2010. These recommendations were sent to WHO AFRO for circulation in countries.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>National regulatory authorities</td>
<td>SAGE agreed on the need to strengthen the capacity of national regulatory authorities and AEFI committees, since they have the primary responsibility for dealing with these events. SAGE encouraged further discussion of these issues with the Global Advisory Committee on Vaccine Safety (GACVS) and encouraged countries in the region to engage with organizations of health-care professionals at the country level.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>The Global Vaccine Safety Blueprint project has been launched to develop the basis of a global consortium aiming at strengthening countries capacity for vaccine safety work. This project is expected to be completed by the summer of 2011. GACVS participates in the project through a consultative committee and also receives regular progress reports at its bi-yearly meetings.</td>
</tr>
<tr>
<td>Optimizing immunization schedules</td>
<td>SAGE requested that the models reflect operational realities – for example, delays in vaccine administration.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>A new contract was issued with the modeller developers to introduce SAGE and QUIVER recommendations. In addition to West Africa data, modellers will analyze the Eastern Africa data. Resource constraints might have a negative impact on the completion of some planned activities.</td>
</tr>
<tr>
<td>Optimizing immunization schedules</td>
<td>SAGE recommended that WHO provide support to country-level policy-makers on the rational use of analyses generated by the boll.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>We have approached SIVAC to collaborate in one African country as a case study (initially Cote d’Ivoire now considering Mozambique).</td>
</tr>
<tr>
<td>Optimizing immunization schedules</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>PCV: Vaccine review completed; epidemiology review planned; model plus Incremental Cost-Effectiveness Analysis (ICEA) ongoing. Hib: vaccine review ongoing; epidemiology review planned; no resources for model and/or ICEA. Rota: vaccine review ongoing; epidemiology review being completed; no resources for model and/or ICEA (trying to &quot;piggy back&quot; on other efforts). For all: review of number of contacts during first years of life (planned); cost of contacts (planned); update on actual age at vaccination data.</td>
</tr>
<tr>
<td>Pertussis</td>
<td>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.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>A proposal was to be presented to the ECBS in October 2010 with a view to give feed-back at the November 2010 SAGE meeting. This was delayed due to protracted discussions with the Pasteur Institute in Paris who was approached as the main partner for the development of the proposal. The following issues will be examined: 1) ownership of the data 2) use of the strains; 3) use of the information generated on these strains. SAGE will be updated as soon as information becomes available.</td>
</tr>
<tr>
<td>Pertussis control</td>
<td>Pertussis surveillance and control needs to be raised and placed the responsibility on the Regions to make this a priority.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>The SAGE recommendation has been flagged at the December 2009 AFR TFI meeting and at the Global Immunization Meeting. Further communication and visibility given with the publication of the update pertussis position paper in October 2010. The discussion will continue at regional TAG meetings.</td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccine</td>
<td>The results of a systematic review of published and unpublished data on serotype replacement will be presented to SAGE in November 2011.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>A grant has been received from the Bill &amp; Melinda Gates Foundation to support the systematic review to be conducted by GAVI Accelerated Vaccine Introduction Technical Advisory Consortium (Johns Hopkins, CDC and PATH) under the supervision of a Technical Advisory Group constituted by WHO and includes 3 SAGE members (Liz Miller, Art Reinglold and Juhani Eskola). The timelines are for the review to be completed by September 2011, discussed at a stakeholder meeting and the final analysis and draft recommendations presented to SAGE in the November 2011 meeting.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Polio</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>Following the publication of the WHO position paper on routine pre-eradication polio vaccination, the SAGE Working Group on IPV policy recommendations. Although it had been anticipated that the WG's second remit, recommendations on post-eradication IPV policies, would be presented to SAGE in April 2011, SAGE decided to extend this timeline by 12 months, as the WG would benefit from additional data from a) field trials of IPV efficacy in Cuba and India, and b) a ‘state of the art’ meeting on vaccine-derived polioviruses, c) further mathematical modeling of post-eradication risks, and d) ongoing projects to work towards assuring a more affordable IPV supply.</td>
</tr>
<tr>
<td>Polio</td>
<td>SAGE noted that high priority must be given to translating the recommendations of the Independent Evaluation and recent clinical trial results into a new, three-year Programme of Work for Interrupting Wild Poliovirus Transmission and agreed to participate in its review, finalization and monitoring, particularly by focusing future SAGE polio sessions on areas or countries where progress is faltering.</td>
<td>Action Agenda item</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>The new 3-year Strategic Plan 2010-2012 was shared with SAGE at the April 2010 meeting and endorsed by the May 2010 World Health Assembly. The plan was launched in June 2010 by the global polio partners, and progress begins to be evident by end-2010. In 2010, both India and Nigeria recorded a 95% reduction in new cases, compared to 2009. Of 15 countries suffering outbreaks following importation of poliovirus in 2009, all had stopped the outbreaks by end-2010. New outbreaks starting in the first 2 quarters of 2010 have been stopped within six months. However, Pakistan, Angola and Democratic Republic of Congo remain affected by uncontrolled transmission. In response, emergency polio eradication action plans were generated in early 2011. An expanding outbreak in Chad underlines the continuing risk of international spread of polio until virus transmission in the endemic countries is finally interrupted.</td>
</tr>
<tr>
<td>Polio</td>
<td>SAGE recommended, given the need for intensive, quarterly oversight of the new plan, that a specific, high-level independent advisory body be constituted by the spearheading partners of the initiative for this purpose.</td>
<td>Action</td>
<td>Apr 2010</td>
<td>Ongoing</td>
<td>In October 2010, the GPEI established a new, high-level advisory body, the ‘Independent Monitoring Board’ (IMB) for the GPEI. The IMB will meet face-to-face or by telephone/video conference on a quarterly basis to evaluate whether each of the major milestones of the GPEI Strategic Plan 2010-2012 is ‘on track’, ‘progressing but with issues of concern’ or ‘at risk for completion’. In nominating and appointing members, a process similar to that instituted for SAGE was used, with similar criteria for eligibility. Members represent appropriate expertise across the major disciplines relevant to optimizing policy and strategy for interrupting WPV transmission and managing risks. The findings and recommendations of the IMB, including the evaluation of each milestone and key corrective action plans from infected countries, will form the basis for the reports of the WHO Secretariat on polio eradication to the Executive Board and the WHA.</td>
</tr>
<tr>
<td>Polio</td>
<td>SAGE recommends that the mathematical model(s) of post-eradication risks be evaluated by the Quantitative Immunization and Vaccine Related Research Advisory Committee (QUIVER).</td>
<td>Action</td>
<td>Nov 2008</td>
<td>Ongoing</td>
<td>The existing models of post-eradication risks were subjected to detailed and comprehensive expert review during the 13-15 October 2009 meeting of the QUIVER committee, followed by specific guidance and recommendations of QUIVER, which were shared with SAGE at its October 2009 meeting. Main recommendation from QUIVER: In view of the important policy implications, QUIVER had recommended to initiate an additional, independent modeling approach. A second modeling effort is already underway, the SAGE IPV working group at its mid-March 2011 meeting, as well as by QUIVER.</td>
</tr>
<tr>
<td>Polio eradication</td>
<td>SAGE strongly recommended that the Independent Monitoring Board should meet as soon as possible.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Completed</td>
<td>The newly designated Independent Monitoring Board (IMB) for the Global Polio Eradication Initiative (GPEI) convened for its first meeting on December 21-22, 2010. The meeting was attended by three polio-infected countries previously identified by SAGE as at highest risk of missing the Strategic Plan's milestones: Pakistan, DR Congo and Angola. Main activities of the IMB at its inaugural meeting were to review progress towards implementing the GPEI's 2010-2012 Strategic Plan, reviewing the epidemiology and polio eradication emergency action plans of the three invited countries, and establishing a method of work for the IMB.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Polio eradication</td>
<td>SAGE requested that the IPV working group report on the near eradication use of trivalent OPV should be replaced with bivalent OPV by November 2011.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>This will be discussed at a 17-18 March 2011 face-to-face meeting of the IPV SAGE Working group</td>
</tr>
<tr>
<td>Prequalification of vaccines</td>
<td>SAGE urged WHO to develop appropriate capacity building tools to provide tech. support to dev. country NRAs that have limited skills to evaluate the quality component of license applications.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>Capacity building for NRAs to evaluate quality components of license applications ongoing via mentoring arrangements, facilitated by WHO, between NRAs.</td>
</tr>
<tr>
<td>Prequalification of vaccines and NRA strengthening</td>
<td>SAGE strongly endorsed work on prequalification of vaccines and NRA strengthening and stressed need to ensure work continues at high professional standards.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>Performance review of vaccines prequalification shows WHO work is on track. NRA strengthening work focusing on strategically important countries. Performance of prequalification group reported to a &quot;Prequalification Stakeholders' meeting in February 2010. WHO D-G confirms that prequalification is a high priority for the Organization. Meeting to review prequalification took place in April 2010 after discussion at the April 2010 SAGE meeting. Revised procedure for prequalification endorsed by ECBS 2010, and will come into force on January 2012.</td>
</tr>
<tr>
<td>Reports from other advisory committees on immunization</td>
<td>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 committee deliberations and to explain the relevance of its work to the broader immunization community.</td>
<td>Action</td>
<td>Nov 2006</td>
<td>Ongoing</td>
<td>A comprehensive review of the work of the ECBS is planned for 2011. The review will include (but not be restricted to) consideration of communication of ECBS outcomes.</td>
</tr>
<tr>
<td>Supplementary Immunization Activity (SIAs)</td>
<td>SAGE noted the positive impact of SIAs on routine immunization in the Western Pacific region but considers that the impact of SIAs in other Regions requires further study.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>The LSHTM has completed a study on the impact of measles SIAs on routine immunization. The results from this study were presented to SAGE as part of the presentation on feasibility of measles eradication during the November 2010 meeting.</td>
</tr>
</tbody>
</table>
### Surveillance

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations/Action item</th>
<th>Category</th>
<th>Meeting Date</th>
<th>Status</th>
<th>Comments and Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>SAGE requested to receive a report on how surveillance networks are being reinforced in countries and regions.</td>
<td>Action</td>
<td>Apr 2008</td>
<td>Ongoing</td>
<td>WHO continues to provide technical support to countries participating in the vaccine preventable invasive bacterial diseases (VP-IBD) and rotavirus surveillance networks. During 2009, 55 countries reported rotavirus data, and 47 countries reported VP-IBD data through WHO. The current critical support of GAVI for this surveillance is reflected by the fact that 34 (61%) and 34 (85%) rotavirus and VP-IBD reporting countries, respectively, received WHO financial support based on their GAVI eligibility. WHO has disseminated the global 2009 data via surveillance bulletins and its website. During 2010, data management of these networks was enhanced. WHO ROs agreed to further strive to ensure adherence to standardized case definitions and surveillance protocols. The remaining WHO Region that has not yet deployed a uniform electronic data management system to the Region’s hospital sentinel sites will do so early in 2011. During 2011, WHO plans to work towards establishing a system to allow monthly review of data and monthly feedback to ROs. WHO will also review the individual Regional VP-IBD surveillance protocols to determine their global consistency of approaches. The global laboratory network includes global reference laboratories which provide support and training to regional reference laboratories that in turn support and train national and sentinel site laboratories. During 2010, substantial investment was provided to hospital sentinel site laboratories in a one-time procurement of laboratory equipment and supplies. Conference calls are held with each RO every month, and include the Global Reference Laboratories every other call, to discuss needs and priorities for the Region. External Quality Assessment and Quality Control will be implemented for both VP-IBD and RV networks during 2011. Countries are being prioritized for WHO on-site support, based on plans to introduce vaccine and surveillance data quality. During 2011, WHO plans to assess selected sentinel sites, using assessment tools developed and finalized during 2010. In a parallel fashion, work has just begun to document the lessons learned in using this surveillance data globally around vaccine introduction decision-making. A pilot project (SURVAC) is ongoing in 3 Central African countries (CAE, CAR, DRC) and seeks to improve surveillance for VPDs, epidemic prone diseases, and other diseases of public health importance in a coordinated fashion. Implementation of epidemiology, laboratory, training, and IT activities has begun in all countries. Lessons learned from SURVAC will be applied globally, as appropriate.</td>
</tr>
<tr>
<td>Surveillance</td>
<td>SAGE supported the European Technical Advisory group of Experts (ETAGE) recommendation that the European Centre for Disease Control (ECDC) and the WHO European Regional Office work towards developing a common surveillance platform for measles and rubella data collection from Member States to avoid redundancy.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>WHO European Regional Office and ECDC have met on two separate occasions to move this recommendation forward. In October 2010, data collection for the European Union resides with EUVAC.NET. There is an ongoing handover to ECDC planned to be completed by late 2011. WHO EURO and ECDC are discussing methods for data sharing and ensuring all data elements are captured to allow for accurate and reliable monitoring towards the measles and rubella elimination goal in the Region.</td>
</tr>
<tr>
<td>Topic</td>
<td>Recommendations/Action item</td>
<td>Category</td>
<td>Meeting Date</td>
<td>Status</td>
<td>Comments and Follow up</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>The epidemiology of unimmunized children and gender-related issues</td>
<td>SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Ongoing</td>
<td>The univariate analysis of predictors of immunization that had been presented to SAGE has now been supplemented by multivariate analysis of the most strongly associated predictors. A framework to increase coverage is being drafted at WHO headquarters and would be shared with the regional offices and other stakeholders for comments. It is expected that this document will be ready by end of 2011.</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Need for feedback from WHO's regional offices and countries to determine how countries could implement SAGE recommendations.</td>
<td>Action</td>
<td>Nov 2007</td>
<td>Ongoing</td>
<td>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.</td>
</tr>
<tr>
<td>Typhoid</td>
<td>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.</td>
<td>Action</td>
<td>Nov 2007</td>
<td>Ongoing</td>
<td>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 the meantime, WHO QSS Team is close to pre-qualifying at least one ViPS vaccine very soon, and working on prequalifying others.</td>
</tr>
<tr>
<td>Unvaccinated infants</td>
<td>SAGE emphasized the need to address the persistent challenge of reaching children not currently reached by immunization services. Local level operational research was considered important for understanding and addressing these gaps. SAGE requested WHO to provide a plan on how these findings can be operationalised at local level to ensure that the 24 million children per annum currently not benefiting from routine immunization are also vaccinated.</td>
<td>Action</td>
<td>Oct 2009</td>
<td>Ongoing</td>
<td>In-depth analysis of survey data has been completed. Review of peer-reviewed and grey literature has been completed. A framework to increase coverage is being drafted at WHO headquarters and would be shared with the regional offices and other stakeholders for comments. It is expected that this document will be ready by end of 2011.</td>
</tr>
<tr>
<td>Vaccines during humanitarian crises</td>
<td>The use of vaccines during humanitarian crises will be discussed at a forthcoming SAGE meeting.</td>
<td>Action</td>
<td>Nov 2010</td>
<td>Pending</td>
<td>A SAGE Working Group on vaccination in humanitarian emergencies is being established that will prepare for a SAGE review in April 2012. A call for nominations of Working Group members has been issued.</td>
</tr>
</tbody>
</table>
SIXTY-FOURTH WORLD HEALTH ASSEMBLY

Progress reports

Report by the Secretariat

GLOBAL IMMUNIZATION VISION AND STRATEGY: Progress report and strategic direction for the 'Decade of Vaccines'

I. INTRODUCTION

This report includes a summary of the progress report on the Global Immunization Vision and Strategy (GIVS) to the Executive Board (EB 128/9) and proposes the strategic direction to achieve vaccine and immunization goals during the next "Decade of Vaccines" (DoV) 2011-2020. The WHA is invited to provide guidance for the finalization of the DoV strategy and action plan.

II. GLOBAL IMMUNIZATION PROGRESS

Routine immunization

By 2009, 109 of 193 Member States had achieved and maintained DPT3 coverage at or above 90% for the previous three years, and an additional 13 attained this level more recently. However, the failure to achieve the set targets\(^1\) in the remaining countries has resulted in over 23 million children failing to receive the required doses of primary immunization in 2009\(^2\). In addition, only 48 countries reported that all their districts had achieved the DTP3 coverage target of 80%. A recent analysis has shown that lack of services due to system weaknesses, low public awareness or fears and misconceptions about vaccines were responsible for a large proportion of children failing to access immunization services or complete their immunization schedule. The increased use of outreach services, integrated delivery of a package of interventions including immunization through Child Health Days/Weeks, and advocacy and public awareness through Regional Immunization Weeks are some of the strategies undertaken to improve community demand for vaccines and delivery of services.

Accelerated disease control initiatives

In 2010, the implementation of the new polio strategic plan requested by resolution WHA61.15 resulted in 82% decline in polio cases in 2010 compared to the same period in 2009 (232 cases in

---

\(^1\) By 2010 or earlier, countries will reach at least 90% national vaccination coverage and at least 80% vaccination coverage in every district or equivalent administrative unit.

\(^2\) Over half of these children, i.e. 11.8 million, live in two countries, namely India and Nigeria.
2010 compared with 1,255 cases in 2009, as of February 2011), including a 95% reduction in reported cases in both Nigeria (21 cases compared with 387 cases) and India (42 cases compared with 741 cases). Afghanistan has reduced case numbers by 35% (25 cases compared with 37 cases) compared to 2009. Outbreaks in West Africa and the Horn of Africa are close to being interrupted. However, challenges remain in Pakistan, where the devastating floods have complicated implementation of the strategy and facilitated the spread of poliovirus, and in Angola, the Democratic Republic of the Congo, and Chad, where poliovirus transmission is still not under control. Emergency action plans for these countries have been developed by national governments and partners with the aim of rapidly bringing transmission under control.

A report on progress towards achievement of measles control was provided to the sixty-third World Health Assembly (A63/18). Measles supplementary immunization activities (SIAs) continue to provide a platform for delivery of other child interventions; 32 millions doses of Vitamin A, and 19 million doses of deworming medicine were distributed through measles SIAs in 2010. Dedicated funding and support are urgently needed to prevent large outbreaks of measles, like those being seen in countries in Africa that had earlier achieved mortality reduction targets, and accelerate progress towards the achievements of the 2015 measles goals proposed in the report to the to the sixty-third World Health Assembly.  

Further reducing child mortality with new vaccines

The introduction of *Haemophilus influenzae* type b (Hib) vaccine in developing countries has gained traction in spite of initial delays, with 158 countries having introduced this vaccine. However, only 48% of the 2009 global birth cohort currently lives in a country with nationwide availability of Hib vaccine, as some large population countries such as China, India, Indonesia and Nigeria, have yet to introduce this vaccine as part of their national programmes.

The recent launch of the Advance Market Commitment (AMC), through the GAVI Alliance has accelerated the introduction of the pneumococcal conjugate vaccine (PCV) in the poorest countries. The vaccine has been introduced in 5 low income countries and another 11 countries are planning to introduce the vaccine in 2011. An increasing number of countries are also expected to introduce rotavirus vaccines starting in 2011. Large scale immunization campaigns with a meningococcal A conjugate vaccine, produced in India through technology transfer facilitated by PATH and WHO and financially supported by the Bill & Melinda Gates Foundation, were initiated in Burkina Faso, Mali and Niger in September 2010. Financial support for procuring this vaccine, which was made available at a price of less than US$ 0.50 per dose, for the preventive campaigns was provided by the GAVI Alliance. Human papilloma virus vaccines are used at national scale only in 26 high income countries.

Recognizing that new vaccines do not address the entirety of major public health problems such as pneumonia, diarrhoea, and cervical cancer, more comprehensive disease prevention and control strategies are being elaborated where vaccination is just one element of a more comprehensive strategy to "Protect, Prevent, and Treat" against these killer diseases.

---

3 Data available at http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
4A63/18: Global eradication of measles. Proposed interim milestones: measles routine immunization coverage >90% nationally and >80% in every district; measles incidence of <5 cases/1 000 000 population; and measles mortality reduction of 95% compared with 2000 levels
Despite recent successes in the introduction of new vaccines, high vaccine prices, weak systems and inadequate management processes remain a challenge to sustained use of these vaccines in many developing countries. Media reports, misinterpretation of data and misinformation related to adverse events following vaccination have led to delayed introduction or even suspension of the use of new vaccines in several countries. Several new initiatives to address these challenges have been initiated and are described in the following sections.

**Surveillance and monitoring**

From the inception of the Expanded Programme on Immunization (EPI) in 1974, disease surveillance and programme monitoring have been stressed as a core component. However, both need further strengthening and expansion in order to measure progress towards achieving disease control goals and facilitate the introduction of new vaccines.

Building on the successful networks for surveillance of poliomyelitis and measles, WHO is now coordinating a network of sentinel sites that is conducting surveillance of invasive bacterial diseases and rotavirus diarrhoea; this network now covers 46 low-income countries and aims to include high and middle income countries into the fold, so that standardized case-based reports available from all countries may be synthesized into a comprehensive review. Work is needed in developing countries to promote greater local ownership of surveillance sites and use of the data for decision-making. Similarly, the improved quality and accuracy of routine coverage and vaccine stock and distribution data and their regular analyses have to be prioritized in national immunization programmes.

Countries are also being supported to establish mechanisms to detect and respond to adverse events following immunization and to communicate with the public in a credible and transparent manner and to allay fears and maintain trust in the programme.

**Vaccine development and production in developing countries**

WHO continues to advise United Nations agencies on the acceptability of vaccines considered for purchase, thereby providing assurance that they comply with WHO standards for quality and safety. In 2009, 10 vaccines or vaccine combinations from 26 manufacturers were prequalified, including products from seven countries with emerging economies.\(^5\)

In order to increase the manufacturing base to include manufacturers in developing countries and facilitate adequate supply of vaccines at affordable prices, two centres of excellence have been established to support technology transfer and provide access to know-how on adjuvants and formulation, at the Netherlands Vaccine Institute, and the University of Lausanne, Switzerland, respectively. Support was provided to 9 emerging manufacturers to develop and produce influenza vaccines.

**Financial sustainability of immunization programmes**

Ownership by countries is crucial to the long-term sustainability of immunization programmes. The proportion of government funding allocated immunization programmes moderately increased in the

---

\(^5\) Brazil, Bulgaria, Cuba, India, Indonesia, Russian Federation and Senegal
period from 2000 to 2008 and a growing number of countries have a budget line item for immunization. Preliminary data from a recent analysis of national multi-year plans for immunization shows that the annual expenditure on immunization for low-income countries increased from an average of US$ 6.00 per live birth (LB) in 2000 to US$25.00/LB in 2008 and is likely to increase further to US$ 64.00/LB in order to accommodate PCV and rotavirus vaccines. In order to make this sustainable, greater efforts would be required to achieve affordable vaccine prices and promote greater investments in immunization programmes, both by the countries themselves as well as by their development partners. Establishment of pooled procurement mechanisms to achieve more favourable prices is being explored in some regions.

III GIVS FRAMEWORK (lessons learned)

GIVS was launched in 2006 as the first-ever 10-year Framework to fully realize the potential of immunization in controlling morbidity and mortality from vaccine preventable diseases. By 2010, GIVS had succeeded as a rallying point globally and was adopted by many countries as an overarching strategic framework for immunization. The global framework was used to develop regional immunization strategies and by many countries to develop comprehensive multi-year national plans for immunization. Several companion documents and action plans were developed by WHO and UNICEF in collaboration with other partner agencies to implement the strategies in the framework.

Some of the successful outcomes of GIVS include i) the development of new recommendations for routine immunization that include new vaccines and goes beyond the traditional infant age group to include children, adolescents and adults; ii) increased use of new vaccines in the developing countries, particularly with support from the GAVI Alliance; iii) the launch of the synergistic approaches to pneumonia, diarrhoea and cervical cancer control, where vaccination formed one of a package of interventions and iv) the establishment of a sentinel site surveillance networks for invasive bacterial diseases and rotavirus diarrhoea as a platform for surveillance for diseases targeted by new vaccines;

The GIVS framework has some limitations, including: i) insufficient engagement of country level policy-makers, civil society organization and professional societies in its development; ii) lack of clear benchmarks and processes for monitoring and evaluation; and iii) inadequate follow up actions to realize the vision of a world in which immunization was valued.

The experience gained from the first five years of GIVS can be applied to build on the achievements to date, to remedy the noted limitations of the GIVS framework and overcome obstacles to its implementation, and develop an even more ambitious vision for the coming decade.

IV. THE DECADE OF VACCINES, 2011-2020: A COMPREHENSIVE VENTURE TO ADVANCE IMMUNIZATION

The Decade of Vaccines (DoV) envisions a world where children, families, and communities enjoy lives free of the fear of vaccine preventable diseases. The goal of the DoV is to extend the full benefits of immunization to all people, regardless of where they live. This goal reflects the perspective that access to safe and effective vaccines is a human right that is not currently enjoyed by all people, particularly in low and middle income countries.

Achieving this goal will require full engagement of the diverse stakeholders needed to facilitate vaccine discovery, development and delivery, including industry, researchers, policy makers, the
private sector and civil society, philanthropy, donor governments, and health workers in the
countries where most vaccine-preventable diseases occur today.

The DoV builds on, learns the lessons from, and extends the fundaments and time period of the
GIVS framework. WHO, UNICEF, the Bill & Melinda Gates Foundation and other partners are
beginning a 12-month DoV Collaboration process to develop a draft Global Vaccine Action Plan for
review by the sixty-fifth World Health Assembly. Such a plan should enable greater coordination
across all stakeholder groups, outline the steps necessary to achieve the vision and goals outlined
above, and identify critical gaps that must be addressed to realize the potential of vaccines by 2020
and beyond. It will comprise four essential components:

1. Establishing and sustaining broad public and political support for the use of vaccines and the
financing of immunization services.

2. Strengthening the equitable delivery of immunization services to achieve universal coverage
of safe and effective vaccines by 2020 in order to prevent, control, eliminate or eradicate
vaccine-preventable diseases.

3. Cultivating a robust scientific enterprise to produce innovation in the discovery and
development of new and improved vaccines and associated technologies for high priority
disease targets.

4. Creating the right market incentives to ensure an adequate and reliable supply of affordable
vaccines.

Delivering Immunization in the Next Decade

This section further elaborates on the DoV Collaboration 'Delivery' workstream, based on initial
discussions carried out with stakeholders and country representatives, under the joint coordination
of WHO and UNICEF. This work stream recognizes the centrality of demand-driven, country-led
approaches and action, based on equity, responsibility and accountability in a spirit of self-reliance
and gradual self-sufficiency to achieve commonly shared global immunization goals.

The overall goal is, throughout the life course, to achieve equity in the delivery of effective and safe
immunization along with other essential health care interventions, in order to prevent, protect,
eliminate or eradicate diseases.

The DoV Delivery Strategy proposes five overarching objectives:

Objective 1: Achieve equity in the use of vaccines: reaching every community with vaccination
through complementary delivery methods that engage all appropriate health service providers in the
public, private and non-governmental sectors; include all persons at risk and not just children,
ensuring that the poorest and least-served are reached; building demand for the wider use of new
vaccines; and strengthening the efforts to eradicate polio, and eliminate measles and maternal and
neonatal tetanus.

Objective 2: Uphold immunization as a human right: creating, increasing and sustaining
community trust in immunization and awareness of this right; and focusing on underserved and
marginalized communities by shifting the current emphasis on “Reaching Every District” to
“Reaching Every Community”.

Objective 3: Seek synergies with other programmes and re-establish immunization as a key component of primary health care: putting increased emphasis on disease burden reduction; encompassing the multiplicity of interventions needed to achieve this reduction with vaccines as an entry point or a complement to other interventions; and participating in collaborative efforts to renovate and strengthen overall health systems.

Objective 4: Develop immunization systems able to meet the challenges posed by the ambitious new goals: improving systems and tools for generating evidence, monitoring programme performance and use of data for action; training, deploying and supporting adequate human resources for programme management and implementation; and building, maintaining and sustaining regular immunization procurement, delivery and effective supply systems.

Objective 5: Bolster national self reliance and partnerships: Strengthening structures and processes for countries to develop immunization policy, strategies, and best practices; promoting greater ownership, political commitment, accountability and self-reliance of immunization programmes; enabling formation of collaborative endeavours and engaging actors with a variety of expertise across different sectors; achieving sustainable immunization financing and sound financial management; and establishing national structures and enforcing processes for accountability.

V. NEXT STEPS

The DoV Collaboration through its secretariat will ensure oversight and coordination of the planning effort through working groups corresponding to each of the proposed four DoV Collaboration components. The process for developing the Global Vaccine Action Plan will include extensive consultations with Member States and also engage with a variety of stakeholders, including civil society organization, professional societies and the private sector and will provide an opportunity to develop cost estimates for implementation of the action plan.

The World Health Assembly is invited to take note of the progress report, provide guidance on the process outlined above and request that a comprehensive Global Vaccine Action Plan for the next decade be presented at its 65th session.
Technical Note
MenAfriVac™ vaccine campaigns in the African meningitis belt
Use of vaccine in pregnant and lactating women
22 November 2010

Purpose
To assess the safety of immunizing pregnant and lactating women during nationwide vaccination campaigns using the new meningococcal A conjugate vaccine, MenAfriVac™.

Background

Product label (package insert): The pregnancy section of the prescribing information for the licensed vaccine carries a caution statement: PREGNANCY AND LACTATION. Adequate human data on use during pregnancy or lactation, and adequate animal reproduction studies are not available. Meningococcal A conjugate vaccine is not recommended in pregnancy unless there is defined risk of group A meningococcal disease. Lactating women also should not be given the vaccine since it is not known whether the vaccine is excreted in human milk.

This manufacturer information is similar to that found on other meningococcal conjugate vaccines product information packages which also list these two conditions as contraindications or as precautions. If pregnant and lactating women are excluded from the planned mass campaigns in endemic areas, to vaccinate all those aged 1-29 years, between a quarter and a third of those at risk of meningitis infection in this age group will be left unvaccinated. The manufacturer did not conduct clinical studies specifically to evaluate the vaccine in pregnant women prior to licensure and the warning in the package insert is a standard precautionary statement, as applied to many other vaccine products.

As is discussed below, there are grounds for believing that the vaccine can be safely administered to pregnant and lactating women and that the vaccine is not contraindicated for use in pregnancy. The real risk of meningitis for women living in endemic areas has to be weighed against the hypothetic risk of vaccinating pregnant and lactating mothers.

Evidence summary

MenAfriVac™

Non-clinical studies
Pre-clinical developmental toxicity studies have been performed prior to licensure on early clinical formulations as well as on the commercial formulation of the vaccine. Pregnancy and lactation animal reproduction and perinatal studies have not demonstrated a risk with respect to effects on pregnancy and embryo-foetal development, parturition and post-natal development, including among lactating dams and their sucklings.
Clinical studies
MenAfriVac™ (PsA-TT) was not administered to pregnant women, an exclusion criterion in all clinical studies. However in completed studies, 14 women are known to have become pregnant shortly after administration (PsA-TT-003 study in 2-29 year-olds). The 14 pregnancies were reported 5 to 12 months after vaccination among subjects in the age group 18-29 years except for one in the age group 11-17 years. All 14 pregnancies were followed until delivery 10 to 19 months after vaccination. Except for a case of a stillborn with no congenital anomaly or birth defect, delivered 13 month after vaccination to a 26 year-old woman who had obstructed labour with a previous history of still births, all deliveries were live born children with no congenital anomaly or birth defect.

Other bacterial vaccines
Studies of vaccination with meningococcal polysaccharide vaccines during pregnancy have not documented adverse effects among either pregnant women or newborns. On the basis of these data, pregnancy has not been judged a contraindication to use of these vaccines in the United States. Similarly, no evidence exists of risk after vaccinating pregnant women with bacterial vaccines or toxoids. In addition, there is no evidence that bacterial vaccines or toxoids given to lactating women can harm a developing child and lactating is not considered as a contraindication for the administration of this type of vaccines. In an authoritative text on vaccines it is stated that meningococcal conjugate and meningococcal polysaccharide vaccines can be safely used for women at increased risk from these types of bacterial infections. Published guidelines indicate that pregnant women who are exposed to certain vaccine-preventable diseases should receive appropriate vaccines, when the risk of serious disease outweighs the theoretical risk of adverse effects on the mother or fetus. These vaccines include hepatitis B vaccine, polyvalent meningococcal conjugate and polysaccharide vaccines and parenteral typhoid vaccine. Studies of vaccination with Hib conjugate vaccine (PRP-T) during pregnancy have not documented adverse effects among either pregnant women or newborns in Africa. Lastly, the risk of developing meningococcal disease in the African meningitis belt is substantial.

Global Advisory Committee on Vaccine Safety (GACVS) recommendation
The GACVS reviewed pre-clinical and clinical data at their biannual meeting on December 2009 (first review) and on June 2010 (second review), and concluded: (1) available data do not indicate any special cause for concern with respect to the safety of the vaccine among those to whom it has been administered in clinical studies; (2) postmarketing surveillance is needed to assess the safety profile of the vaccine, including targeted studies to assess vaccine safety in pregnancy and where possible a continuation of the phased roll-out of the vaccine so that additional safety data may be accumulated through careful postmarketing surveillance.
Postmarketing surveillance protocol

Ministries of Health in the first three countries to introduce MenAfriVac™ have developed a common pharmacovigilance protocol for the detection, assessment, handling and reporting of Adverse Events Following Immunization (AEFIs), during the mass vaccination campaigns to take place in 2010-2011 in Burkina Faso, Mali and Niger. The protocol comprises a section for monitoring of pregnant women. Pregnant women who receive the vaccine will be followed. An identification sheet for these women will be completed and a register will be used to monitor these pregnant women and their infants at birth.15

Statement

The target population for this vaccine is all aged 1-29 years in areas at high risk of infection with meningococcus A. This population includes substantial numbers of women of childbearing age. Because of the risk and severity of meningococcal group A disease, vaccinating pregnant and lactating women is an important priority.

The WHO recommends that pregnant and lactating women residing in the meningitis belt receive the MenA conjugate vaccine during any stage of pregnancy or lactation. This recommendation is based on the increased risks of meningococcal disease and its complications for pregnant women residing in the meningitis belt, the protection that the MenA conjugate vaccine can provide for both pregnant and lactating women, and the track record of safety of the licensed bacterial vaccines in pregnant and lactating women.

WHO and partners are advising government health authorities in countries of the meningitis belt on the implementation of pharmacovigilance activities during and after the MenAfriVac™ vaccination campaigns in all populations, including pregnant and lactating women. As part of these activities, it is advised that communication materials be developed and that pregnancy exposure registries be implemented as a phase 4 commitment to collect health information from women who are given the vaccine when they are pregnant. No such registries will be needed for lactating women as the risk is thought to be biologically very unlikely. In addition, registries could be developed at prenatal clinics to collect health information about women and their newborns at time of delivery and to link this information to the mothers vaccination status.

1 The electronic Medicines Compendium (eMC). Datafarm 2010, United Kingdom: http://www.medicines.org.uk/emc/.
3 Data on file at Serum Institute of India Limited.


Recommendations from the 17th - 18th Task Force on Immunization (TFI) Meetings held in Addis Ababa, Ethiopia, 20th- 21st April 2010 and Ouagadougou, Burkina Faso, 3rd - 4th December 2010

During the 17th TFI meeting held from 20th to 21st April 2010 in Addis Ababa, Ethiopia, detailed discussions were held covering the following topics and key recommendations were made;

Key topics covered
1. Polio eradication in AFR
2. Reduction of un/under-immunized children in AFR
3. Introduction of the conjugate MenA vaccine
4. African Vaccination Week

Key recommendations;
1. Polio Eradication in the African Region

- The TFI commended the significant progress made in reducing the number of WPV cases in Nigeria as well as efforts to stop transmission in the Horn of Africa. Despite these encouraging results, TFI recognized that the progress made towards polio eradication was still fragile largely due to the continuing low routine immunization coverage in most African countries.
- TFI noted with great concern the continued transmission of WPV in Senegal, Mauritania and Chad, as well as the danger this poses to its neighboring countries (Niger, Nigeria, Sudan, Central African Republic and Cameroon).
- TFI also noted that in addition to low routine immunization, the continued circulation of WPV in the region was related to weak health
service infrastructure, limited resources to support immunization in these countries and sub optimal quality of SIA’s.

**TFI recommended:**

1. In order to achieve the polio eradication targets, WHO/AFRO hold high level advocacy meetings with authorities in countries that still have circulating WPV and/or are deemed to be at high risk for importing or exporting WPV. These countries are: Angola; Chad; DRC; Mauritania and Senegal. The suggested activity above should also include advocacy for improving routine immunization.

2. In order to maintain and sustain the Polio achievements, it is essential to continue high quality SIA’s (at least 2 rounds over and above planned interventions) for the next 3 years in most countries in the region. At the same time every effort should be directed towards improving and strengthening routine immunization in all the countries.

3. The example of the involvement of the political, traditional and religious leadership in Nigeria should act as a source of inspiration to other countries in the region. This experience should be documented and disseminated to other countries, in order to help them devise country specific implementation strategies within their national context.

**2. Reduction of un/under-immunized children**

- TFI noted with concern that routine immunisation coverage rates have stagnated at around 80% in the African Region for the last three years. Moreover there were still around 5.2 million DPT3 under immunized children in 2009.
- TFI also noted with concern that among the top ten countries with
large numbers of un/under immunised children, Ethiopia, Angola,
Kenya, Cameroon and Cote d’Ivoire, have recorded increased
numbers of un/under vaccinated children, in 2009 compared to 2008.
- In addition, TFI noted that Nigeria, the most populous country of the
region recorded some progress in improving routine immunization in
2009 compared to 2008 although more effort is needed to ensure
reduction of under/un immunized children.
- TFI noted that all countries of the Region especially those with large
populations will have to make considerable efforts in order to attain
the regional goal of reducing the number of un/ under immunised
children by 50% by the end of 2010 and 75% by the end of 2011.

The TFI Recommended that:

4. Conclusions of the recent literature reviews presented at the SAGE
meetings and studies conducted in countries in the African region on
the causes of un/under immunised should be urgently and widely
disseminated to member states.
5. WHO/AFRO and partners should provide technical assistance to all
countries with sub optimal performance, to perform situation analysis
by mid June 2010.
6. WHO/AFRO and partners should assist countries in putting in place
data quality verification mechanisms previously recommended by
TFI, particularly those countries reporting striking improvements in
performance.

3. Introduction of the conjugate MenA vaccine

- The TFI noted with concern that Meningitis epidemics due to
Meningococcal Serotype A continues to occur across the meningitis
belt in Africa extending from Ethiopia in Eastern Africa to Senegal in Western Africa.

- Furthermore, the TFI noted that in 2009, a total of 83,774 cases and 4,747 deaths were reported to WHO with Neisseria meningitidis serogroup A accounting for 53% of these cases.
- TFI appreciated the work of the Meningitis Vaccine Project, which has resulted in the development and evaluation of a new Men A conjugate vaccine as well as the licensing of this product in India and the ongoing WHO prequalification process.
- The TFI noted that the vaccine focuses on Meningitis Serogroup A and that available data show that it is efficacious, safe with higher immunogenicity compared to polysaccharide vaccine. The low cost of this vaccine ($0.4 per dose) was appreciated.
- The TFI acknowledged the proposed phased introduction of this vaccine in Burkina Faso targeting age groups 1-29 years and urged strengthening of pharmacovigilance in this country should be part of priority activities

**The TFI recommended that:**

7. The Men A conjugate Vaccine be urgently introduced in the first group of countries (Burkina Faso, Niger and Mali) immediately after prequalification status is obtained.
8. The Men A conjugate vaccine introduction should thereafter be accelerated in the remaining meningitis belt countries
9. WHO should support countries to strengthen epidemiological and laboratory based surveillance for bacterial meningitis in pre and post introduction phase.
10. WHO and partners should continue advocating for the transfer of production technology to vaccine manufacturers in developing countries.
4. African Vaccination Week

- The TFI acknowledged earlier recommendations on the establishment of Immunisation week in the African region.
- The TFI noted the establishment of similar initiatives in other WHO regions such as PAHO, EURO and EMRO and the pending discussion and possible resolution of the WHA on the implementation of a global immunisation week in 2011.
- TFI also recognised the potential benefit of the African Immunization Week in enhancing immunisation demand and utilisation of services in the region.
- TFI recognised the need for harmonisation and collaboration between AFRO and EMRO for conducting an all-Africa immunization week.

The TFI recommended that:

11. An all-Africa Immunization Week be established not later than the end of 2011 to serve as a platform to advocate and broaden awareness about vaccine preventable diseases and immunisation services in Africa so as to increase provision and utilisation as well as to mobilise more resource for immunisation activities.

During the 18th TFI meeting; Ouagadougou, Burkina Faso, 3rd-4th December 2010 the following key topics were discussed in detail and recommendations made:

1. Viral Hepatitis Infection Control in the African Region.
2. Interruption of Endemic & Re-established WPV Transmission in Africa
3. African Vaccination Week.
4. Reduction of un/under-immunized children by 50% by end-2010
5. MenA conjugate vaccine introduction

1. Viral Hepatitis Infection Control in the African Region
   - The TFI noted with concern that Viral hepatitis infections constitute a major global as well as regional public health problem.
   - The TFI also noted that to date efforts for the prevention and control of viral hepatitis have been fragmented;
   - The TFI acknowledged WHO AFRO efforts in developing a comprehensive strategy for viral hepatitis infection prevention and control. The document, “Strategies for the control of viral hepatitis infection in the WHO African Region” was reviewed and endorsed by TFI.

   The TFI recommended that:

   1. WHO AFRO and member states should identify appropriate strategy to integrate viral hepatitis infection control within the broader health system context.
   2. WHO AFRO and partners should initiate wide scale mobilization of financial resources within the country and among external partners to meet additional costs of HepB mono vaccine and other related costs.

2. Interruption of WPV Transmission in Africa
   - The TFI commended the progress made in Chad and the commended the progress in Nigeria as well as in the importation countries. However, the TFI noted with concern the outbreaks in 2010 in Angola and the DRC, and the confirmation of an orphan virus in Uganda linked to WPV circulation in Kenya in 2009. TFI further noted with concern the massive outbreak of wild polio virus type 1 in Congo Brazzaville affecting mostly adults.
The TFI commended the efforts to ensure high political commitment in Angola to address the outbreak and to strengthen routine immunization, but noted with concern that a similar commitment is not evident in the DRC.

The TFI acknowledged the involvement of civil societies (traditional, religious and other leaders) in the successful campaigns in Nigeria and Angola.

The TFI Recommended that:

3. AFRO pursues every effort to encourage the DRC to have the highest level of political commitment towards polio eradication, in order to stop polio transmission by 2011

4. AFRO make every effort to sustain the political commitment in Nigeria and Chad, and to continue advocacy efforts in Western Africa countries.

5. AFRO develop a document that outlines the risk factors for outbreaks, to enable better prediction of their occurrence and rapid response.

6. Civil societies be fully engaged in all countries to advocate for polio eradication in the region.

3. African Vaccination Week

- TFI noted that African Immunization Week (AIW) initiative has been discussed during the recent African Regional Meeting of the Ministers of Health; and the resolution was adopted.

- WHO AFRO organized a planning workshop in Ghana in September 2010 to elaborate the concept paper and develop tools for implementation. In addition, TFI noted plans were underway to initiate the AIW in April 2011.

- TFI noted that 38 countries in the region were already conducting child health weeks. It was expected that the AIW will complement
such activities and can be used to mobilize more resources for immunization and raise awareness on immunization.

**TFI Recommended that:**

7. In view of the short time remaining to inaugurate the AIW: WHO AFRO intensify efforts to mobilize required resources, (human, financial and logistics).

**4. Reduction of un/under-immunized children**

- TFI noted with concern that routine immunization in Africa has not improved substantially and coverage has even decreased in many countries.
- TFI also noted that among the 10 countries with largest number of immunized in the region there has been some improvement in 70% of the countries, while in 3 countries coverage has decreased.
- TFI also noted that Ethiopia is using a successful innovative approach to reach under/un immunized children

**TFI recommended;**

8. AFRO review the TFI the recommendations on routine immunization made in Harare in 2009 and implement them fully.
9. AFRO documents innovative best practices for increasing routine immunisation coverage such as the P4P/PBF, the community extension workers and other country based initiatives.
10. Strengthen the commitment to Primary Health Care and to extend the reach of services using innovative methods such as those used in Ethiopia to register and involve the community in a structured manner.
11. AFRO assist countries to link with both local and international research institutions to conduct research in the area of operational and systems to provide evidence based approach to improve service delivery.

12. Annual African Immunization Week be used to strengthen routine immunization.

5. MenA conjugate vaccine introduction
   - TFI noted with satisfaction that WHO AFRO has assisted countries with registration and licensure of MenAfriVac vaccine and has prepared a strategy for the roll out of the vaccine in the Meningitis belt countries, to generate good public health standards.
   - TFI appreciated the ongoing efforts of WHO AFRO in strengthening pharmacovigilance in Burkina Faso, Mali and Niger.
   - TFI recognized that for the vaccine to be introduced in all countries in the meningitis belt, additional financial resources are needed.

The TFI Recommended that:

13. Impact assessment for phase 1 be conducted in one country where the vaccine introduction has commenced.

14. The pharmacovigilance system established in Burkina Faso be replicated in other countries targeted for vaccine introduction in 2011.

15. Countries with support from WHO AFRO and partners mobilize financial resources to cover preventive meningitis campaigns in the meningitis belt.
The 26th meeting of EPI Regional Technical Advisory Group (RTAG) was held in Cairo on 8 July 2010, following the 26th Inter-country Meeting of National Managers of the Expanded Programme on Immunization (4 – 7 July 2010).

The meeting was opened by Dr. Jaouad Mahjour, Director, Communicable Disease Control, WHO/EMRO. Dr. Mahjour welcomed the members of the RTAG and expressed his deep appreciation to their effort in supporting immunization programme in the region. He also shed light on the importance of each of the agenda items for the ongoing regional activities and the need for direction and insight of the RTAG to move forward.

RTAG members expressed their appreciation and satisfaction with the way the 26th Inter-country Meeting of National Managers of the Expanded Programme on Immunization was organized. The Chairman of the RTAG officially commended WHO Secretariat for the way the above mentioned meeting was organized and held.

Two topics discussed during the meeting were measles elimination, regional hepatitis B reduction target and strengthening NITAG

I. Measles Elimination

The RTAG was updated on the progress in achieving measles elimination and the development in the process of the validation of measles elimination in the Region. The following was discussed:

1. Regional measles validation process:
   - WHO/EMRO developed guidelines for the validation of measles elimination. These guidelines were field tested in 5 countries: Jordan, Syria, Iran, Oman and Bahrain. The guidelines were updated using the feedback from the field testing and was shared with RTAG members before RTAG meeting
   - RTAG members were requested to provide their feedback on the guidelines before final sharing with EPI managers during Measles meeting 2010.

2. Regional measles elimination validation commission and national validation committee:
   - A proposal will be submitted to the EMRO Regional Director for the establishment of the Regional Measles Elimination Validation Commission (RVC)
• Guiding notes on establishing National Validation Committees (NVC) will be provided to the countries.

• RTAG members were requested to discuss both guidelines and provide their feedback during the meeting

It was agreed that countries are encouraged to utilize polio national certification committee (NCC), with addition of members as required, to serve as measles NVC in order to benefit from the experience and expertise of the polio NCC and to revitalize the functions and the roles of the later in countries that have been polio free for very long period. The chairman of the NITAG may also become one of the non-voting members. The EPI programme is to serve as secretariat of the NVC. Manager and the surveillance officer should both be members of the secretariat.

3. Postponement of the target date for regional measles elimination:

• The current situation of measles elimination in countries of the eastern Mediterranean Region and the impossibility to achieve the target on the specified date, 2010, were discussed. In view of the discussion of the RTAG, and taking into consideration input of the EPI managers during the EPI managers meeting, 4-7 July 2010 concerning the feasible new target date it was agreed that:
  
  o As 7 countries of the EMR are close to achieving elimination target, EMRO to undertake validation of measles elimination in any country ready for that exercise
  
  o All other countries should strive for achieving elimination soonerest possible
  
  o Postponing the target date of regional measles elimination to 2015.

• The question whether there is a need to present a technical paper to the Regional Committee (RC) in regards to postponement of the target date was brought to the attention of the RTAG members. As it was too late to bring the issue to RC Meeting of the present year, it was agreed to included postponement of the target in the RD’s report

• The financial support provided by Measles Partnership has so far was acknowledged and uncertainty about future support was brought up. The necessity of seeking other sources of funds and the importance of mobilizing funds to support Somalia and Southern Sudan, two areas lagging behind the other countries, should be given special attention.

II. Regional Hepatitis B reduction target

The RTAG was briefed on the RC resolution on Hepatitis B control target resolved October 2010. Current regional situation of chronic Hepatitis B and hepatitis B
vaccination programme was presented. The regional strategy to achieve the target that was shared with RTAG members in advance was also discussed.

The RTAG input in the following points was requested:
1. Is the regional strategy OK, can we move with sharing it with the Ministries of Health?
2. How to proceed with HepB Birth dose

1. The Regional strategy on Hepatitis B prevention and control:
   - The RTAG members agreed that the Regional Strategy for Achieving the Hepatitis B Reduction Target in the Eastern Mediterranean Region is completed and should be distributed.
   - Quality of the reported data, specially birth dose coverage, should be verified to monitor progress
   - As some countries in the region have already achieved HbS antigen prevalence lower than the target level, it was agreed to consider that the target level (<1% among under five years children by 2015) as the minimum target levels and the ultimate target should be hepatitis B elimination rather than reduction.

2. Implementation of Hepatitis B birth-dose
   - Implementation of Hepatitis B birth-dose correctly (within 24 hours of delivery) is the main concern. Since, in several countries, small proportions of the annual deliveries take place hospitals and health institutions. Therefore, reaching all infants with birth-dose seems not be a realistic option in those countries.
   - Innovative approaches are required to ensure reaching all newborns within 24 hours from delivery. Guidelines are required to be developed to provide all options and approaches to reach all infants within 24 hours of delivery.
   - All countries should strive for reaching all newborns with hepatitis B vaccine within 24 hours of birth. However, since there is substantial gain at any level of coverage with the birth dose, countries can start with deliveries in hospitals and health facilities and develop plans for expansion.
   - Social mobilization and communication in reaching all newborns cannot be more emphasized particularly in countries where the proportion of deliveries in health facilities is low. Communication strategies should aim at urging mothers to seek immunization for newborns and to create demand.

**III. Strengthening NITAG**

Based on the discussion during the NITAG session of the EPI managers meeting, 4-7 July, RTAG suggested that a half-day session should be organized for meeting of chairperson of the NITAG and RTAG members. It was also suggested that NITAG members should be more exposed to training and structured briefing sessions on NITAG
functions. A virtual forum may be established to keep NITAG members informed of new ideas and information. NITAG chairpersons need to be well and better informed to be able to make correct and appropriate decisions. Selected NITAG chairpersons may also be invited to participate in SAGE meetings as observer.
1 Welcome, Executive Session, and Approval of Outstanding Minutes

Finding a quorum of members present\(^1\), the meeting commenced at 8.30 on 30 November 2010. Mary Robinson, Chair of the GAVI Alliance Board, chaired the meeting. The meeting began in executive session to discuss the appointment of a new Chair. Dagfinn Høibraaten, Unaffiliated Board Member, did not attend this session. The Board then moved into general session at 9.51.

The Chair noted that it was a wonderful opportunity to have the meeting in Rwanda during the Mother and Child Health Week in Rwanda. She noted the success of the launch event which took place on 29 November 2010 at the Roeser Health Clinic in the Northern Province of Rwanda to launch the nationwide campaign focusing on helping communities to make more informed health decisions.

The Chair highlighted recent GAVI news, including IFFIm’s entry into the Australian bond market with the successful launch of a Kangaroo bond, and the recent drop in price of the pentavalent vaccine. She welcomed the new Board members and alternates who were attending their first Board meeting, and invited Leone Gianturco, the Governance Committee’s nominee as the Italy/Spain constituency alternate, to sit at the Board table as the constituency’s representative until his formal appointment. The Chair recognised this would be the final meeting for Anders Molin and thanked him for his time and dedication.

The Board considered approval of outstanding minutes (Doc #1 in the board pack).

 Resolution One
The GAVI Alliance Board resolved to:

- Approve the minutes of its meeting on 16-17 June 2010.

\(^1\) Board member participants are listed in Attachment A.
2 Report of the Governance Committee

Mary Robinson, Governance Committee Chair, delivered a review of committee activity since the June Board meeting (Doc# 2). She reported that the Governance Committee had met three times since the June Board meeting, focusing on the search for a new CEO and a new Chair of the Board.

She announced that the Board in its executive session unanimously appointed Mr Høybråten to serve as Board Chair for a two-year term. Mrs Robinson congratulated Mr Høybråten on his appointment, noting he has “all the qualities, complete commitment and understanding of developing countries, and is ready for the burden of time commitment.” Discussion followed:

• George W. Wellde, Jr., chair of the search committee described the process that led to the recommendation of Mr Høybråten. The search committee had been impressed by his management skills, leadership, financial management, and answers to hard questions.

• Board members expressed their gratitude to the search committee and the process it used to identify a candidate for this appointment.

• Mr Høybråten was unanimously supported by Board members and Board members’ constituencies and a number of individual expressions of goodwill and support for Mr Høybråten’s appointment were provided by members of the Board.

• Mr Høybråten thanked the Board members for their support and goodwill and pledged to put his full heart into his new post. He acknowledged the challenges ahead but also the potential good that could come from success. He reiterated his commitment to remain independent and concluded by thanking Mrs Robinson for her service.

• Finally, Mr Wellde recognised Mrs Robinson’s service to GAVI over the past decade and submitted a formal resolution, unanimously adopted by the Board, to thank her for her contribution on behalf of children and mothers.

Resolution Two

The GAVI Alliance Board resolved to:

• **Appoint** Dagfinn Høybråten as Chair of the Board with individual signatory authority as of 1 January 2011 until 31 December 2012.

  *Mr Høybråten did not participate in the above decision.*

• **Recognise** Mary Robinson, Chair of the GAVI Alliance, for her commitment to ensure all children have access to immunisation and enjoy the right to the highest attainable standard of health. Since Nelson Mandela invited her to join the Vaccine Fund in 2001, Mary Robinson has contributed her energy,
insight, and vision to bringing about a world where children have the opportunity to start life with the prospect of living a healthy life. To date, GAVI has saved more than five million lives in its first decade and has protected many others from falling ill or suffering disabilities. Through her leadership, Mary Robinson has advocated how modern development should be undertaken, how empowering women can help families reach their full potential, and that the world has a responsibility to children who do not have a voice. Mary Robinson has been their voice, reminding humanity of a right to health for every child, everywhere.

The Chair continued with the Report of the Governance Committee and presented the Committee’s nominations for seats on the Board (Doc #02). She highlighted the nomination of the representative as alternate to Minister Guillermo González González representing the Developing Country constituency as being an exception to the Guidelines on the GAVI Alliance Board Gender Balance. The Committee carefully considered this nomination and recognised in particular the communication difficulties because of different languages among the various constituents within this constituency group. The Chair noted that the Governance Committee was recommending a shorter term than would normally be the case to allow the constituency to be represented while allowing time to find a replacement alternate Board member in keeping with the Guidelines on Board Gender Balance.

The Chair reminded the Board of the Guidelines on Board Gender Balance which had been approved by the Board and asked the Board to ensure future compliance.

The Chair presented the Governance Committee recommendations for committee membership and chairs.

The Chair highlighted that Gavin McGillivray was stepping down from his role as a member of the Audit & Finance Committee. She noted that the Board wanted to express appreciation to him for his long service to GAVI.

The Chair invited Mr Høybråten to update the Board on the CEO search. Mr Høybråten reported that in August, the Board appointed a CEO search group, consisting of the Chair, Vice Chair, the Interim CEO, Mr Wellde, and a wider group of Board members as a reference group. He noted that the search group has carried on a transparent process and involved the entire reference group in every step of the process. A long list of candidates was presented to the entire reference group from Egon Zehnder, the search consultant, and the search group is working to shorten the list to a group for interview in late January 2011.

The Chair then invited Debbie Adams, Managing Director of Law & Governance, to present the Governance Committee’s recommendation to amend the By-Laws which would allow minutes to be approved through a no-objection voting procedure (Doc #02b). Ms Adams presented the recommendation of the Governance Committee and suggested that the Board consider revised wording for the amendment of the By-Laws.
After discussion it was agreed that the Governance Committee recommendation of a minimum of five business days to review draft minutes may not allow enough time and the Board agreed on providing eight business days for such review.

Resolution Three
The GAVI Alliance Board resolved to:

- **(Re)appoint** the following members of the GAVI Alliance Board with the following terms:
  - Wayne Berson as an Unaffiliated Board Member effective immediately and until 31 December 2013
  - Dwight Bush as an Unaffiliated Board Member effective immediately and until 31 December 2013
  - George W. Wellde Jr as an Unaffiliated Board Member effective immediately and until 31 December 2013
  - Flavia Bustreo as Board Member representing the World Health Organization effective immediately and until her successor is appointed and qualified
  - Anders Nordström as Board Member representing Donor Governments to succeed Anders Molin effective immediately and until 31 December 2011
  - Leone Gianturco as Alternate Board Member representing Donor Governments effective immediately and until 31 December 2011
  - Elías Antonio Guevara Ordóñez as Alternate Board Member to Minister Guillermo González González representing Developing Country Governments to succeed Nora Del Transito Orozco Chamorro effective immediately and until 31 June 2011.

- **Reappoint** the following members of the Audit and Finance Committee until the Committees are refreshed for the 2012 year:
  - Magid Al-Gunaid
  - Wayne Berson
  - Dwight Bush
  - David Crush
  - Clarisse Paolini
  - Anne Schuchat

- **(Re)appoint** the following members of the Governance Committee until the Committees are refreshed for the 2012 year:
  - Amie Batson
  - Alan Hinman
  - Dagfinn Høybråten
  - Jaime Sepulveda
  - Richard Sezibera
  - Pascal Villeneuve
  - Sian Clayden
  - George W. Wellde Jr
  - Helen Evans (non-voting).
• **Reappoint** the following members of the Investment Committee until the Committees are refreshed for the 2012 year:
  - Dwight Bush
  - Abigail Robinson
  - George W. Weilide Jr.

• **(Re)appoint** the following members of the Programme and Policy Committee until the Committees are refreshed for the 2012 year:
  - Magid Al-Gunaied
  - Joan Awunyo Akaba
  - Mickey Chopra
  - Paul Fife
  - Ashutosh Garg
  - Leone Gianturco
  - Gustavo Gonzalez-Canali
  - Nguyen Tran Hien
  - Suresh Jadhav
  - Rama Lakshminarayanan
  - Steve Landry
  - Susan McKinney
  - Jean-Marie Okwo-Bele
  - Anders Nordstrom
  - Olga Popova
  - Anne Schuchat
  - Helen Evans (non-voting)
  - Helen Rees (non-voting expert advisor)

• **(Re)appoint** the following Chairs of the Committees:
  - Wayne Berson as Chair of the Audit and Finance Committee
  - Dagfinn Høybråten as Chair of the Governance Committee
  - Jaime Sepúlveda as Vice Chair of the Governance Committee
  - George W. Weilide Jr as Chair of the Investment Committee
  - Gustavo Gonzalez-Canali as Chair of the Programme and Policy Committee

• **Appoint** the following member of the Executive Committee until the Committee is refreshed for the 2012 year:
  - Amie Batson in the seat currently occupied by Gustavo Gonzalez-Canali

• **Amend** the By-Laws of the GAVI Alliance as follows:
  - Introduce a new By-Laws section 2.7.3.3:

    The Board may approve the minutes of its meetings on a no-objection basis. On such basis, and subject to further procedures set by the Board, a motion to approve the minutes shall be deemed approved if the following conditions are met: (i) draft minutes are circulated to the Board at least once for review and comment; (ii) a period of no less than 8 business days is given for Board Members
to provide comments to the initial draft minutes (“Review Period”), (iii) Notice of a request to approve the minutes is made after the conclusion of the Review Period in writing and sent by mail to the last recorded address of each Board Member, or by email, (iv) a period of no less than 10 calendar days is given for Board Members to signal an objection in writing or by email (“Objection Period”), and (v) no objections to the motion are received by the Chair, CEO, or Secretary by the conclusion of the Objection Period.

3 Country Report
Dr Richard Sezibera, Minister of Health of Rwanda, delivered a report on his country’s progress in reaching the Millennium Development Goals. He presented trends in immunisation coverage and highlighted the GAVI contribution to immunisation services and other factors. Finally, Dr Sezibera provided information on how health workers are using technology, particularly texting to collect and transmit data.

- Many Board members commented on the quality of the presentation and the impressiveness of Rwanda’s achievements, citing the increase in immunisation coverage and decline in infant mortality. Board members praised the commitment of the Rwandan Government to health for all.

4 CEO Report
Helen Evans, Interim CEO, delivered a presentation on GAVI Alliance achievements and challenges (Doc #4). Ms Evans began with the Rwanda immunisation success story, highlighting the fact that Rwanda had one of the highest immunisation rates in the world and that Minister Sezibera has been one of immunisation’s biggest proponents.

Next, Ms Evans provided an overview of the key decisions being asked of the Board and summarised GAVI achievements to date, including over five million future deaths prevented since inception, noting that the estimate includes deaths prevented through the introduction of pneumococcal and rotavirus vaccine. She also profiled challenges GAVI faces, including the goal of raising an addition US$3.7 billion to fully fund the Alliance’s ambition to 2015, and the fact that 20 countries still have a DTP3 coverage rate of less than 70%. Finally, Ms Evans highlighted the success of awareness efforts such as World Pneumonia Day and then reported on resource needs, ending with a call for action and support. Discussion followed:

- Board members congratulated Ms Evans on her stewardship of GAVI during this interim period.

- The decline in the price of pentavalent vaccine is welcome as the funding challenge will not only be closed by donations, but also by price drops.
• Board members recognised Secretariat and partner efforts to reduce administrative costs and to continue diligence around staffing needs.

• Several positive comments were made on GAVI’s involvement with meningitis A vaccine rollout. Meningitis takes the form of rolling epidemics and not only kills and disables young people under 30 years old, but has a debilitating effect on families and the community.

• Finally, some Board members discussed their concern about the GAVI eligible countries which are screened out for new vaccines because of their low DTP3 coverage. GAVI and its partners need to ensure a strategy to focus on these countries.

5 Financial Forecast Update
Barry Greene, Managing Director, Finance and Operations presented the Financial Forecast Update (Doc #09b). He explained in detail the US$ 7.7 billion in projected cash outflows and the funding challenge of $3.7 billion for the period 2010-2015. The funding challenge had reduced by $600 million since March 2010 due to pledges of contributions received since then. He also presented several scenarios for cash inflows and what those would entail for programme support. Following discussion:

• Mr Greene confirmed that the pentavalent price reduction is not yet included in the forecast.

• The United Kingdom offered to co-host the pledging conference in London next June. France and the Bill & Melinda Gates Foundation offered to work with the UK to mobilise support for the conference.

• Paul Fife, Board member representing donor governments Norway/United Kingdom/Ireland announced that Norway was working to secure an 8% increase to its multiyear contribution.

• Anders Molin, Board member representing Netherlands/Sweden/Denmark announced that, as of January 2011, Sweden’s relationship with GAVI would transfer from SIDA to the Ministry of Foreign Affairs. He noted that the average annual contribution has been roughly 100 million SKr and that the intention was to increase this number by 50% starting in 2011.

6 Resource Mobilisation and Innovative Finance
Joelle Tanguy, Managing Director, External Relations delivered a report on GAVI’s resource mobilisation efforts and Paolo Sison, Director, Innovative Finance gave a brief overview of the work of the Innovative Finance team (Doc #06). Over the next five years, support from GAVI can help immunise 243 million children compared to 256 million children immunised in GAVI’s first 10 years. If donors sustain current levels of commitments, GAVI would face a US$ 2.5 billion funding gap. Therefore, a step-change is required by 2012 when demand may plateau at approximately US$
1.5 billion per year. Ms Tanguy pointed to the strong preference for a new “multi-year pledging system” to better align with the multiyear nature of programme commitments. She reviewed the funding scenarios presented earlier, referencing what could and, in some cases, would not be achieved given donor pledges. Discussion followed:

- There are two principal inflows that will address the funding challenge: direct contributions and innovative finance. To date, innovative financing projects have been donor driven and Board members expressed a desire to see IFFIm continue to be promoted and further funded. Further, Board members wish to see new project ideas for mobilising additional resources from the private sector. The Secretariat noted there are interesting ideas around private sector engagement but that it is difficult at this time to quantify the resources that could be generated and to determine timing.

- As part of the resource mobilisation strategy, the Board would like to see a number of messages and outcomes promoted, including:
  - Vaccine price reductions
  - A focus on the opportunity to save five million lives over the next five years;
  - A need to maintain consistency in delivery and ensure that vaccine programmes continue on pace;
  - Create and nurture political will to ensure governments continue to champion vaccination (both donor and recipient countries); and
  - Better reach and influence the tax payer with the GAVI message;
  - Increased mobilisation of resources from the private sector.

7 Report of the Executive Committee
Jaime Sepulveda, Chair of the Executive Committee delivered a report on the activities of the Committee since the Board meeting in June 2010 (Doc #07). He discussed the Committee’s decision to recommend the business plan and to call for a new round of programme applications with a deadline of 15 May 2011, noting the need to maintain momentum and confidence in GAVI. He also stressed that the financial challenge is the single most important issue facing GAVI, and the GAVI Alliance must find the right balance between optimism and prudence.

8 GAVI Alliance Strategy
Ms Evans presented the Business Plan 2011–2015 (Doc #07a–f). Since June 2010, the GAVI strategy for 2011-2015 has gone through a review process and a few amendments have been recommended by the Executive Committee. Ms Evans noted in particular that the Secretariat and partners had clearly heard the Board’s request for a flat line budget and had in fact brought in a business plan budget for 2011 that was lower than the 2010 budget. The Secretariat plans to establish a performance unit to measure performance and report on deliverables.

Ms Evans highlighted the principal risks with the business plan and drew the Board’s attention to three high risks areas, also noted by the Director of Internal Audit:
resource requirements, misuse of funds, and Secretariat capacity. She also reviewed amendments to the strategy document recommended by the Executive Committee. Discussion followed.

- Several Board members preferred the original wording for strategic goal #4 (“Shape vaccine markets”) as opposed to the suggested wording (“Shape vaccine markets for poor countries”), arguing that while the current wording may be seen as overly ambitious, the ambition serves GAVI’s interests. Furthermore, the term “poor countries” is vague. After discussion, the Board decided to leave the wording in the form agreed at the June 2010 Board meeting.

- Cristian Baeza, Board member representing the World Bank commented that there are conflicts of interest involved in moving partner organisations which have Board representation to performance-based contracting and that the World Bank had declined funding from GAVI for this reason. He requested the Governance Committee review these arrangements. It was noted that this risk had been added to the risk register.

- The Board agreed that the business plan is a living document and may therefore require changes from time to time.

Resolution Four

The GAVI Alliance Board resolved to:

- **Approve** the following revisions to the GAVI Alliance Strategy 2011 – 2015
  - Add: Operating Principle 6: “Ensuring gender equity in all areas of engagement.”
  - Amend: Strategic Goal 2, Strategic Objective 2: “Increase equity in access to services.”
  - Delete: Strategic Goal 4, Goal level indicator 2 in its entirety.
  - Delete: Strategic Goal 4: Strategic Objectives 1-4.
  - Add New: Strategic Goal 4: Strategic Objective 1: “Ensure adequate supply to meet demand.”
  - Add New: Strategic Goal 4: Strategic Objective 2: “Minimise costs of vaccines to GAVI and countries.”

- **Approve** the GAVI Alliance Business Plan 2011–2015 as described in Docs #07b and 07c

9 GAVI Alliance Business Plan Budget

Mr Greene presented the business plan’s associated budget (Doc #07g) and noted that the Audit and Finance Committee and Executive Committee had reviewed it. Mr Greene highlighted in particular that the budget represents 13% of GAVI’s total expenditure in 2011 and is a 9% reduction over the 2010 budget. Discussion followed:
• The Board noted that eleven of the nineteen staff positions being requested as part of this budget were to address two key areas of risk: resource requirements and misuse of funds. In addition, the Secretariat’s administrative costs are low compared to similar organisations, a conclusion highlighted in the evaluation.

• The Board requested an analysis on how GAVI funds multilateral partners. It was noted that a task team may be set up to examine this issue.

• Ms Evans highlighted that the business plan included a wage freeze, reduction in use of consultants, cutbacks in travel, and a move towards a strict economy regime for travel.

Resolution Five
The GAVI Alliance Board resolved to:

• Approve the GAVI Alliance Business Plan Budget as follows:
  o US$ 126 million for 2011 for programme implementation and mission support
  o US$ 1.8 million for 2011 for capital expenditure; and
  o US$ 126 million provisionally for 2012

• Request the Secretariat to present a detailed budget for 2012 to the Executive Committee for guidance and further recommendation to the Board.

10 Report of the Investment Committee Chair
George W. Wellde, Jr., Investment Committee Chair provided an overview on the capital markets environment, focusing on emerging market countries and an update on GAVI’s investment portfolio. The portfolio performed in line with expectations and exceeded its benchmark. It was noted that GAVI continues to diversify investment managers and their mandates.

11 Report of the Audit and Finance Committee Chair
Wayne Berson, Audit and Finance Committee Chair delivered a report on the activities of the Committee since the June Board meeting (Doc #09). The Committee tabled audit and tax engagement letters and recommended them for approval (Doc #09a). It was noted that there is a slight increase in fees measured in US Dollars but this is a result of depreciation of the US Dollar against the Swiss Franc.

Resolution Six
The GAVI Alliance Board resolved to:

• Appoint KPMG SA/AG as the independent auditor of the GAVI Alliance for 2010
• Appoint KPMG SA/AG to provide Swiss tax services for the GAVI Alliance for 2010
• **Appoint** KPMG LLP to provide United States tax services for the GAVI Alliance for 2010
• **Approve** the 2010 audit and tax engagement letters with KPMG SA/AG and KPMG LLP.

### 12 Risk Oversight

Cees Klumper, Director of Internal Audit delivered a report on risk management (Doc #10). He talked about the Board’s role in risk management, discussed how risk is monitored, and how identified risks are mitigated and managed. Following discussion:

- The Board recommended that brand management should be added to the risk register since the GAVI brand forms part of the basis to raise funds and fulfil the mission.

### 13 Report of the Evaluation Advisory Committee

In 2009, the Board commissioned a second evaluation of GAVI, focusing on the years 2006 to 2010.\(^2\) It was completed in September 2010 (Doc #05) and distributed to the Board. Ms Evans reported that Bernhard Schwartländer, Evaluation Advisory Committee Chair was unable at short notice, to attend the Kigali meeting. This being the case it seemed more appropriate to defer a more detailed discussion of the evaluation until the Board retreat in April 2011 when the evaluator would also be able to attend. Richard Sezibera, a member of the Evaluation Advisory Committee provided an overview of the oversight process for the evaluation, noting that the report is comprehensive and well-balanced.

### 14 Report of the Programme and Policy Committee Chair

Gustavo Gonzalez-Canali, Programme and Policy Committee (PPC) Chair updated the Board on the activities of the Committee since the June 2010 Board meeting (Doc #11). He commented on the work of the Co-financing Task Team and that a Supply Strategy Task Team intended to provide a report to the Board during 2011.

Dr Gonzalez-Canali reminded the Board that it had asked the PPC to review the indicator used to assess financial sustainability, which is included as a component in the pilot prioritisation mechanism.\(^3\) While registering the strong objection of committee member, Majid Al-Gunaid and his constituency, and acknowledging its limitations, the PPC confirmed its recommendation to the Board that general government expenditure on health as a percentage of total government expenditure continued to be most PPC members’ preferred indicator. Vice Minister Al-Gunaid confirmed to the Board his and his constituency’s continued objection to the indicator.

---

\(^2\) See Section 7 of the 2-3 June 2009 Minutes
\(^3\) See Resolution 5 in the 16-17 June 2010 Minutes
15 Health System Strengthening (HSS) Window

Carole Presern, Managing Director, Special Projects reported on the Health Systems Funding Platform, (Doc #11a-b) requesting approval on two issues: country eligibility for GAVI HSS programmes and the use of the unallocated notional amount of funds from the original HSS funding envelope for HSS programmes. As part of the report, Dr Presern updated the Board on platform activities and plans for 2011. Discussion followed.

- Different eligibility requirements are confusing to countries and excluding low-middle income countries sends the wrong message. It was agreed that GAVI should rely on the prioritisation mechanism should sufficient funds not be available.

- It would be helpful to develop indicators focusing on how funding for health systems impact immunisation goals.

- GAVI should engage more proactively with civil society in administering the HSFP.

- Given the development of the HSFP, the original window should be closed and the notional amount of US$ 179 million in that original window should be available for any programme funding.

Resolution Seven

The GAVI Alliance Board resolved to:

- **Decide** that all GAVI eligible countries should be eligible for the health system funding platform;

- **Decide** to close the original Health Systems Strengthening (HSS) window and release the notional amount of US$ 179 million that remains unallocated from that original window;

- **Decide** that the projected three-year rolling average share of expenditure on cash-based programmes within GAVI’s overall programmatic expenditure should be within the range of 15-25% of the total;

- **Request** annual projections of expenditure on cash-based programmes within GAVI’s overall programmatic expenditure to inform decision making on resource allocation and routinely report on the impact of this investment on improving immunisation;

- **Request** the Secretariat to establish mechanisms to ensure that GAVI funding through the cash-based programmes are designed to have a reasonable and demonstrable impact on immunisation programmes in the context of integrated service delivery, and that immunisation coverage is a credible outcome indicator for these activities;
- **Request** that, in light of the proposed changes to GAVI’s cash based programmes and the new resource envelope, an evaluation of the projected impact of these investments on improving immunisation programmes be conducted within two years in the context of the evaluation plan; and

- **Request** the PPC to review the prioritisation mechanism to take into account the Board’s discussion on income levels.

### 16 Incentives for Routine Immunisation Strengthening (IRIS)

Peter Hansen, Director, Monitoring & Evaluation presented the PPC recommendations on a proposed new performance-based funding window – Incentives for Routine Immunisation Strengthening (IRIS). IRIS was designed to increase immunisation coverage and equity in countries with DTP3 coverage of less than 70%.

Dr Hansen addressed the need to assess the suitability of IRIS in India and Nigeria. He then discussed the phase out of ISS and the details of the IRIS window, including the fact that IRIS grants would be comprised of both a fixed payment and a performance payment. Discussion followed.

- The Board generally welcomed the concept of a results based financing initiative, but there was concern that countries, particularly those with low immunisation coverage indicating weak systems, may find IRIS complex and difficult to implement. Also, questions were raised about where IRIS fits into GAVI’s overall cash programmes framework.

- Regarding whether or not the ISS window should continue, some Board members expressed concern over the fact that a number of countries would be excluded under IRIS if support were limited to those countries with less than 70% DTP3 coverage as recommended by the PPC. Other Board members referred to the earlier decision to allow all countries to access HSS as a mitigating factor.

- Notably, ISS is not benefitting countries with less than 70% DTP3 coverage as last year none of these countries received an ISS reward. Nevertheless, developing country representatives strongly objected to the decision to close the ISS window, on the grounds that it is an important source of support to countries.

### Resolution Eight

The GAVI Alliance Board resolved to:

- **Decide** to pilot IRIS;

- **Decide** to suspend the November 2009 decision of the Board to raise the filter to 70% thereby reestablishing the filter to 50% for DTP3 coverage for the November 2010 round of applications;
• Request the PPC to provide the Board at the retreat in April 2011 with a comprehensive approach on cash-based support to countries including a strategy for countries that are below 70% DTP3 coverage or have stagnating or declining coverage; and

• Request the PPC to define the implementation of the IRIS pilot.

17 Co-financing Policy Revisions
Santiago Cornejo, Acting Director, Country Grants and Reviews, Programme Delivery presented the PPC recommendation for a proposed revised Co-financing Policy (Doc #11d). The PPC proposed new country groupings, revised co-financing levels and process for graduating countries. Discussion followed:

• Minister Sezibera brought to the Board's attention a letter from Minister González, Board member representing Latin America and Eastern Europe expressing reservations with the co-financing policy and proposing an alternative approach.

• Board members expressed concern on sustainability for graduating countries and stressed the importance of in-country dialogue and a clear communication strategy with these countries.

• It was noted that co-financing for rotavirus vaccine, which is available in a 2 and 3 dose presentations, would be reviewed by the Supply Strategy Task Team in due course.

Resolution Nine
The GAVI Alliance Board resolved to:

• Approve the revised GAVI Alliance Co-Financing Policy as presented in Doc#11d, pages 13-15; and

• Request that the PPC review the concerns raised by Minister Guillermo González González in a letter to the Chair of the PPC and report to the Board in June 2011.

18 Accelerated Vaccine Introduction (AVI) Progress Report
Jon Pearman, Director AVI provided an update (Doc 11e). The GAVI Alliance target is that the pneumococcal vaccine is rolled out in 45 countries by 2015 and rotavirus vaccine in 33 countries – assuming no financial constraint. He highlighted that the pneumococcal vaccine supply is tight for 2011-12, but is being managed. Beyond 2013, supply appears to be solid based on indications from suppliers. Mr. Pearman ended by discussing other challenges preventing introduction of new vaccines. Discussion followed:
• The Chair noted the importance of linking AVI activities with broader advocacy messages and the GAVI replenishment.

• It was noted that AVI has created an effective platform for, and provided important lessons on, the roll out of future vaccines.

19 Update on Country Programmes
Mercy Ahun, Managing Director, Programme Delivery provided an update on country programmes. Dr Ahun noted that nineteen countries introduced pentavalent this year, the highest number in any single year. The number of children not immunised with basic vaccines (DTP3) globally has decreased by 15% from 26.7 million in 2005 to 23.2 million in 2009, but there are still challenges with large numbers of unimmunised children in GAVI eligible countries. Dr Ahun also reviewed progress on cash programmes and highlighted success in countries such as Vietnam, Cambodia and Rwanda, but pointed to challenges related to delayed implementation by certain countries or delayed disbursement by GAVI.

20 Civil Society and the GAVI Alliance
Faruque Ahmed, Board Member representing civil society, Valerie Browning, Programme Coordinator, Afar Pastorialist Development Association and Legesse Kidanne, Programme Developer presented a video on CSOs and delivered a short presentation on civil society and GAVI.

Ms Browning and Mr Kidanne thanked GAVI for its support of immunisation efforts in Ethiopia and presented a video which highlighted some of the challenges to providing immunisation in Ethiopia and how GAVI and other partners have helped to overcome those challenges. There was a concern that the Ethiopia project’s funding could be terminated; the Secretariat agreed to look into the situation.

21 Closing
The Chair concluded the meeting by giving special thanks to Minister Sezibera and his staff for all their hard work in hosting the Board meeting, for the site visits and dinner and congratulated the Board on an excellent meeting.

There being no further business, the meeting was brought to a close.

Ms Debbie Adams
Secretary to the Board
Participants

Board Member Participants
- Mary Robinson, Chair
- Jaime Sepulveda, Vice Chair
- Faruque Ahmed
- Cristian Baeza
- Amie Batson
- Wayne Berson
- Toupta Boguena
- Dwight Bush
- Paul Fife
- Ashutosh Garg
- Leone Gianturco (Alternate)*
- Gustavo Gonzalez-Canali
- Magid Al-Gunaid (Alternate)
- Saad Houry
- Dagfinn Heybráten
- Suresh Jadhav
- Anders Molin
- Jean-Marie Okwo-Bele (Alternate)
- Anne Schuchat
- Richard Sezibera
- Jean Stéphenne
- George W. Wellide Jr.
- Helen Evans (Non-voting)

Regrets
- Guillermo González González
- Trinh Quan Huan

Alternates Observing
- Agnès Binagwaho
- Sian Clayden
- Alan Hinman
- Stefan Kaufmann
- Abigail Robinson
- Rajeev Venkayya**
- Annie Vestjens

* Elected at this meeting
** Served as the eligible organisation’s voting member per Section 2.6.5 of the By-Laws

Additional Attendees

WHO
- Lidija Kamara, Partnership Coordinator
- Patrick Kadama

UNICEF
- Ibrahim El-Ziq, Chief of Immunisation, Supply Division
- Ann Ottosen, Contracts Manager, Supply Division

THE WORLD BANK
- David Crush, Senior Financial Officer, Multilateral Trusteeship and Innovative Financing

BILL & MELINDA GATES FOUNDATION
- Steve Landry, Deputy Director
- Rob Lin, Deputy Director, Global Health, FP&A
- Violaíne Mitchell, Senior Program Officer
- Nicole Bates, Senior Program Officer, Global Health Policy & Advocacy

AUSTRALIA
- Timothy Poletti, Health Adviser, Development Cooperation, AusAID
- Natalie Cohen, Director, Health and HIV Thematic Group, AusAID

CANADA
- David Stevenson, Director General, Canadian International Development Agency (CIDA)
- Zuzanna Lipa, Development Officer, Canadian International Development Agency (CIDA)

EUROPEAN COMMISSION
- José António Valente, Head of Health Sector, Unit C4, Centralised Operations for the ACP countries
FRANCE

ANGEHKA SCHRETTENBRUNNER, ADVISER TO THE MINISTRY OF ECONOMIC COOPERATION AND DEVELOPMENT (BMZ)

GERMANY

ITALY

LENÉ LØTHE, SENIOR HEALTH ADVISER, NORAD

SPAIN

MIGUEL CASADO GÓMEZ, CHIEF OF HEALTH SECTOR, PLANNING AND EVALUATION OF DEVELOPMENT POLICIES, SECRETARY OF STATE FOR INTERNATIONAL COOPERATION

SWEDEN

OSCAR EKÉUS, DESK OFFICER, MINISTRY FOR FOREIGN AFFAIRS

UNITED KINGDOM

JULIA WATSON, SENIOR HEALTH ECONOMIST, DFID

UNITED STATES OF AMERICA

SUSAN MCKINNEY, SENIOR TECHNICAL ADVISOR FOR IMMUNIZATION, USAID

CIVIL SOCIETY ORGANISATIONS

JOAN AWUNYO-AKABA, NATIONAL VICE CHAIRPERSON, COALITION OF NGOs IN HEALTH, GHANA

VALERIE BROWNING, PROGRAMME COORDINATOR, AFAR PASTORALIST DEVELOPMENT ASSOCIATION, ETHIOPIA

SABRINA BAKEERA-KITAKA, PRESIDENT, UGANDA PEDIATRICS ASSOCIATION

LEGESSE KIDANNE, PROGRAMME DIRECTOR, CONSORTIUM OF CHRISTIAN RELIEF AND DEVELOPMENT ASSOCIATIONS (CCRDA/ CORE GROUP), ETHIOPIA

VACCINE INDUSTRY - DEVELOPING COUNTRY

VACCINE INDUSTRY - INDUSTRIALISED COUNTRY

JOANNE VANDEDAEL BAUDRIHAYE, DIRECTOR, INTERNATIONAL RELATIONS, POLICIES AND PARTNERSHIPS, GSK BIOLOGICALS

OLGA POPOVA, SENIOR DIRECTOR, GOVERNMENT AND MEDICAL AFFAIRS, CRUCELL SWITZERLAND AG

JOAN BENSON, EXECUTIVE DIRECTOR, INTERNATIONAL ORGANISATIONS, MERCK

JACQUELINE KEITH, VICE PRESIDENT, INTERNATIONAL TRADE RELATIONS AND HEALTH AFFAIRS, PFIZER INC.

LYNN BODARKY, SENIOR DIRECTOR, PFIZER INC.

ISABELLE DESCHAMPS, DIRECTOR, GLOBAL IMMUNISATION POLICY, SANOFI PASTEUR

RESEARCH AND TECHNICAL HEALTH INSTITUTES

JOHN WECKER, GLOBAL PROGRAMME LEADER, VACCINE ACCESS AND DELIVERY, PATH

PHILIPPE STOECKEL, CHAIRMAN, AGENCE DE MÉDECINE PRÉVENTIVE (AMP) À L’INSTITUT PASTEUR

ALFRED DA SILVA, EXECUTIVE DIRECTOR, AGENCE DE MÉDECINE PRÉVENTIVE (AMP) À L’INSTITUT PASTEUR

ADDITIONAL OBSERVERS

LOAY AL-ASWADI, SPECIAL ADVISER TO THE MINISTER OF HEALTH, YEMEN

SEAN CARNEY, AUDIT COMMITTEE CHAIR, IFFIm BOARD

MARTA ESPELTA, PROGRAMME OFFICER, LA CAIXA FOUNDATION

4 REPRESENTED BY GUSTAVO GONZALEZ-CANALI, BOARD MEMBER

5 REPRESENTED BY LEONE GIANTURCO, ALTERNATE BOARD MEMBER

6 REPRESENTED BY SURESH JADHAV, BOARD MEMBER
Attachment A

- Alan Gillespie, Board Chair, IFFIm Board
- Tim Siegenbeek van Heukelom, Research Associate, Pacific Friends of the Global Fund, Australia
- Clifford Wurie Kamara, Senior Programme Officer, Sabin Vaccine Institute/Chair, GAVI Alliance Independent Review Committee (IRC)
- Hyunjoo Kim, Third Secretary, Development Cooperation Division, Ministry of Foreign Affairs and Trade, Republic of Korea
- Claire Mahon, Special Adviser to Mary Robinson, Board Chair
- Ian McConnell, Director, Vaccine Support Team, Clinton Health Access Initiative
- Bill Roedy, Chief Executive Officer, MTV
- Olivier Sabot, Executive Vice President, Expanded Initiatives, Clinton Health Access Initiative
- Odd-Jostein Saeter, Senior Advisor to Dagfinn Heybråten, Christian Democratic Party Stortinget
- Gina Tambini, Area Manager Family and Community Health Area, Pan American Health Organization

GAVI ALLIANCE SECRETARIAT

- Debbie Adams, Managing Director, Legal and Governance
- Geoff Adlade, Director, Advocacy and Public Policy
- Mercy Ahun, Managing Director, Programme Delivery
- Anthony Brown, Senior Legal Counsel
- Santiago Cornejo, Acting Director, Country Reviews and Grant Renewals
- Tony Dutson, Senior Director and Chief Accounting Officer, Finance
- Barry Greene, Managing Director, Finance and Operations
- Jean Gruener, Senior Administrative Assistant, Governance
- Peter Hansen, Director, Monitoring and Evaluation, Policy and Performance
- Jorn Heldrup, Senior Programme Manager, Programme Delivery
- Paul Kelly, Director, Country Programmes, Programme Delivery
- Cees Klumper, Director of Internal Audit
- Doreen Mackay, Executive Assistant to the Chief Executive Officer
- Meegan Murray-Lopez, Executive Officer
- Stephen Nurse-Findlay, Programme Officer, Governance
- Alex Palacios, Director, Special Representative to the U.S.
- Jon Pearson, Director, Accelerated Vaccine Introduction, Policy and Performance
- Carole Presern, Managing Director, Special Projects
- Jason Ray, Head, Information Systems and User Support
- Pierre Richard, IT Manager, Information Technology
- Jeffrey Rowland, Director, Media and Communications, External Relations
- Nina Schwalbe, Managing Director, Policy and Performance
- Paolo Sison, Director, Innovative Finance
- Alexandra Laheurte Sloyka, Administrative Assistant, Governance
- Joelle Tanguy, Managing Director, External Relations
- Dan Thomas, Head, Media and Communications, External Relations
- Daniel Thornton, Senior Adviser to the CEO
- Françoise Welter, Senior Administrative Assistant, Executive Office
Meeting of the Global Advisory Committee on Vaccine Safety, December 2010

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 23rd meeting in Geneva, Switzerland, in December 2010.2 The committee reviewed (i) new data related to the risk of intussusception after rotavirus vaccination, (ii) new data on the safety of pandemic influenza A (H1N1) 2009 vaccines, (iii) examined the experience of using yellow fever vaccines among HIV-positive people, and (iv) reviewed the experiences of 3 West African countries which monitor the safety of a new meningitis A conjugate vaccine.

Rotavirus vaccine and intussusception

In December 2009, WHO recommended that all infants be routinely immunized to prevent rotavirus disease, the most common cause of serious gastroenteritis among infants worldwide. Two rotavirus vaccines are available: Rotarix (manufactured by GSK Biologicals) and RotaTeq (manufactured by Merck & Co., Inc.). Because a previous rotavirus vaccine (Rotashield, manufactured by Wyeth) was associated with an increased incidence of intussusception,3 WHO recommended the routine use of the newer rotavirus vaccines.4

1 See No. 41, 1999, pp. 337–338.
2 GACVS invited additional experts to discuss evidence related to particular topics. These experts included people affiliated with the Therapeutic Goods Administration in Woden, Australia and the United States Centers for Disease Control and Prevention in Atlanta, GA, USA, on rotavirus vaccines; the Ministry of Health in Beijing, China, and University of Laval in Quebec, Canada, about pandemic influenza vaccines; and the Ministry of Health, Ouagadougou, Burkina Faso, on conjugate meningococcal A vaccine.
intussusception, an uncommon form of bowel obstruction, the risk of this adverse event was specifically evaluated in prelicensure trials of the currently licensed vaccines. In trials prior to registration no increased risk of intussusception was observed: each trial involved >70,000 participants. The trials were conducted mainly in Finland and the United States of America for RotaTeq, and in 11 countries in Latin America for Rotarix. Nonetheless, WHO has recommended that postmarketing monitoring for this adverse event should continue whenever these vaccines are introduced into new populations. On 6 and 13 August 2010, GACVS reviewed (during a teleconference) the preliminary data from post-marketing studies that suggested an increased risk of intussusception associated with Rotarix in some populations. On 22 September 2010, the United States Food and Drug Administration approved a label change for Rotarix advising practitioners of the new data on intussusception, and WHO provided an update related to the preliminary findings from those active surveillance studies.\(^1\)

Since 2007, the Pan American Health Organization has collaborated with ministries of health, the United States Centers for Disease Control and Prevention (CDC), and PATH to evaluate the potential risk of intussusception after routine use of Rotarix in Brazil and Mexico. Preliminary analyses of the surveillance data have identified 18 hospitalizations following intussusception (none of which were associated with death). These occurred within 1–7 days after administration of the first dose in Mexico; after adjusting for age, this rate is about 4–5 times higher than that occurring during later periods after vaccination. No similar excess was observed after administration of the first dose in Brazil. A case-control analysis of the data from Mexico found an association similar to that in the case-only analysis. These data from Mexico correspond to a risk of about 1–2 additional hospitalizations for intussusception per 100,000 infants vaccinated, or about 20–40 additional cases per year nationwide at current vaccination rates (the Mexican birth cohort is approximately 2 million). A similar study sponsored by GSK Biologicals in a different population in Mexico also found an increased risk of intussusception: an approximately 1.7-fold increase during the 30 days following the first dose, with a cluster of cases occurring during the first week after vaccination.

In Australia, postmarketing surveillance studies found no increased risk of intussusception among children aged ≤9 months with either vaccine; however, the study on a specifically evaluated the risk of a similar manifestation undesirable in the trials before homologation of the vaccines actually on the market. In these trials, no additional risk of UICollectionView was observed: each trial involved >70,000 participants. The trials were conducted mainly in Finland and the United States of America for RotaTeq and in 11 countries in Latin America for Rotarix. Nonetheless, WHO has recommended that postmarketing monitoring for this adverse event should continue whenever these vaccines are introduced into new populations. On 6 and 13 August 2010, GACVS reviewed (during a teleconference) the preliminary data from post-marketing studies that suggested an increased risk of intussusception associated with Rotarix in some populations. On 22 September 2010, the United States Food and Drug Administration approved a label change for Rotarix advising practitioners of the new data on intussusception, and WHO provided an update related to the preliminary findings from those active surveillance studies.\(^1\)

Depuis 2007, l’Organisation panaméricaine de la Santé a collaboré avec les ministères de la santé, les Centers for Disease Control and Prevention (CDC) des États-Unis et le PATH afin d’évaluer le risque potentiel d’invagination faisant suite à l’utilisation systématique du Rotarix au Brésil et au Mexique. Les analyses préliminaires des données de la surveillance ont permis de recenser 18 hospitalisations faisant suite à une invagination (dont aucune ne s’est soldée par un décès). Ces cas sont produits dans les 1 à 7 jours suivant l’administration de la première dose du vaccin au Mexique; après ajustement sur l’âge, ce taux est de 4 à 5 fois supérieur à celui survenant ultérieurement suite à la vaccination. Aucun accès de risque du même ordre n’a été observé après administration de la première dose au Brésil. Une analyse cas-témoins des données provenant du Mexique a permis de trouver une association comparable à celle observée dans l’analyse des seuls cas. Ces données du Mexique se traduisent par un risque d’environ 1 à 2 hospitalisations supplémentaires pour invagination pour 100,000 nourrissons vaccinés, soit environ 20 à 40 cas supplémentaires par an dans tout le pays au rythme des vaccinations actuelles (la cohorte de naissances mexicaine représente environ 2 millions de sujets). Une étude comparable parrainée par GSK Biologicals dans une population différente du Mexique a également trouvé un risque accru d’invagination, qui est multiplié par environ 1,7 au cours des 30 jours suivant la première dose, un groupe de cas survenant dans la semaine suivant la vaccination.

En Australie, les études de surveillance après commercialisation n’ont pas permis d’observer un risque accru d’invagination chez les enfants âgés de ≤9 mois suite à l’administration de...
ies found a temporal increase in intussusception with both vaccines during the first week after vaccination, although these findings were based on relatively few cases. In the United States, data from both the CDC and from an evaluation sponsored by Merck & Co., Inc., did not show evidence of an increased risk of intussusception with RotaTeq; however, the population of children under active surveillance in the United States who have received RotaTeq is not yet large enough to rule out the level of risk during the first week after vaccination that has been suggested by preliminary analyses of Rotarix in Mexico and with both vaccines in Australia.

In summary, postmarketing surveillance indicates the possibility of an increased risk of intussusception shortly after the first dose of rotavirus vaccine in some populations. If the findings are confirmed, the level of risk observed in these studies is substantially lower than the risk of 1 case/5000–10 000 in infants who received the Rotashield vaccine. The benefits of rotavirus vaccination in preventing rotavirus gastroenteritis and its consequences are substantial. For example, in Mexico it is estimated that nationwide use of Rotarix would prevent approximately 12 000 hospitalizations and 700 deaths from diarrhea each year, a benefit that greatly outweighs the potential risk of 20–40 cases of vaccine-associated intussusception found in these preliminary analyses. Additional data are being collected and analysed from Latin America and other areas. GACVS will continue to review these data as they become available.

Safety of pandemic influenza A(H1N1) 2009 vaccines

GACVS reviewed data on the safety of pandemic influenza A (H1N1) 2009 vaccines. Overall, safety information for the pandemic influenza vaccines continues to be reassuring. Since the committee’s earlier report in June 2010, data from passive surveillance from different countries has not generated any new safety concerns other than reports of narcolepsy from Finland and Sweden in August. These reports are being investigated by independent groups in Europe. Preliminary analyses of active surveillance studies for Guillain–Barré syndrome, which have evaluated both adjuvanted and unadjuvanted vaccines, suggest that there may be a small risk associated with vaccination (1–2 cases per million doses of vaccine administered). Even if this finding is confirmed, the data suggest that the risk would be much lower than that observed following the 1976 swine influenza vaccination campaign in United States; it would be similar to the risk that has been associated in some, but not all, studies with the use of seasonal influenza vaccine (an excess risk of the order of 1–2 cases/million doses). Final analyses of active surveillance studies are expected to be completed by late 2011.
Yellow fever vaccine and HIV infection

WHO recommends that all people aged ≥9 months living or travelling in areas where there is a risk of yellow fever transmission should be vaccinated. However, the vaccine is contraindicated for people who are severely immunocompromised. The benefits of mass vaccination campaigns for yellow fever are recognized in endemic countries, and millions of individuals are vaccinated against the disease every year in countries where the prevalence of HIV is 1–5% among those aged 15–49 years. In many places access to laboratory testing and other resources for diagnosing and treating HIV infection is poor, and many people with undiagnosed advanced HIV infection are likely to have received the vaccine.

At its June 2008 session, GACVS recommended that in light of the significant number of doses of yellow fever vaccine being delivered (and planned to be delivered) in preventive vaccination campaigns in endemic countries, some of which have a significant prevalence of HIV infection, appropriate follow-up studies after vaccine use should be conducted to improve the data on the safety and immunogenicity of this vaccine in individuals infected with HIV. GACVS has reviewed the latest data from the limited published literature and the preliminary reports of experience monitoring vaccination campaigns in Africa and Latin America.

Published studies on the safety and immunogenicity of yellow fever vaccines in HIV-positive people are limited to small studies and case reports, mainly of travellers with CD4 >200 cells/mm³. With the exception of 1 case of fatal meningoencephalitis, these studies did not detect any other serious adverse events following immunization (AEFI) among HIV-positive individuals. However, little evidence has accumulated about the safety of this vaccine in people with advanced HIV infection. Data about the immune response to the vaccine are scarce but show consistent immunogenicity in HIV-positive people with CD4 counts >200 cells/mm³.

In West and Central Africa, between 2007 and 2010, 10 countries undertook vaccination campaigns against yellow fever, during which about 50 million people were vaccinated. In these countries, surveillance efforts have been implemented in collaboration with national health authorities and local expert committees. Analyses of the safety data are continuing in 7 countries, but so far around 194 serious AEFI have been reported, and more than three quarters of patients have been tested for HIV. Only a few individual cases of serious AEFI have occurred in HIV-positive individuals. Similar findings have been reported from vaccination campaigns in Latin America.

Vaccin antiamaril et infection à VIH

L’OMS recommande de vacciner tous les sujets âgés de ≥9 mois vivant ou se rendant dans des zones où il y a un risque de transmission de la fièvre jaune. Toutefois, ce vaccin est contre-indiqué chez les sujets gravement immunodéprimés. Les avantages des campagnes de vaccination de masse contre la fièvre jaune sont reconnus dans les pays d’endémie et, chaque année, des millions de sujets sont vaccinés contre cette maladie dans des pays où la prévalence du VIH est de l’ordre de 1 à 5% chez les 15-49 ans. Dans bien des endroits, l’accès à des analyses de laboratoire et autres ressources pour le diagnostic et le traitement de l’infection à VIH est médiocre, et il est probable que beaucoup de gens ayant une infection à VIH avancée non diagnostiquée ont reçu le vaccin.

Lors de sa réunion de juin 2008, le GACVS avait recommandé qu’en raison du nombre important de doses de vaccin antiamaril administrées (ou dont l’administration était prévue) lors des campagnes de vaccination préventive dans les pays d’endémie, dont certains ont une prévalence importante de l’infection à VIH, on effectue des études de suivi appropriées après vaccination afin d’obtenir de meilleures données relatives à l’innocuité et à l’immunogénicité de ce vaccin chez les sujets infectés par le VIH. Le GACVS a examiné les données les plus récentes de la littérature publiée, qui est limitée, et les rapports préliminaires de la surveillance des campagnes de vaccination en Afrique et en Amérique latine.

Les études publiées relatives à l’innocuité et à l’immunogénicité des vaccins antiamarils chez les sujets VIH positifs se limitent à de petites études et à des rapports de cas concernant principalement des voyageurs ayant un taux de CD4 >200 lymphocytes/mm³. À l’exception d’un cas de méningoencéphalite mortelle, ces études n’ont décelé aucune autre manifestation postvaccinale indésirable (MPI) grave chez les sujets VIH-positifs. Cependant, peu de données relatives à l’innocuité de ce vaccin chez les sujets présentant une infection à VIH avancée ont été accumulées. Les données relatives à la réponse immunitaire au vaccin sont rares mais montrent constamment son immunogénicité chez les sujets VIH-positifs ayant une numération des CD4 >200 lymphocytes/mm³.

En Afrique de l’Ouest et en Afrique centrale, 10 pays ont entrepris entre 2007 et 2010 des campagnes de vaccination antiamarile au cours desquelles près de 50 millions de personnes ont été vaccinées. Dans ces pays, des efforts de surveillance ont été mis en œuvre en collaboration avec les autorités nationales de la santé et les comités d’experts locaux. L’analyse des données relatives à l’innocuité se poursuit dans 7 pays mais, jusqu’ici, on a enregistré environ 194 MPI graves et plus des trois quarts des patients ont subi un test de dépistage du VIH. Seuls quelques cas individuels de MPI graves se sont produits chez des sujets VIH positifs. Des résultats comparables ont été rapportés à la suite des campagnes de vaccination menées en Amérique latine.

---


---

Based on GACVS’s recommendations, the 3 countries have developed a modified postmarketing surveillance plan for the next phase of vaccine introduction in order to generate additional data on safety. The committee recognized that it would not be practical to adopt a

Meningitis A conjugate vaccine

The committee was updated on vaccine safety data relating to the introduction of MenAfriVac vaccine collected in the 3 early-adopter countries (Burkina Faso, Mali and Niger) during September 2010. The data previously presented from 7 clinical trials from 5 sites (Gambia, Ghana, India, Mali and Senegal), involving 4614 participants, did not identify any unexpected safety issues with this lyophilized meningitis A conjugate vaccine. During the initial phase, 4 districts in the 3 countries were selected for vaccine introduction. Spontaneous AEFI reporting was stimulated during preparatory training activities and supported by national AEFI review committees in all 3 countries.

A total of 215 reports of AEFI, including 34 serious adverse events, were received after 1.04 million people were vaccinated. Based on a review by national expert committees, only 1 serious AEFI (an anaphylactic reaction) was classified as related to vaccination. So far, these data do not suggest that there should be any special concern about safety. However, GACVS had concerns about the completeness of ascertainment of AEFI. Data were collected largely through existing passive surveillance systems, and could not be compared to background rates of occurrence of the conditions of interest in the same populations.

Based on GACVS’s recommendations, the 3 countries interest in the same populations. background rates of occurrence of the conditions of surveillance systems, and could not be compared to Data were collected largely through existing passive concern about safety. However, GACVS had con- these data do not suggest that there should be any spe- tion) was classified as related to vaccination. So far, this lyophilized meningitis A conjugate vaccine. During the initial phase, 4 districts in the 3 countries were selected for vaccine introduction. Spontaneous AEFI reporting was stimulated during preparatory training activities and supported by national AEFI review committees in all 3 countries.

A total of 215 reports of AEFI, including 34 serious adverse events, were received after 1.04 million people were vaccinated. Based on a review by national expert committees, only 1 serious AEFI (an anaphylactic reaction) was classified as related to vaccination. So far, these data do not suggest that there should be any special concern about safety. However, GACVS had concerns about the completeness of ascertainment of AEFI. Data were collected largely through existing passive surveillance systems, and could not be compared to background rates of occurrence of the conditions of interest in the same populations.

Based on GACVS’s recommendations, the 3 countries have developed a modified postmarketing surveillance plan for the next phase of vaccine introduction in order to generate additional data on safety. The committee recognized that it would not be practical to adopt a

Vaccin conjugué contre la méningite A

En septembre 2010, le Comité a été informé des données relatives à l’innocuité collectées dans les 3 pays qui ont introduit rapidement le MenAfriVac (le Burkina Faso, le Mali et le Niger). Les données présentées précédemment et relatives aux 7 essais cliniques réalisés dans 5 sites (Gambie, Ghana, Inde, Mali et Sénégal) portant sur 4614 participants n’ont pas permis d’identifier des problèmes d’innocuité inattendus liés à ce vaccin antiméningococcique A conjugué lyophilisé. Au cours de la phase initiale, 4 districts ont été choisis dans les 3 pays pour y introduire le vaccin. La notification spontanée des MPI a été encouragée au cours des activités de formation préparatoires et soutenue par les comités nationaux d’examen des MPI dans les 3 pays.

Suite à la vaccination de 1.04 million de personnes, un total de 215 rapports faisant état de MPI, y compris 34 manifestations indésirables graves, ont été reçus. D’après un examen réalisé par les comités d’experts nationaux, seule une MPI grave (une réaction anaphylactique) a été considérée comme liée à la vaccination. Jusqu’ici, ces données ne laissent pas à penser qu’il puisse y avoir des préoccupations particulières liées à l’innocuité de ce vaccin. Toutefois, le GACVS s’est inquiété de l’exhaustivité des vérifications faites pour les MPI. Les données ont été en grande partie collectées par le biais des systèmes de surveillance passive existants et n’ont pas pu être comparées à des taux initiaux de survenue des maladies considérées dans les mêmes populations.

En s’inspirant des recommandations du GACVS, les 3 pays ont élaboré un plan modifié de pharmacovigilance pour la phase suivante de l’introduction du vaccin de façon à obtenir des données supplémentaires concernant son innocuité. Le Comité a reconnu qu’il ne serait pas pratique d’adopter une stratégie
large-scale active surveillance approach and therefore recommended giving priority to enhancing existing surveillance systems. Active surveillance, focusing on selected syndromes of interest, will be conducted in sentinel sites that have adequate infrastructure.

The committee also addressed precautions from the package insert recommending that the vaccine should not be administered during pregnancy unless there is definite risk of group A meningococcal disease, and lactating women should not be given the vaccine since it is not known whether it is excreted in breast milk. The committee noted that this kind of precautionary statement has also been used for other inactivated vaccines, including other meningococcal conjugate vaccines, and is not based on any known risks to these groups. Given the clear benefits of the vaccine, the increased risk of disease in the geographical area and past experiences using similar vaccines in comparable conditions, GACVS supported WHO’s technical guidance that MenAfriVac should be offered to pregnant and lactating women residing in the meningitis belt during any stage of pregnancy or lactation. A plan should be developed to follow up vaccinated pregnant women in antenatal or obstetric clinics, and to monitor pregnancy outcomes by making appropriate comparisons with unvaccinated pregnant women.

GACVS highlighted the importance of developing a robust postmarketing surveillance plan for any new vaccine before it is introduced. Furthermore, GACVS emphasized the importance of considering whether to conduct studies in specific groups during the product development stage, especially those groups which may be at higher risk of disease from vaccination.

GACVS concluded that the data for MenAfriVac vaccine had identified no safety concerns regarding the use of this vaccine. However, GACVS emphasized the need for additional effective postmarketing surveillance to provide more complete information about the safety profile of the vaccine, including its effects in specific groups, especially pregnant women.

Le Comité s’est également penché sur les précautions figurant dans la notice d’emballage recommandant que ce vaccin ne soit pas administré aux femmes enceintes, sauf s’il y a un risque avéré de méningite A, ni aux femmes qui allaient puisqu’ils ignore s’il est excrété dans le lait maternel. Il a noté que ce type de formule de précaution a également été utilisé pour d’autres vaccins inactifs, notamment d’autres vaccins antiméningococ- ciques conjugués, mais qu’elle ne repose sur aucun risque connu pour ces groupes. Étant donné les avantages manifestes de ce vaccin, le risque accru de maladie dans cette zone géogra- phique et les expériences antérieures d’utilisation de vaccin comparables dans des conditions analogues, le GACVS a soutenu la recommandation technique de l’OMS suivant laquelle le MenAfriVac devrait être offert aux femmes enceintes ou qui allaient résidant dans la ceinture de la méningite, quel que soit le stade de la grossesse ou de l’allaitement. Il faudrait élaborer un plan pour assurer le suivi des femmes enceintes vaccinées dans les dispensaires de soins prénatals ou obstétricaux et suivre l’issue des grossesses en établissant des comparaisons appropriées avec des femmes enceintes non vaccinées.

La GACVS a souligné qu’il est important d’élaborer un solide plan de pharmacovigilance pour tout nouveau vaccin avant son introduction. En outre, il a insisté sur le fait qu’il est important de s’interroger sur la nécessité de mener des études dans des groupes spécifiques au stade du développement des produits, surtout dans les groupes qui pourraient être exposés à un risque accru de maladie suite à la vaccination.

Le GACVS a conclu que les données relatives au vaccin MenA- friVac n’avaient pas révélé d’inquiétudes liées à l’innocuité de ce vaccin. Cependant, il a insisté sur la nécessité d’une pharma- covigilance efficace pour obtenir des informations plus complètes concernant le profil d’innocuité du vaccin, notamment ses effets dans des groupes spécifiques et en particulier chez la femme enceinte.
Global Advisory Committee on Vaccine Safety

Statement on Fluzone and febrile seizures

24 January 2011

The U.S. Food and Drug Administration and Centers for Disease Control and Prevention have recently detected an increase in the number of reports to the Vaccine Adverse Event Reporting System (VAERS) of febrile seizures following vaccination with the trivalent inactivated influenza vaccine, Fluzone. The reported febrile seizures have mainly been seen in children younger than 2 years of age.

GACVS has been informed about this finding and notes that in the cases reported, all children recovered with no lasting effects seen. It is also noted that no increase in VAERS reports of febrile seizures in people older than 2 years of age has been detected.

Based on the information presented, GACVS concurs that further investigation is needed to clarify the nature and magnitude of any increased risk, but on the basis of the data currently available does not recommend any change to the WHO recommendations for the use of seasonal influenza vaccine (http://www.who.int/wer/2005/wer8033.pdf). GACVS will continue reviewing data related to these reports as they become available.
Global Advisory Committee on Vaccine Safety

Statement on narcolepsy and vaccination

8 February 2011

Since August 2010, following widespread use of vaccines against influenza (H1N1) 2009, cases of narcolepsy, especially in children and adolescents, have been reported from at least 12 countries. Narcolepsy is a rare sleep disorder that causes a person to fall asleep suddenly and unexpectedly. The rates reported from Sweden, Finland and Iceland have been notably higher than those from other countries. The National Institute for Health and Welfare of Finland issued a preliminary statement on 1 February 2011 following an investigation into the cases in Finland. A systematic retrospective registry-based review was conducted of all new narcolepsy cases diagnosed during 2006-2010 and cases in 2009-2010, born in 1990 or later, were reviewed using newly developed Brighton collaboration criteria for the disease. During 2009-2010 they found a higher risk of narcolepsy among those aged 4-19 years old who had received the vaccination against influenza (H1N1) 2009 compared with those who had not been vaccinated. The only pandemic vaccine used in Finland was Pandemrix, an adjuvanted influenza (H1N1) 2009 mono-ovalent vaccine manufactured by GlaxoSmithKline. Pandemrix vaccine was used in 47 countries worldwide during the 2009-2010 season. Studies are ongoing to determine if the apparent increased risk of narcolepsy reported in Sweden is higher in vaccinated persons.

The National Institute in Finland (on the advice of the Finnish National Narcolepsy Task Force) has concluded that the risk of developing narcolepsy among those vaccinated aged between 4 and 19 years is about nine times greater than those unvaccinated in the same age group, corresponding to a risk of about 1 case of narcolepsy per 12,000 vaccinated in this age group. The increased risk has not been seen in younger or older age groups. Narcolepsy is a condition that has a strong genetic linkage, being almost uniquely seen in persons who have the (HLA) DQB1*0602 genotype. Of the cases of narcolepsy tested so far in Finland (n=22), diagnosed during 2009-2010, all have that genotype. The National Institute considers it probable that the Pandemrix vaccine was a contributing factor to this observed increase, and has called for further investigation of other co-factors that may be associated with the increased risk. They consider it most likely that the Pandemrix vaccine increased the risk of narcolepsy in a joint effect in those genetically disposed with some other, still unknown, genetic and/or environmental factor. The final report from the Finnish National Narcolepsy Task Force is expected by 31 August 2011.

WHO’s Global Advisory Committee on Vaccine Safety (GACVS) reviewed this data by telephone conference on 4 February 2011. GACVS agrees
that further investigation is warranted concerning narcolepsy and vaccination against influenza (H1N1) 2009 with Pandemrix and other pandemic H1N1 vaccines. An increased risk of narcolepsy has not been observed in association with the use of any vaccines whether against influenza or other diseases in the past. Even at this stage, it does not appear that narcolepsy following vaccination against pandemic influenza is a general worldwide phenomenon and this complicates interpretation of the findings in Finland. In collaboration with a number of European Union member states, the European Centre for Disease Prevention and Control (ECDC) is currently conducting epidemiological studies of narcolepsy and pandemic influenza vaccines. The findings from these studies and others, including further investigations in Finland, may help clarify the determinants of any increased risk of narcolepsy which currently appears to be restricted to the months following vaccination and by age group and country.

GACVS will continue to monitor the situation closely and updates will be provided as further information becomes available and is assessed.
Report of the Review Committee on the Functioning of the International Health Regulations (2005) and on Pandemic Influenza A (H1N1) 2009

For discussion at the meeting of the Review Committee, 28 March 2011
INTRODUCTION

In January 2010, at its 126th session, WHO’s Executive Board welcomed the Director-General’s proposal to convene a Review Committee provided for in Chapter III of Part IX of the International Health Regulations 2005 (IHR). The Director-General’s proposal included a request for the Committee to review the experience gained in the global response to the influenza A (H1N1) 2009 pandemic, in order to inform the review of the functioning of the Regulations; to help assess and, where appropriate, to modify the ongoing response; and to strengthen preparedness for future pandemics. The Committee’s remit follows:

The assessment of the global response to the pandemic H1N1 will be conducted by the International Health Regulations Review Committee, a committee of experts with a broad mix of scientific expertise and practical experience in public health. The members are some of the leading experts in the world in their respective fields.

The International Health Regulations (IHR) is an international legal agreement that is binding on 194 States’ Parties across the globe, including all of the Member States of WHO. The basic purpose of the IHR is to help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide. In January 2010, the WHO Executive Board requested a proposal from the Director-General on how to assess the international response to the pandemic influenza, and then approved her suggestion to convene the IHR Review Committee to review both the pandemic response and the functioning of the IHR.

The pandemic H1N1 is the first Public Health Emergency of International Concern to occur since the revised IHR came into force. The IHR played a central role in the global response to the pandemic and so review of the IHR and review of the global handling of the pandemic influenza are closely related.

The IHR facilitate coordinated international action by requiring countries to report certain disease outbreaks and public health events to WHO so that global reporting of important public health events is timely and open.

The IHR were first implemented (i.e. “entered into force”) worldwide in 2007 and the Health Assembly determined that a first review of its functioning is to take place by the Sixty-third World Health Assembly in May 2010.
Objectives

- Assess the functioning of the International Health Regulations (2005);
- Assess the ongoing global response to the pandemic H1N1 (including the role of WHO); and
- Identify lessons learnt important for strengthening preparedness and response for future pandemics and public health emergencies.

Members of the Review Committee are listed at the end of this document.

METHOD OF WORK

The Review Committee conducted a major portion of its work through plenary meetings at WHO’s headquarters in Geneva. For transparency, these meetings were open to the media. The Committee heard testimony from individuals representing States Parties, National IHR Focal Points, intergovernmental organizations, nongovernmental organizations, United Nations agencies, industry, health professionals, experts, members of the media, chairs of relevant committees and the WHO Secretariat.

The full Committee and its working groups also met for deliberative sessions in Geneva, open only to members of the Committee and its immediate support staff. Further consultations took place among the support staff, the chair and working groups of the Committee by means of telephone conferences and e-mail exchange.

While operating independently, the Review Committee frequently sought information from WHO’s Secretariat, asking for clarification of issues that arose during the information-gathering and report-writing periods. WHO staff provided written responses to many questions posed by the Committee and spoke informally with Committee members. WHO provided the Committee with unfettered access to internal documents and Committee members signed non-disclosure agreements in order to review confidential legal documents.

The WHO Secretariat developed a series of briefing notes for the Committee, providing background on issues such as: the IHR; pandemic preparedness; pandemic phases; pandemic severity; pandemic vaccine; antiviral drugs; virological monitoring; disease monitoring; laboratory response; public health measures; and the Open-ended Working Group of Member States on Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits. The Committee had access to a series of studies that evaluated the functioning of Annex 2 of the IHR (i.e. the decision instrument for States Parties’ assessment and notification of public health events) as
well as progress reports on the implementation of the IHR. At the Committee’s request, the WHO Secretariat devised a matrix of the key public health functions of the IHR and identified a broad range of non-pandemic events that had been notified to WHO since the IHR came into force. The Committee selected 18 events and directed the Secretariat to prepare a summary of each event to facilitate its assessment of the public health functions of the IHR.

The Committee sought to document WHO’s role and management in response to the pandemic and to evaluate the effectiveness of the IHR. This required a thorough investigation of events and decisions in the course of the pandemic, an examination of criticisms of the Organization and an assessment of its achievements. The goal from the outset has been to identify the best ways to protect the world in the next public health emergency. Throughout its deliberations, the Committee has aimed to be thorough, systematic, open and objective. The final report will provide a full description of the evidence presented to the Committee in interviews and documents, and the Committee’s assessment and interpretation of that evidence.

**ORGANIZATION OF THE FINAL REPORT**

The final report will have three main components. The first section describes the development and functions of the IHR. It also assesses pandemic preparedness in the context of earlier infectious outbreaks, such as severe acute respiratory syndrome (SARS) and avian influenza A (H5N1), and how these historic events shaped the global response to the pandemic in 2009.

The second section includes a chronology of the events of the pandemic. It provides a snapshot of decision-making in the early days of the outbreak.

Section three assesses the public health functions of the IHR in relationship to the pandemic and other events. It describes the global response to the pandemic and evaluates how WHO and the IHR performed in light of the first Public Health Emergency of International Concern, as defined by the IHR.
BACKGROUND AND CONTEXT

The IHR establish a regime for the routine protection of public health and provide for the management of disease threats, both in countries and at their borders. They also provide a framework for coordinated and proportionate responses to significant emerging disease threats. Such threats may range from public health events affecting one or more countries to events of global public health significance. The provisions of the IHR are legally binding on States Parties and WHO. The IHR introduced a number of key innovations, including the replacement of a list of notifiable diseases with a decision instrument (Annex 2), to assist countries to determine whether an event may constitute a Public Health Emergency of International Concern. The 2009 pandemic was the first major test of the IHR.

A review of the functioning of the IHR and how successfully WHO performed in response to the pandemic requires an understanding of the context of the pandemic. The Review Committee identified five factors that framed the events and help explain what happened in the pandemic response. Expressed simply, they are:

• the core values of public health;
• the unpredictable nature of influenza;
• the threat of avian influenza A (H5N1) and how it shaped general pandemic preparedness;
• WHO’s dual role as a moral voice for health in the world and as a servant of its Member States;
• the limitations of systems that were designed to respond to a geographically focal, short-term emergency, rather than a global, sustained, long-term event.

The core values of public health shaped the response of public health leaders around the world to the pandemic. The main ethos of public health is one of prevention: to prevent disease and avert avoidable deaths. The response of WHO and many countries to the pandemic was a reflection of this mindset. This was affirmed in the sentiments expressed by many Member States to the Review Committee: in the face of uncertainty and potentially serious harm, it is better to err on the side of safety. Public health officials believe and act on this conviction. It is incumbent upon political leaders and policy-makers to understand this core value of public health and how it pervades thinking in the field.

Influenza pandemics will continue to occur, if history and science are any guide. In this sense, influenza is grossly predictable. However, exactly when, where and how severe the next influenza pandemic will be, no one can predict. Because pandemics occur infrequently, there is a tendency to
over-interpret the patterns of the past. For example, it may be tempting when considering the
pandemics of 1918, 1957, 1968 and 2009 to conclude that successive pandemics tend to decline in
severity. However, four observations are too few to support this conclusion. Research, especially on
genetic markers of the virus and on host factors, may eventually increase the accuracy of predictions,
but at present, lack of certainty is an inescapable reality when it comes to influenza. One key
implication is the importance of flexibility to accommodate unexpected and changing conditions. The
ability to take action in the face of uncertainty and to adapt rapidly to new circumstances are hallmarks
of sound public health practice and emergency management.

The response to the emergence of pandemic influenza A (H1N1) 2009 was the result of a
decade of pandemic planning, largely centred on the threat of an avian influenza A (H5N1) pandemic.
However, H5N1 and H1N1 have markedly different characteristics. H5N1 infection in humans results
in about 60% mortality among confirmed cases, yet it is only sporadically transmitted to humans and
even less often between humans. When thinking about a potential H5N1 pandemic, large numbers of
fatalities could be assumed because the virus had proved itself to be highly lethal. Since H5N1 was not
easily transmissible from human to human, suppression of an outbreak through the use of antiviral
drugs and other measures could be thought feasible. WHO’s web site has described the prospect of
severe disease in a possible pandemic, which was understandable in the context of expectations about
H5N1. But the reality of H1N1 was quite different. Because H1N1 caused illness that did not require
hospitalization in the vast majority of cases, the question of severity of the pandemic and how to
characterize it became a key challenge. As the H1N1 virus spread to several countries within days, the
possibility of rapid containment, a tenet of planning in WHO’s multi-stage response, was never really
feasible.

Another reality that shaped the response to the pandemic is the nature of WHO itself. WHO has
a dual character and mission: as a moral voice for global health, and as a servant of its Member States.
As the directing and coordinating authority on international health within the United Nations system,
WHO is well-positioned to be a champion for health as a human right. Its policy and technical
leadership can help countries cope with an array of public health concerns. At the same time, WHO is
a servant of its 193 Member States, which meet every year at the World Health Assembly in Geneva
to set policy for the Organization, approve the Organization’s budget and plans, and, through the
Assembly’s Executive Board, elect the Director-General every five years. WHO’s scientific and
technical aspirations for global health are constantly conditioned by the multiplicity of views, needs
and preferences of its Member States.
WHO's internal response capacities to health emergencies are geared towards relatively short-term, geographically focal events, a type that WHO confronts many times each year. By contrast, the pandemic required a worldwide response lasting one to two years. Before the pandemic, SARS was the only global emergency in recent decades that provided WHO with a foretaste of the demands that a pandemic might entail. However, SARS lasted but a few months and affected only about two dozen countries.

CONCLUSIONS AND RECOMMENDATIONS

With this background and context, the Review Committee offers three overarching conclusions:

Summary conclusion 1
The IHR helped make the world better prepared to cope with public health emergencies. The core national and local capacities called for in the IHR are not yet fully operational and are not now on a path to timely implementation worldwide.

Summary conclusion 2
WHO performed well in many ways during the pandemic, confronted systemic difficulties and demonstrated some shortcomings. The Committee found no evidence of malfeasance.

Summary conclusion 3
The world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public health emergency. Beyond implementation of core public health capacities called for in the IHR, global preparedness can be advanced through research, strengthened health-care delivery systems, economic development in low- and middle-income countries and improved health status.

The remainder of this document summarizes the Committee’s findings and reasoning and the recommendations that follow each conclusion.

Summary conclusion 1
The IHR helped make the world better prepared to cope with public health emergencies. The core national and local capacities called for in the IHR are not yet fully operational and are not now on a path to timely implementation worldwide.

Development of the IHR required more than a decade of complex deliberations. While the IHR are not perfect, they significantly advance the protection of global health. The Committee has focused its recommendations on how ongoing implementation of the IHR can be strengthened. The IHR seek
to balance the sovereignty of individual States Parties with the common good of the international
community, and take account of economic and social interests as well as the protection of health. The
Committee’s recommendations acknowledge these inherent tensions and focus on actions that can
enhance the shared goal of global public health security.

The Committee commends the following provisions of the IHR:

- The IHR oblige WHO to obtain expert advice on the declaration and discontinuation of
  a Public Health Emergency of International Concern.
- The IHR strongly encourage countries to provide each other with technical cooperation
  and logistical support for capacity building.
- The IHR encourage establishment of systematic approaches to surveillance, early
  warning systems and response in Member States.
- The IHR required the establishment of National IHR Focal Points to create a clear two-
  way channel of communication between WHO and Member States.
- The IHR led a number of countries to strengthen surveillance, risk assessment,
  response capacity and reporting procedures for public health risks.
- The IHR introduced a decision instrument (Annex 2) for public health action that has
  proved more flexible and useful than the list of notifiable diseases it replaced.
- The IHR require countries to share information relevant to public health risks.
- The IHR require States Parties that implement additional health measures significantly
  interfering with international traffic and trade to inform WHO about these measures,
  and to provide the public health rationale and relevant scientific information for them.

Despite these positive features of the IHR, many States Parties lack core capacities to detect,
assess and report potential health threats and are not on a path to complete their obligations for plans
and infrastructure by the 2012 deadline specified in the IHR. Continuing on the current trajectory will
not enable countries to develop these capacities and fully implement the IHR. Of the 194 States
Parties, 128, or 66%, responded to a recent WHO questionnaire on their progress. Only 58% of the
respondents reported having developed national plans to meet core capacity requirements, and as few
as 10% of reporting countries indicated that they had fully established the capacities envisaged by the
IHR. Further, as documented by external studies and a WHO questionnaire, in some countries,
National IHR Focal Points lack the authority to communicate information related to public health
emergencies to WHO in a timely manner.
The most important structural shortcoming of the IHR is the lack of enforceable sanctions. For example, if a country fails to explain why it has adopted more restrictive traffic and trade measures than those recommended by WHO, no legal consequences follow.

To remedy a number of these problems, the Committee recommends the following:

**Recommendation 1**

Accele... core capacities required by the IHR. WHO and States Parties should refine and update their strategies for implementing the capacity-building requirements of the IHR, focusing first on those countries that will have difficulty meeting the 2012 deadline for core capacities.

One possible way to support and accelerate implementation would be for WHO to enlist appropriate agencies and organizations that would be willing to provide technical assistance to help interested countries assess their needs and make the business case for investment. Making the case for investment in IHR capacity building and subsequent resource mobilization would increase the likelihood that more States Parties could come into compliance with the IHR.

**Recommendation 2**

Enhance the WHO Event Information Site. WHO should enhance its Event Information Site to make it an authoritative resource for disseminating reliable, up-to-date and readily accessible international epidemic information. States Parties should be able to rely on the Event Information Site as a primary source for such information.

**Recommendation 3**

Reinforce evidence-based decisions on traffic and trade. When States Parties implement traffic and trade measures more restrictive than those recommended by WHO, IHR Article 43 provides that the States Parties shall inform WHO of their actions. WHO should energetically seek to obtain the public health rationale and relevant scientific information, share it with other States Parties, and, where appropriate, request reconsideration, as stipulated under Article 43. WHO should convene an expert panel to review and assess the effectiveness and impact of border measures taken during the pandemic to support evidence-based guidance for future events.

**Recommendation 4**

Ensure necessary authority and resources for all National IHR Focal Points. States Parties should ensure that designated National IHR Focal Points have the authority, resources, procedures,
knowledge and training to communicate with all levels of their governments and on behalf of their governments as necessary.

Summary conclusion 2

WHO performed well in many ways during the pandemic, confronted systemic difficulties and demonstrated some shortcomings. The Committee found no evidence of malfeasance.

As noted in testimony by States Parties, WHO provided welcome leadership in coordinating the global response throughout the pandemic. WHO’s epidemic intelligence functions have strengthened in recent years as a result of the Event Management System, increases in Regional Office capacity, and the Global Outbreak Alert and Response Network.

The Committee commends the following actions by WHO and other partners:

- Development of influenza preparedness and response guidance to help inform national plans. Pandemic preparedness plans were in place in 74% of countries when the pandemic began.
- Effective partnering and interagency coordination (with the United Nations Children’s Fund and the United Nations Office for Project Services), including close cooperation with the animal health sector (the World Organisation for Animal Health, and the Food and Agriculture Organization) on technical and policy issues.
- Rapid field deployment and early guidance and assistance to affected countries.
- Timely detection, identification, initial characterization and monitoring of the pandemic (H1N1) 2009 virus through the Global Influenza Surveillance Network.
- Selection of the pandemic vaccine virus and development of the first-candidate vaccine reassortant virus within 32 days of declaration of the Public Health Emergency of International Concern.
- Vaccine seed strains and control reagents made available within a few weeks.
- Early policy recommendations on target groups and dosage of vaccines by the WHO Strategic Advisory Group of Experts (SAGE).
- Weekly collation, analysis and reporting of global epidemiological, virological and clinical surveillance data.
- Prompt appointment of an Emergency Committee with well-qualified individuals, which was convened within 48 hours of activation of IHR provisions.
- Efficient distribution of more than 3 million treatment courses of antiviral drugs to 72 countries.
• Establishment of a mechanism to help countries monitor their development of IHR core capacities.

The Committee also noted systemic difficulties that confronted WHO and some shortcomings on the part of WHO:

• The absence of a consistent, measurable and understandable depiction of severity of the pandemic. Even if the definition of a pandemic depends exclusively on spread, its degree of severity affects policy choices, personal decisions and the public interest. What is needed is a proper assessment of severity at national and sub-national levels. These data would inform WHO's analysis of the global situation as it evolves, allowing WHO to provide timely information to Member States. The Committee does, however, recognize that characterization of severity is complex and difficult to operationalize.

• Inadequately dispelling confusion about the definition of a pandemic. One online WHO document described pandemics as causing “enormous numbers of deaths and illness”, while the official definition of a pandemic was based only on the degree of spread. When, without notice or explanation, WHO altered some of its online documents to be more consistent with its intended definition of a pandemic, the Organization invited suspicion of a surreptitious shift in definition rather than an effort to make its descriptions of a pandemic more precise and consistent. Reluctance to acknowledge its part in allowing misunderstanding of the intended definition fuelled suspicion of the Organization.

• A pandemic phase structure that was needlessly complex. The multi-phase structure contains more stages than differentiated responses. Defined phases leading to a pandemic are more useful for planning purposes than for operational management.

• Weekly requests for specific data were overwhelming to some countries, particularly those with limited epidemiological and laboratory capacity. Country officials were not always convinced the data they submitted were being analysed and used, particularly as the epidemic progressed. Continued counting of cases yielded less useful information than would have been provided by rates of hospitalization, complications and death in countries affected early on in the pandemic.

• The decision to keep confidential the identities of Emergency Committee members. Although confidentiality represented an understandable effort to protect the members from external pressures, this paradoxically fed suspicions that the Organization had something to hide. While the decision was consistent with WHO practices for other
expert committees, whose identities are normally divulged only at the end of what is often a one-day consultation, this practice was not well-suited to a Committee whose service would extend over many months.

• Lack of a sufficiently robust, systematic and open set of procedures for disclosing, recognizing and managing conflicts of interest among expert advisers. In particular, potential conflicts of interest among Emergency Committee members were not managed in a timely fashion by WHO. Five members of the Emergency Committee and an Adviser to the Emergency Committee declared potential conflicts of interest. None of these were determined sufficiently important to merit the members’ exclusion from the Emergency Committee. The relationships in question were published, along with the names of the members of the Emergency Committee, when the pandemic was declared over on 10 August 2010. Before this information was published; however, assumptions about potential ties between Emergency Committee members and industry led some to suspect wrongdoing. The Review Committee recognizes that WHO is taking steps to improve its management of conflicts of interest, even as this review has proceeded.

• At a critical point of decision-making about the pandemic (moving from Phase 4 to 5), conferring with only a subset of the Emergency Committee rather than inviting input from the full Emergency Committee.

• The decision to diminish proactive communication with the media after declaring Phase 6 (for example, by discontinuing routine press conferences focused on the evolving pandemic) was ill- advised.

• Failure to acknowledge legitimate reasons for some criticism, in particular, inconsistent descriptions of a pandemic, or the lack of timely disclosure of relationships potentially constituting a conflict of interest among experts who advised on plans and response to the pandemic. In such instances, WHO may have inadvertently contributed to confusion and suspicion.

• Responding with insufficient vigour to criticisms that questioned the integrity of the Organization.

• Despite the ultimate deployment of 78 million doses of pandemic influenza vaccine to 77 countries, numerous systemic difficulties impeded WHO’s ability to achieve a timely distribution of donated vaccines. Negotiations over legal agreements with manufacturers were protracted and in some cases unsuccessful. Excessive complexity in donor and recipient agreements hindered timely execution. Obtaining regulatory
approvals, dealing with liability concerns over vaccine used in recipient countries, assuring maintenance of the cold chain throughout vaccine distribution and securing plans for local vaccine administration added to the delays. These difficulties proved daunting in the midst of a pandemic; some could have been reduced by more concerted preparation and arrangements in advance of a pandemic.

- Lack of timely guidance in all official languages of WHO.
- Lack of a cohesive, overarching set of procedures and priorities for publishing consistent and timely technical guidance resulted in a multiplicity of technical units within the Organization individually generating an unmanageable number of documents.

Critics assert that WHO vastly overstated the seriousness of the pandemic. However, reasonable criticism can be based only on what was known at the time and not on what was later learnt. The Committee found that evidence from early outbreaks led many experts at WHO and elsewhere to anticipate a potentially more severe pandemic than subsequently occurred. The degree of severity of the pandemic was very uncertain throughout the summer of 2009, well past the time, for example, when countries would have needed to place orders for vaccine. An observational study of 899 patients hospitalized in Mexico between late March and 1 June 2009, showed that pandemic (H1N1) 2009 disproportionately affected young people. Fifty-eight patients (6.5% of those hospitalized) became critically ill, with complications including severe acute respiratory distress syndrome and shock. Among those who became critically ill, the mortality rate was 41% (1). These statistics were alarming. Even a reported mortality rate of one third that level among critically ill patients in Canada was worrisome (2). In August 2009, the President’s Council of Advisors on Science and Technology in the United States of America released a report positing a possible scenario of 30 000–90 000 deaths from pandemic (H1N1) 2009 in the United States alone (3). The mid-point and upper level of this scenario turned out to be five times higher than the post-pandemic estimates of the actual number of deaths (4). Even so, 87% of deaths occurred in those under age 65, with the risk of death among children and working adults seven times and 12 times greater, respectively, than during typical seasonal influenza (4).

Some commentators accused WHO of rushing to announce Phase 6 and suggested the reason was to enrich vaccine manufacturers, some of whose advance-purchase agreements would be triggered by the declaration of Phase 6. Far from accelerating the declaration of Phase 6, WHO delayed declaration until evidence of sustained community spread in multiple regions of the world was undeniably occurring. As far as the Review Committee can determine, no critic of WHO has produced
any direct evidence of commercial influence on decision-making. In its interviews with staff and advisory committee members, including the Strategic Advisory Group of Experts and the Emergency Committee, and with representatives of industry, and through its review of internal and external documents, the Review Committee found no evidence of attempted or actual influence by commercial interests on advice given to or decisions made by WHO. In the Committee’s view, the inference by some critics that invisible commercial influences must account for WHO’s actions ignores the power of the core public health ethos to prevent disease and save lives.

The Review Committee offers the following recommendations:

**Recommendation 5**

**Strengthen WHO’s internal capacity for sustained response.** WHO should strengthen its internal capacity to respond to a sustained Public Health Emergency of International Concern, such as a pandemic, identifying the skills, resources and internal arrangements to support a response that extends beyond a few months. Among the internal arrangements that WHO should reinforce are:

- Identify the skills, resources and adjustments needed for WHO to carry out its role in coordination and global support.
- Establish an internal, trained, multi-disciplinary staff group who will be automatically released from their normal duties for an unspecified duration, with a relief rotation after a designated interval.
- Ensure a 24/7 capacity to meet the personal needs for accommodation, meals, transportation and childcare of WHO staff enlisted in a sustained emergency response.
- Establish an event management structure that could be maintained throughout a future pandemic or other sustained global public health emergency.

**Recommendation 6**

**Improve practices for appointment of an Emergency Committee.** WHO should adopt policies, standards and procedures for the appointment and management of an Emergency Committee that assure an appropriate spectrum of expertise on the committee, inclusive consultation and transparency with respect to freedom from conflicts of interest.

- As provided for in Article 48 of the IHR, WHO should appoint an Emergency Committee with the spectrum of expertise appropriate for each event. For an influenza pandemic, this expertise includes virology, laboratory assessment, epidemiology, public health field and leadership experience, risk assessment and risk communication.
• To ensure that the full range of views is presented, WHO should invite all members of an Emergency Committee to participate in all of its major deliberations.

• WHO should clarify its standards and adopt more transparent procedures for the appointment of members of expert committees, such as the Emergency Committee, with respect to potential conflicts of interest. The identity and relevant background, experience and relationships of Emergency Committee members should be publicly disclosed at the time of their proposed appointment, with an opportunity for public comment. WHO should have clear standards for determining when a conflict of interest exists that warrants disqualifying an individual, and have clear procedures to determine when and on what basis exceptions may be made to obtain necessary expertise or balance. The Review Committee appreciates the need for expert consultations to be held in confidence so that the Director-General will have the benefit of candid discussion and advice. The desirability of confidential consultation heightens the burden of transparency on standards for appointment.

• As part of a more proactive and rigorous approach to managing conflicts of interest, WHO should appoint a designated ethics officer.

**Recommendation 7**

**Revise pandemic preparedness guidance.** WHO should revise its Pandemic Preparedness Guidance in order to: simplify the phase structure (one possible paradigm would include only three phases – baseline, alert phase, pandemic); emphasize a risk-based approach to enable a more flexible response to different scenarios; and include further guidance on risk assessment.

**Recommendation 8**

**Develop and apply measures to assess severity.** WHO should develop and apply measures that can be used to assess the severity of every influenza epidemic. By applying, evaluating and refining tools to measure severity every year, WHO and Member States can be better prepared to assess severity in the next pandemic. Assessing severity does not require altering the definition of a pandemic to depend on anything other than the degree of spread. Rather, while not part of the definition of a pandemic, measured and projected severity are key components of decision-making in the face of a pandemic.

The Committee recognizes that estimating severity is especially difficult in the early phase of an outbreak, that severity typically varies by place and over time, and that severity has multiple dimensions (deaths, hospitalizations and illness, with each varying by age and other attributes, such as pre-existing health conditions and access to care; burden on a health system; and social and economic...
factors). Descriptive terms used to characterize severity, such as mild, moderate and severe, should be quantitatively defined in future WHO guidelines so that they may be used consistently by different observers and in different settings. The Committee urges consideration of adaptive measures that would move as rapidly as possible from early counts of cases, hospitalizations and deaths to population-based rates. Severity should be assessed as early as possible during a pandemic and continually re-assessed as the pandemic evolves and new information becomes available. Severity might be assessed using a basket of indicators in a pre-agreed minimum data set (e.g. hospitalization rates, mortality data, identification of vulnerable populations and an assessment of the impact on health systems). Estimates of severity should be accompanied by expressions of confidence or uncertainty around the estimates.

**Recommendation 9**

**Streamline management of guidance documents.** WHO needs a strategy and document management system to cope with the development, clearance, translation and dissemination of guidance and other technical documents in a timely and consistent way during a public health emergency. Interim guidance should be revised as data become available. When feasible, if the guidelines have potential policy implications, WHO should make every effort to consult with Member States.

**Recommendation 10**

**Develop and implement a strategic, organization-wide communications policy.** WHO should develop an organization-wide communications policy and a strategic approach to improve routine and emergency communications. A strategic approach entails matching the content, form and style of communication with selected media, timing and frequency in order to reach the intended audience and serve the intended purpose. WHO should be prepared to sustain active, long-term communications outreach when circumstances require, to acknowledge mistakes and to respond professionally and vigorously to unwarranted criticisms. Web publishing procedures should be clarified so that changes in web pages can be historically tracked and archived. WHO should invest in a robust social media presence for rapid communication to a wider, more diverse audience.
Recommendation 11

Set up advance agreements for vaccine distribution and delivery. In concert with efforts by Member States, and building on existing vaccine distribution systems, WHO should set up advance agreements with appropriate agencies and authorities in Member States, vaccine manufacturers and other relevant parties that would facilitate approval and delivery of pandemic vaccines to low-resource countries, to increase equity in supply and support advance planning for administration of vaccines.

Summary conclusion 3

The world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained, and threatening public health emergency. Beyond implementation of core public health capacities called for in the IHR, global preparedness can be advanced through research, strengthened health-care delivery systems, economic development in low and middle-income countries and improved health status.

Despite the progress that the IHR represent and WHO’s success in mobilizing contributions from the global community, the unavoidable reality is that tens of millions of people would be at risk of dying in a severe global pandemic. Unless this fundamental gap between global need and global capacity is closed, we invite future catastrophe.

Beyond the specific measures recommended above to complete implementation of the IHR provisions and improve the functions of WHO, the world can be better prepared for the next public health emergency through advance commitment by Member States acting individually and collectively with WHO.

The Review Committee offers the following recommendations:

Recommendation 12

Establish a more extensive global, public health reserve corps. Member States, in concert with WHO, should establish a more extensive global reserve corps of experts and public health professionals to be mobilized as part of a sustained response to a global health emergency and deployed for service in countries that request such assistance. The size, composition and governing rules for activating and deploying the Global Health Emergency Corps should be developed through consultation and mutual agreement among the Member States and WHO. The number and particular skills of the experts deployed will depend on specific characteristics of the emergency to which the corps is responding. This corps would significantly expand the current Global Outbreak and Alert
Response Network by strengthening its composition, resources and capacity, with a view towards better support for sustained responses to public health emergencies.

At present, WHO’s capacity to prepare and respond in a sustained way to any public health emergency is severely limited by chronic funding shortfalls, compounded by restrictions on the use of funds from Member States, partners and other donors. Mindful of concerns about efficiency and accountability that motivate some of the restrictions, the Committee concludes that the establishment of a contingency fund outside of WHO, but available for deployment by WHO at the time of a public health emergency, will be a prudent step to assure an immediate and effective global response.

**Recommendation 13**

Create a contingency fund for public health emergencies. Member States should establish a public health emergency fund of at least US$ 100 million, to be held in trust at an institution such as the World Bank. The fund, which would support surge capacity, not the purchase of materials, would be released in part or whole during a declared Public Health Emergency of International Concern, based on approval of a plan for expenditures and accountability submitted by WHO. The precise conditions for use of the fund should be negotiated among the Member States in consultation with WHO.

The Review Committee commends the effort by Member States to reach agreement on virus sharing and vaccine distribution. The Review Committee believes that success will depend on a mutual expectation of proportionate, balanced benefit and contribution by all stakeholders. An agreement that is one-sided or that expects contribution without benefit, or vice versa, will be neither acceptable nor sustainable. The Review Committee also believes that obligations and benefits not linked to a legal framework are unlikely to last.

**Recommendation 14**

Reach agreement on sharing of viruses and access to vaccines. The Review Committee urges Member States and WHO to conclude negotiations under the Open-ended Working Group of Member States on Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits. A successful conclusion to this negotiation will lead to wider availability of vaccines and greater equity in the face of the next pandemic, as well as continued timely sharing of influenza viruses.

The Review Committee offers the following elements for consideration as part of an acceptable agreement.
Measures to expand global influenza vaccine production capacity:

• WHO should continue its practice of working with public health laboratories to make seed vaccine strains widely available to all vaccine manufacturers.

• In so far as it is consistent with national priorities, risk assessments and resources, the Review Committee urges countries to immunize their populations yearly against seasonal influenza. This can reduce the burden of disease, add to widespread local production, distribution and delivery experience, and support increased global capacity for vaccine production. More generally, experience with comprehensive programmes during seasonal influenza (in such areas as surveillance, communication, professional and public education, health protection measures and pharmaceuticals) provides valuable preparation in advance of a major pandemic.

• The Committee urges countries to strengthen their capacity to receive, store, distribute and administer vaccines. Technological advances that reduce reliance on a cold chain and otherwise simplify administration will streamline these processes.

• The Committee urges countries to aid the transfer of technologies for vaccine and adjuvant production in parts of the world currently lacking this capacity through established programmes such as the Global Pandemic Influenza Action Plan to Increase Vaccine Supply (GAP).

Measures to increase access, affordability and deployment of pandemic vaccine:

• All vaccine manufacturers should commit to a contribution of 10% of pandemic influenza vaccine from each production run to a global redistribution pool. WHO should be responsible for managing allocations from this pool based on advice from a consultative committee.

• Increased access to vaccines and antiviral drugs can be achieved through advance agreements between industry, WHO and countries. These agreements should be negotiated without regard to virus subtype, for a specified period of time (e.g. three to five years), and should be regularly reviewed and renewed.

• Other measures that may promote greater and more equitable access to vaccine include differential pricing, direct economic aid to low-resource countries and additional donations of vaccine from purchasing countries or manufacturers.

• Countries that receive donated vaccine should adhere to the same practices of releasing and indemnifying manufacturers from certain legal liabilities as any purchaser of the vaccine.
Measures to detect and promptly identify potential pandemic influenza viruses:

- Every Member State should commit to share promptly with WHO collaborating laboratories any biological specimens and viral isolates that may be related to a new or emerging influenza virus in human or animal populations.

The world’s capacity to prevent and limit a severe pandemic is constrained by many factors: predominant reliance on vaccine production technology that is little changed in 60 years; the need to match vaccine to particular viral strains; the inability to predict which influenza viruses will be dangerous to human health; uncertainty about the effectiveness of many pharmaceutical and public health measures; the lack of field-based, rapid, affordable, highly sensitive and specific diagnostic tests; and limitations of infrastructure, resources and capacities in many countries. Also needed are improved knowledge of and practical strategies for implementing public health and personal protective measures, such as hand washing, respiratory etiquette, isolation and social distancing.

Some of these limitations can be reduced over time through national and international research. Further, the results of research on personal and public health protective measures may apply to any emerging public health threat, especially when few or no drugs or vaccines exist. Because assessment of public health measures typically must occur in real time in the midst of an outbreak, it is crucial to design and prepare research protocols and plans in advance. Beyond research advances, global resilience depends on host and environmental factors, so that improving health status, promoting economic development and strengthening health systems can mitigate the impact of a future pandemic virus.

**Recommendation 15**

**Pursue a comprehensive influenza research programme.** Member States, individually and in cooperation with one another, and WHO should pursue a comprehensive influenza research programme. Key research goals include: strengthen surveillance technology and epidemiological and laboratory capacity to improve detection, characterization and monitoring of new viruses; identify viral and host determinants of transmissibility and virulence; develop rapid, accurate, inexpensive point-of-care diagnostic tests; enhance the accuracy and timeliness of modelling projections; create broader spectrum, highly effective, safe and longer-lasting vaccines; hasten vaccine production and increase throughput; devise more effective antiviral drugs and antimicrobials to treat bacterial complications; evaluate the effectiveness of drug, vaccine, personal protective equipment and social interventions; and enhance risk communication.
Despite everything that was done in the pandemic, the major determinant of the consequences was the virus that caused it. In the face of a virulent influenza pandemic, or any similarly global, sustained and threatening public health emergency, the world remains at risk of massive disruption, suffering and loss of life. The Committee hopes that these recommendations will help WHO and its Member States be better prepared to avert, mitigate and cope with future threats to health.
REFERENCES


MEMBERS OF THE COMMITTEE

Dr Preben Aavitsland, Department Director/State Epidemiologist, Department of Infectious Disease Epidemiology, Norwegian Institute of Public Health, Oslo, Norway

Professor Tjandra Aditama, Director General of Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia

Dr Silvia Bino (Rapporteur), Associate Professor of Infectious Diseases, Head, Control of Infectious Diseases Department, Institute of Public Health, Tirana, Albania

Dr Eduardo Hage Carmo, Former Director, Epidemiologic Surveillance, Ministry of Health, Brasilia, Brazil

Dr Martin Cetron, Director, Division of Global Migration and Quarantine, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Dr Omar El Menzhi, Director, Directorate of Epidemiology and Disease Control, Ministry of Health, Rabat, Morocco

Dr Yuri Fedorov, Deputy Director, Federal Centre on Plague Control, Federal Service for Surveillance of Consumer Rights Protection and Human Well-Being, Moscow, Russian Federation

Dr Harvey V. Fineberg (Chair), President, Institute of Medicine, Washington, D.C., United States of America
Mr Andrew Forsyth, Team Leader, Public Health Legislation and Policy, Office of the Director of Public Health, Ministry of Health, Wellington, New Zealand

Dr Claudia González, Partner-Director, Epi-Sur Consultores, and Professor, Center of Epidemiology and Public Health Policy, Universidad del Desarrollo, Santiago, Chile

Dr Mohammad Mehdi Gouya, Director-General, Centre for Disease Control, Ministry of Health and Medical Education, Tehran, Iran

Dr Amr Mohamed Kandeel, Chief of Cabinet, Minister's Office, Ministry of Health, Cairo, Egypt

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

Professor Abdulsalami Nasidi, Former Director, Public Health, Federal Ministry of Health, Abuja, Nigeria

Professor Paul Odehouri-Koudou, Director, National Institute of Public Hygiene, Abidjan, Côte d’Ivoire

Dr Nobuhiko Okabe, Director of Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan

Dr Palliri Ravindran, Director, Emergency Medical Relief, Directorate General of Health Services, Ministry of Health, New Delhi, India

Professor Dr Mahmudur Rahman, Director of the Institute of Epidemiology, Disease Control and Research and National Influenza Centre, Ministry of Health and Family Welfare, Dhaka, Bangladesh

Professor José Ignacio Santos, Professor and Head of the Infectious Diseases Unit, Department of Experimental Medicine, Faculty of Medicine, National Autonomous University of Mexico, Mexico City, Mexico

Ms Palanitina Tuipimatagi Toelupe, Director General of Health and Chief Executive Officer of the Ministry of Health, Samoa

Professor Patricia Ann Troop, Independent, Former Chief Executive, Health Protection Agency, London, United Kingdom of Great Britain and Northern Ireland

Dr Kumnuan Ungehusak, Senior Expert in Preventive Medicine, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Bangkok, Thailand

Professor Kuku Voyi, Professor and Department Head, School of Health Systems and Public Health, University of Pretoria, Pretoria, South Africa
Professor Yu Wang, Director General of Chinese Center for Disease Control and Prevention, Beijing, China

Dr Sam Zaramba, Senior Consultant Surgeon, Former Director General of Health Services, Ministry of Health, Kampala, Uganda

Note: The Review Committee wishes to acknowledge the participation of the following members who resigned during the course of its work: Dr Anthony Evans, Professor John Mackenzie, Dr Ziad Memish, and Dr Babatunde Osotimehin. The Committee expresses deep appreciation to its Secretariat for their assistance. The Committee is especially grateful to WHO staff members at headquarters and the Regional Offices for their cooperation, to representatives of Member States and to all those whom the Committee interviewed and who otherwise contributed to its deliberations.
1. Welcome and opening remarks:

Joachim Hombach welcomed meeting participants and introduced the WHO secretariat to the SAGE Working Group on Influenza Vaccines and Immunization (WG). John Tam was introduced as the new WG focal point from the secretariat. Elizabeth Miller, the chair, welcomed everyone to the second meeting of the WG, and outlined the agenda to be covered over the next two days.

2. Review of previous meeting, action items and needed reports/statements for SAGE

The WG were reminded of its Terms of Reference (ToR) which were as follows:

- 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 (LMI) in order to update the 2005 WHO influenza vaccine position paper.
- 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.
- 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.
- Provide advice about pandemic vaccine preparedness.

Where appropriate, advice from other advisory committees such as GACVS and QUIVER would be sought on specific issues.

A summary of the key recommendations from the Nov 2010 SAGE meeting was also presented. Those relevant to the WG’s deliberations were as follows:

1. The draft conceptual framework that would provide the structure for the position paper was approved by SAGE with the recommendation that health care workers should be added as a key target group

2. SAGE endorsed the WG’s suggestion that as part of its activities it should develop an influenza research agenda
3. With the dissolution of the Influenza pandemic influenza H5N1 WG, SAGE recommended that the Influenza WG re-consider options for the nature, deployment and storage of the remaining doses of H5N1 vaccine pledged for the WHO stockpile, taking account of logistic and other lessons learned from deployment of the H1N1 (2009) pandemic vaccine stockpile.

The expectations for this meeting were as follows:

- Review details of the conceptual matrix and identify information gaps and needed research
- Review disease burden in the key target groups
- Consider the options for the H5N1 pandemic stockpile and if possible submit draft recommendations for consideration at the April 2011 SAGE.
- Consider the implications of the recent data on the possible link between Pandemrix H1N1 vaccine and narcolepsy for future recommendations about the use of oil-in-water adjuvanted vaccines
- Agree timelines and future WG meetings for completion of the WG’s remit

It was noted that while key WG recommendations would need to be subject to the GRADE system of evidence, this method was not appropriate for statements about the burden of disease due to influenza. Furthermore since the GRADE system in its current form was not always appropriate for evaluating the strength of the evidence for vaccine policy recommendations (which need to take account of factors such as herd immunity that could only be assessed in observational post-licensure studies) WHO was reconsidering how the GRADE system could be adapted for SAGE vaccine recommendations. The WG would be kept informed of these deliberations by the SAGE secretariat.

3. Update on activities of the WHO Global Influenza Programme

The WG received an update from Dr. Nahoko Shindo of the WHO Global Influenza Programme on its recent report to the WHA in relation to existing resolutions that impacted on influenza. She presented an overview of current burden of disease data collated by the Global Influenza Programme (GIP), with special emphasis on the LMI countries. The WG received a tabled report from GIP of a systematic literature review on seasonal influenza disease burden and a summary presentation of a meta-analysis on global burden of influenza in children, together with an analysis on risk factors for severe pandemic 2009 influenza infection. Data from LMI countries are currently insufficient to allow most to prioritize strategies for influenza prevention and control over other interventions.

The WG was reminded that the WHA resolution on the prevention and treatment of pneumonia (WHA63.24) was also relevant to its deliberations. Currently, the resolution focuses on bacterial pneumonia and emphasizes treatment in the form of Integrated Management of Childhood Illnesses and use of PCV and Hib vaccines. However, the resolution recognizes the impact of the 2009 influenza pandemic and mentions respiratory syncytial virus and seasonal influenza as the most common non-bacterial cause of pneumonia. Thus the outcome of the Influenza WG’s discussions may influence WHO’s pneumonia control strategies.

---

Resolution WHA 56.19, that identifies the elderly as the highest risk group for influenza-associated severe illness and mortality, was discussed by the WG. In relation to recommendations that would have relevance for LMI countries it was noted that the age structure of the population in resource poor countries is different to that in high income countries where the elderly formed a relatively larger proportion of the population. In LMI countries, influenza in the very young (<2 years of age) is potentially more important in terms of overall population burden of disease than influenza in the elderly. This is because young children are at higher risk of influenza-associated hospitalization (e.g. pneumonia) and comprise a larger proportion of the population than in high income countries. Given the positive impact of maternal and childhood influenza immunization on influenza-related morbidity in young children that has been demonstrated in recent studies and the high proportion of the population comprising young children and pregnant women in developing countries, the WG agreed that it was important to provide clear recommendations to SAGE for these groups.

4. Presentation of the conceptual matrix on WG activities

The conceptual matrix that will frame the work of the WG was presented (See matrix in appendix). It included:

Identification of 5 key population groups:

1. children < 2 years,
2. elderly,
3. pregnant women,
4. high risk groups
5. health care workers (HCWs).

For each of these population groups the following data was required

- burden of disease
- vaccine performance and cost effectiveness
- operational issues affecting vaccine delivery

Questions to populate the matrix:

- What data exists?
- What additional data are needed?
- What are the gaps?
- What infrastructure or technology could address these issues in the future?
- What information is being collected and when will they become available?
- What additional activity is needed to identify and/or compile the data?
Discussion on needed research associated with the conceptual matrix to inform development of a Research Agenda

Key issues:
- Health care workers were considered a priority group; a key issue to tackle was how to address their reluctance to receive vaccine. The importance of getting evidence on the benefit of influenza immunization in this group was stressed. The concept of vaccinating not only for the protection of HCWs but also as a duty of care for protection of vulnerable patients was considered to have special value. Review of evidence (using GRADE criteria) of the need for and benefits of vaccinating HCWs with a strong policy statement was needed.
- There is also an information gap on disease burden and vaccine effectiveness for children < 2 years. Of these children < 6 months of age formed a special group as they could be protected by maternal immunization.
- Burden of disease data for the remaining groups (elderly, pregnant women and other high risk groups) were considered adequate. Use of the H1N1 (2009) experience for assessing the increased risk in these groups was considered appropriate for extrapolation to seasonal influenza.

Burden of disease: The need for better burden of disease data on children <2 years of age who would be a potential target group for seasonal influenza vaccine was identified as a high priority. CDC is currently conducting an extensive review of the global burden of influenza disease (see below) and agreed to assess whether the data collated for this review could be re-analysed to identify the burden of influenza in <6months and 6 months to <2 years to help inform the WG’s deliberations.

Vaccine performance (efficacy, effectiveness, safety) for different vaccines i.e. Live attenuated influenza vaccine (LAIV, traditional trivalent inactivated vaccines, and inactivated vaccines with new adjuvants): Ideally effectiveness data by vaccine type in the 5 key population groups would be required in order to define which type of vaccine would be best in which group. However, it was unlikely that the necessary data would exist for all groups and, where considered clinically appropriate, extrapolations from the available data would need to be made.

Vaccine effectiveness and cost effectiveness: The Secretariat may commission a systematic literature review to assess the available data and if there is sufficient, to initiate a meta-analysis of vaccine effectiveness and cost-effectiveness particularly for LMI countries. This should include review of the available evidence on the newly licensed LAIV for seasonal influenza. The potential value of oil-in-water adjuvanted vaccines should be considered.

Operational issues: These would differ depending on the type of vaccine, age and population group under consideration.

It was agreed that an influenza vaccination programme targeted at pregnant women and infants was the most feasible to implement in LMI countries given the existing vaccination programmes for these groups. School age children were considered a potentially important target group for influenza vaccination, especially as they may have a key role in transmission as suggested by studies in developed countries. However, the applicability of these findings for LMI countries would require knowledge of mixing patterns, e.g. how social networks are established and how children gather in different settings, which would vary with the local setting. A study had been sponsored by IVR to define contact matrices in developing countries.
Communication issues were considered important but not the main focus of the WG. Evaluating the evidence on the impact of different communication strategies will be helpful. Learning from the experience of regions and countries would also be of value, especially when considering targeting specific risk groups like pregnant women and HCWs.

Issues on vaccine production capacity were also discussed. The report from the Open-Ended Working Group of Member States on Pandemic Influenza Preparedness: sharing of influenza viruses and access to vaccines and other benefits (OEWG) meeting is expected to provide key information in this regard. There is a need to increase global seasonal influenza vaccine production capacity; for example in China the vaccine production capacity fell substantially short of the number of dose needed to cover the targeted groups. Regulatory issues could be an obstacle in certain countries.

Efficient deployment of seasonal influenza vaccines required better information on seasonality and the circulating strains, especially from countries in tropical areas.

Vaccine stability: There are operational advantages of having a more stable formulation and encouragement for further research needs to be highlighted.

5. Review of disease burden and risk factors for severe disease

In the 2005 influenza vaccine position paper, five priorities groups were recommended to receive influenza vaccination:

- Residents of institutions for elderly people and the disabled,
- Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies
- All individuals >6 months of age with any of the conditions listed above
- Elderly individuals above a nationally defined age limit, irrespective of other risk factors
- Other groups defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6-23 months of age.

These groups were defined based largely on data from industrialized countries. The WG were presented with new data on the epidemiology, risk factors and burden of disease by the GIP and CDC. The data presented focused on newer studies from LMI countries and from ongoing work with influenza disease burden models. Data from the 2009-10 H1N1 pandemic were highlighted in many of the discussions.

Disease burden:

One information gap that has made the development of global influenza vaccine policy difficult is valid estimates of global or regional disease burden. Countries with robust data on disease burden, mostly high-income countries, have used the data to create policy and to implement vaccine programs, while most other countries where data are few haven’t had the necessary information for decisions. The WG were presented with the preliminary results of two models of global disease burden – one for children under 5 years and one for global pandemic mortality in all ages.
An ongoing collaboration between many sites worldwide and chaired by researchers at the University of Edinburgh has estimated the total < 5 years influenza-associated respiratory disease burden. They have estimated that influenza accounts for 13% of all acute lower respiratory illnesses among this age group and 7% of all hospitalized ALRIs. This disease burden indicates that influenza accounts for greater numbers of ALRI than other vaccine preventable diseases, pneumococcal and Hib-associated disease, but fewer than RSV. They concluded that that there was evidence of 1-3 fold increases in the rate of ALRI and severe ALRI in developing country settings compared with developed country settings. Though the relative increase in developing countries seemed higher for ALRI this may be due differences in the surveillance method, with ALRI being ascertained by active rather than passive methods. The risk of both outcomes was higher in children under 2 years than those 2-5 years.

A model created by US CDC has estimated the global burden of disease associated with pandemic influenza, which the WG considered contained lessons for seasonal influenza-associated disease burden. While the overall estimates of pandemic-associated deaths ranged widely from 100,000 - 578,000, the model found that more than half the deaths were among persons living in Africa and Southeast Asia. These results confirmed other studies that have demonstrated greater pandemic burdens in developing countries and an association between income level and lower pandemic mortality rates from earlier pandemics.

**Identification of high risk groups**

**Age:** Data presented from GIP and CDC also focused on recent data on groups at high-risk for severe influenza or influenza-associated complications. Relevant data were presented both from seasonal and H1N1 pandemic studies.

While actual rates of influenza-associated deaths vary greatly from year-to-year and study to study, elderly persons are clearly at higher risk of death from influenza. New data from limited LMI countries confirm that the risk of influenza-associated death among elderly persons in developing countries (e.g. South Africa) may be several times higher than among similarly aged persons in high-income countries.

Children in LMI countries also appear to have higher rates of hospitalizations associated with influenza, though where access to health care is poor hospitalisation rates may be lower than in high income countries. In LMI countries the hospitalisation rates in children are similar to those in the elderly while mortality is much lower. And while data are available to estimate relative burden of influenza among children (see models above), it was acknowledged by the WG that a better understanding of the effects of influenza on the youngest children (<2 years) and those <6 months would be helpful for developing policy for vaccination. It was noted that studies may have underestimated pediatric disease rates. Because of the differences in rates of elderly and pediatric outcomes in limited studies, the WG indicated that extrapolation of rates of severe outcomes from high-income to LMI countries would be problematic.

The relatively high burden of influenza in low resource settings might be due to age structure differences; higher proportion of pregnant women in the population; limited access to health care; malnutrition; increased secondary bacterial infections that are not well treated; lower pneumococcal/influenza vaccination rates, different co-morbidities; and untreated co-morbidities.
Continued efforts to understand these factors and how they might effect vaccine strategies were called for.

It was also stressed that estimating possible impacts of an influenza vaccine program must account for the age distribution in the population and the effectiveness of vaccine in the populations. So while elderly persons may be at highest risk of death from influenza, it is conceivable that greater disease reduction might be achieved by focusing vaccination programs on young children or other groups. Additional work needs to be done in modelling the possible effects of various immunization strategies.

**Underlying health conditions:** Data were also presented regarding groups at high risk of severe influenza due to underlying condition. It was agreed that the effect of underlying clinical conditions was likely to be similar in high income and LMI countries. Data clearly indicated that pregnant women were at particularly high risk of severe complication and deaths from influenza (including seasonal and pandemic, and possibly avian influenza H5N1). And while pregnancy alone is a risk factor, the presence of co-morbidities (obesity, asthma, diabetes, etc) conferred even higher risk.

Also, abundant data exist that underlying chronic medical conditions (e.g. lung disease, including asthma, heart disease, endocrine disorders, neurological diseases etc.) confer higher risk of severe disease and death associated with influenza. It was concluded, however, that more data were needed on the effect of chronic infections such as HIV/AIDS and TB in LMI countries, where these conditions were less likely to be treated than in high income countries. Finally, data from the pandemic on 2009-10 clearly demonstrated that indigenous populations were at high risk of complications from influenza.

**Summary**

Several conclusions could reasonably be drawn from the discussions:

- Acknowledging the limitations of the data, influenza hospitalization and death rates are likely higher in LMI settings than in high-income settings. A substantial proportion of pandemic mortality may have occurred in these settings.
- Some data from high-income countries, such as identification of likely high risk groups, can reasonably be applied to LMI countries where such data are sparse. However, one can’t reliably extrapolate age-specific outcome rates from high-income to LMI settings. Ongoing efforts to model disease burden in LMI countries based on data from these settings will be important to establish appropriate vaccine policies.
- Pregnant women and young children are at high risk of hospitalizations, and depending on demographic characteristics of a population in LMI countries, may represent important targets for prevention through influenza vaccination.
- Significant gaps remain to fully understand the burden and risk groups for severe influenza in LMI countries. Better data on the effects of underlying illnesses common in LMI countries (e.g. TB and HIV), of malnutrition, of local bacterial pathogens, and of seasonality will be important to design and evaluate optimal prevention programs.
- The WG supports continued work to fill these gaps.
Discussion on knowledge gaps and future actions for disease burden analysis in key target groups

The University of Edinburgh global burden of disease review and other papers on the pandemic disease burden estimates will be published over the next few months (timeline not specified). It was recognised that, while these publications will be very helpful, there will inevitably be a lack of reliable data on the effect of age and co-morbidities on mortality in LMI countries. However, extrapolation of disease severity and burden from high to low income countries using both seasonal and pandemic H1N1 (2009) influenza should be possible for the following risk conditions:

- pregnant women
- people with underlying diseases
- AIDS/immunocompromised

Co-morbidity: incidence/mortality multiplier will be higher in developing countries since control of disease is poorer in such countries. It would be helpful if the available data on mortality could be presented by age (children <2 years, adults and elderly) and risk group and not just geographically.

In addition, any information on the follow questions also can be helpful:

- Is there an increase in pneumococcal infections during influenza seasons?
- Is there a significant burden of influenza illness that may not present with fever and thus not be picked up in surveillance based on influenza like illness for which fever is a necessary symptom?
- How do socioeconomic factors affect severity and mortality?

6. Preliminary findings: 2010 Survey for the global mapping on the use of seasonal influenza vaccine II

The main source of information for this presentation was data from the WHO 2010 Global Influenza Vaccine Survey that is currently taking place. Other sources of information considered included the survey undertaken by the Vaccine European New Integrated Collaboration Effort (VENICE) project in 2008 across 27 EU Member States, Norway and Iceland, the research article published in 2009 in BMC on the Expansion of seasonal influenza vaccination in the Americas, the study done in Sep 2010 by the International Federation of Pharmaceutical Manufacturers, and the Join Reporting Form (JRF) between UNICEF and WHO.

Member States with seasonal influenza in national immunization schedule varies from region to region. Findings were described as follow:

- In AFR according to the JRF, only Algeria, Mauritius, and South Africa recommend vaccination for specific target groups.
- In AMR 91% of the countries have annual seasonal influenza vaccination as part of the national immunization, and Dominica is expected to introduce it soon.
- In EMR, 33% of the countries have an annual seasonal influenza vaccination and one country (Iraq) is expected to do so by 2012.
- In EUR, information from 27 EU countries showed that all of them recommend seasonal influenza vaccination.
- In SEAR, only Thailand recently introduced seasonal influenza vaccination.
In WPR, 6 countries already have seasonal influenza as part of national immunization schedule and by 2012 Singapore and the Philippines are expected to include it.

It is worth noting that some countries offer vaccination in the private sector even though it is not part of the national immunization schedule.

The following target groups are recommended to be vaccinated according to the WHO survey data available by the date of this presentation:

- In AMR 83% of the countries are recommending vaccination among children, 53% of the countries in the region recommend vaccination in adults, 94% of the countries recommend to vaccinate the elderly, and 70% of the countries recommend to vaccinate at risk groups.
- In EUR, data included from the VENICE survey indicated that 85% of the countries recommend vaccinating the elderly, and 100% of the countries recommend vaccinating at risk groups.
- Globally, 90% of the countries consider chronic pulmonary and cardiovascular disease when recommending vaccination for at risk groups.
- Pregnant women are recommended to get vaccine in around 45% of the countries.
- As for essential personnel, the majority of the countries considered health care workers, lab workers and field workers that investigate outbreaks as the main groups to be vaccinated.
- Other groups such as travelers, military and other sectors were also considered but in a minor proportion.

Data were presented as percentage of countries provided recommendations to the total countries that responded to the survey. WG members suggested further examination of the survey methods and how these data were calculated.

Another aspect that the survey is trying to elucidate is the vaccination coverage rates by target groups. Unfortunately, it cannot be calculated at this stage, due to the fact that many countries do not register the number of people being vaccinated by groups. For the regions that are able to calculate coverage, data is inconsistent and is difficult to provide generalizations.

Seasonal influenza vaccine is administered in both public and private sector. When administered in the public sector, the vaccine is free of charge in the majority of the cases.

The WHA 56.19 set the goal of achieving 75% influenza vaccination coverage among the elderly in those Member States having a national influenza vaccination programme targeting the elderly. According to survey results, this goal is difficult to achieve. By the date of this report, 13 countries in AMR, five in WPR and only one in EUR have achieved this goal.

The source of seasonal influenza vaccine varies from region to region, for example, in PAHO it is mainly through the bulk purchase mechanism. In EMRO vaccine is acquired through a combination between bulk purchase and direct purchase and in WPRO it comes from UNICEF, direct purchase and donations.

According to the IFPMA, the total number of doses distributed worldwide has increased by 72% rising from 262 million doses in 2004 to 449 million in 2009. Growth occurred in all of the six WHO regions, although distribution in the Americas peaked in 2007 and subsequently fell by approximately
6%. The combined WHO provision of seasonal influenza vaccines in 157 countries showed that Europe and Americas regions accounted for 75 - 80% of the total doses distributed each year.

Regarding H5N1 pandemic vaccine, the percentage of countries potentially requesting H5N1 vaccine doses from WHO stockpile would be around 85%. The essential personnel that would require H5N1 vaccination includes HCWs, lab workers, field workers investigating animal and human outbreaks, security forces and other sectors. The percentage of H5N1 vaccine doses required for essential personnel in the different regions varies from 7% in AMRO/PAHO, 6% in SEARO and 17% in EMRO. However, these percentages should be considered cautiously as it only represents small portion of the regional population. In those countries that may potentially require more doses, the list of essential personnel proposed includes a larger part of the total population.

EURO data from JRF will be checked regarding non EU countries. The WHO survey will be shared with the group to identify which data might be useful for further analysis. Draft report from the 2010 WHO survey for global mapping use of seasonal influenza vaccine will be available by the end of April 2011.

7. Discussions on pandemic H5N1 stockpile

**Background**

The following background information was provided to the WG in a verbal briefing from Dr. Marie-Paule Kieny

- In May 2007 The World Health Assembly recommended to the DG of WHO that an international stockpile of H5N1 vaccine should be established.
- In November 2007, after reviewing available safety and immunogenicity data on H5N1 vaccines, the WHO SAGE recommended that WHO establish a stockpile of around 150 million doses.
- Based on scenarios explored by two mathematical models, the advice from SAGE was to reserve 50 million doses for an immediate containment operation in the countries with sustained community spread with the objective of aborting or delaying the nascent pandemic.
- The remaining 100 million doses were to be deployed to low and middle income countries in amounts proportional to their population size (sufficient for ~1% of the population, assuming a two dose schedule) to protect public health by helping to maintain essential services. Health care workers were identified as a key target group.
- Two manufacturers responded with pledges to donate vaccine to the WHO stockpile. GSK pledged 50 million doses and Sanofi-Pasteur 60 million.
- With Gates Foundation funding an external company, Oliver Wyman, was commissioned to consider logistic and financial implications of these recommendations. Considerable cost implications were associated with maintaining a physical stockpile, particularly in filled doses as would be required for mounting a rapid containment operation. Other options of having a virtual H5N1 stockpile were also explored.
- The analysis of lessons learnt from the H1N1 pandemic promoted a review of the SAGE recommendations on deployment of the stockpile, its composition and storage in the light of the following:
  - Containment strategies designed to shut down a nascent pandemic for which 50 million doses had been reserved were no longer considered feasible.
• Experience with the unexpected emergence of H1N1 highlighted the risk with commitment to a physical stockpile of H5N1 i.e. all pledged vaccine potentially being the wrong strain.

• GSK and Sanofi in recognition of their previous H5N1 pledge agreed to "convert" this pledge into H1N1 pandemic vaccine. Subsequently, these pledges were increased to 60 million from GSK and 100 million from Sanofi Pasteur. Of these potential 160 M doses of H1N1 vaccine, some 40 million doses were used by WHO for deployment in low and middle income countries. This reduced the remaining number of pledged pandemic vaccine doses to around 120 million.

• As a result of the experience in switching their pledged H5N1 doses to a different strain, manufacturers indicated greater flexibility in relation to their original H5N1 stockpile commitment.
  – Under the option of committing to a virtual rather than a physical stockpile they would be able to switch production to the relevant pandemic strain when it emerged and not be restrained by their pledge to provide H5N1 pandemic vaccine (as exemplified by their response to the H1N1 pandemic).
  – If a physical stockpile was required then this would have to be H5N1 (as this is the only subtype whose production is currently supported by a few paying customers) but could be stored by the manufacturer.

In the light of points above the Influenza Working Group was asked to re-consider options for the nature, deployment and storage of the remaining 120 doses of pledged vaccine.

WG discussion and draft recommendations

There was initial discussion on whether the existing SAGE recommendations on the pre-pandemic use of available H5N1 vaccine should be reconsidered, given the emerging information on safety and efficacy of the H1N1 pandemic vaccine and the recognition that pandemic vaccine manufactured once the next pandemic was declared would likely be deployed too late to prevent a substantial proportion of cases (as with H1N1 vaccine).

• The current SAGE recommendation did not recommend pre-pandemic use of H5N1 vaccine, with the exception of laboratory staff handling the virus and animal workers who may be exposed to highly pathogenic avian viruses. However, there was provision for review of this recommendation if circumstances or knowledge changed. It was suggested in discussion by members of the WG that further consideration be given to the wider pre-pandemic use of H5N1 vaccine with the intention of priming key target populations to allow boosting with a single dose should an H5N1 pandemic emerge with a different H5 virus.

• After discussion it was agreed that there was currently no new information or risk assessment that would merit a change in the existing SAGE recommendation regarding pre-pandemic use of H5N1 vaccine. Despite the generally encouraging safety profile of the various H1N1 vaccines used in 2009/10, narcolepsy had emerged as a potential safety signal with one vaccine and was still under investigation. Also in view of the H1N1 experience there was now more caution in assuming that the next pandemic would be H5N1. In the absence of a quantifiable risk of H5N1 infection, the risk benefit of more widespread vaccination remained unfavourable at the present time. In addition, the key target group of health-care workers is notoriously reluctant to influenza immunization, predicting very poor acceptance.

• However, in line with the SAGE recommendation this would be kept under view, and revisited should circumstances change. The potential availability of new seasonal vaccines
containing putative pandemic antigens that could be used for priming at the same time as providing annual protection against seasonal influenza strains was noted.

- In relation to the use of the pledged 110 million doses of pandemic vaccine, the WG considered three main options:
  - To generate a physical H5N1 stockpile, stored largely as bulk, possibly held by the manufacturer. The issue of replenishment would arise when the stockpile became out of date and all pledged doses would be committed to H5N1. There are also issues (cost, location etc.) relating to the identification and qualification of an independent fill-finish facility that can rapidly response to the emergence of a H5 pandemic.
  - To keep all the vaccine as a virtual stockpile, only specifying the strain when the pandemic emerged. This was the least costly option and least risky in terms of expending the pledged doses on the wrong virus. To ensure as timely delivery as possible, manufacturers would be asked to reserve 10% of the filled doses produced each week under contract for countries buying their own vaccine for the WHO stockpile.
  - As b above but to have a small quantity of the pledged doses (say 1% of the total, ~ 1 million) as a physical H5N1 vaccine stockpile in filled vials that could be immediately deployed as part of a local H5N1 outbreak control measure in the event of enhanced person to person spread in one or more countries. This use was not the same as the containment policy as the intention was to provide protection for those at immediate risk (such as those needed to maintain essential health services), not for the interruption of transmission of a nascent pandemic.

- Option c was favoured as it would provide reassurance to countries without their own H5N1 stockpile that in the event of an outbreak with a highly pathogenic H5N1 virus, some protection could be offered to those in the exposed local population. Although the physical stockpile would need replenishing at regular intervals, it would not materially deplete the remaining number of pledged doses in the virtual stockpile.

- A number of practical questions followed from option c.
  - Could this small physical stockpile be held by the manufacture?
  - If the manufacturer was producing H5N1 vaccine to provide for countries compiling their own stockpiles in filled doses, could the WHO stockpile for immediate deployment be cycled within that ongoing stock?
  - Countries wishing to be able to access this physical stockpile would need to develop an implementation plan to ensure that it could be rapidly deployment as part of an outbreak control measure.
  - WHO would need to have criteria and plans for the rapid despatch of H5N1 vaccine to an outbreak area and criteria for release in response to a county’s request.
  - In deciding on the number of doses in this small stockpile it would be helpful to know how storage costs (if not borne by the manufacturer) relate to the number of doses held – say over the range 100,000 to 2 million) and to draft potential scenario of stockpile use.
  - WHO should ensure that all existing licensed pandemic or pre-pandemic H5N1 vaccines, and those in the physical stockpile, are pre-qualified. Since vaccine in the virtual stockpile could be of any strain e.g. H9, H7, then pre-qualification of a generic vaccine from a manufacturer based on the EMA “mock up” dossier principle should be pursued.
In summary, the WG concluded that the virtual stockpile option with a small physical stockpile of filled doses of H5N1 vaccine for outbreak control would provide maximum flexibility, minimize costs especially those involved with replenishment, obviate the risk of expending the pledged doses on the wrong vaccine and simplify the logistics of storage. WHO should ensure that it has procedures in place to facilitate the earliest possible receipt and deployment of pandemic strain vaccine to the low and middle income countries who would be dependent on the WHO stockpile in the event of another pandemic, and that procedures are in place for rapid delivery and utilization of the physical H5N1 stockpile released for outbreak control. The Chair of the WG will present the recommendations for consideration by SAGE at its meeting in April, 2011.

8. Information on adjuvanted H1N1 vaccine and narcolepsy

The WG was provided with an update on the position with respect to the reported association between narcolepsy and Pandemrix as this may have bearing on any draft recommendations on the use of seasonal influenza vaccines containing an oil in water adjuvant. The WG was informed that:

- Following widespread use of vaccines against influenza (H1N1) 2009, cases of narcolepsy, especially in children and adolescents, have been reported from at least 12 countries. Rates reported from Sweden, Finland and Iceland have been notably higher than those from other countries.
- Studies are ongoing to determine if the apparent increased risk of narcolepsy reported in Sweden is higher in vaccinated persons.
- In Finland, the risk of developing narcolepsy among those vaccinated with Pandemrix aged between 4 and 19 years is about nine times greater than those unvaccinated in the same age group, corresponding to a risk of about 1 case of narcolepsy per 12,000 vaccinated in this age group. The increased risk has not been seen in younger or older age groups in Finland. 22/22 cases of narcolepsy tested so far in Finland has the (HLA) DQB1*0602 genotype.
- The only pandemic vaccine used in Finland was Pandemrix, an adjuvanted influenza (H1N1) 2009 monovalent vaccine manufactured by GlaxoSmithKline. Finnish authorities consider it probable that Pandemrix vaccine was a contributing factor to the observed increase in narcolepsy, and has called for further investigation of other co-factors that may be associated with the increased risk.

The WG noted the GACVS risk assessment that concluded:

- An increased risk of narcolepsy has not been observed in association with the use of any vaccines whether against influenza or other diseases in the past. Pandemrix vaccine was used in 47 countries worldwide during the 2009-2010, and it does not appear that narcolepsy following vaccination against pandemic influenza is a general worldwide phenomenon, and this complicates interpretation of the findings in Finland.
- Any increased risk of narcolepsy currently appears to be restricted to the months following vaccination and by age group and country. GACVS agrees that further investigation is warranted concerning narcolepsy and vaccination against influenza (H1N1) 2009 with Pandemrix and other pandemic H1N1 vaccines and GACVS will continue monitoring the situation closely.

The WG also noted that there was no change to the current WHO position on the use of pandemic influenza vaccines which was that countries should continue vaccinating against H1N1 to immunize
persons at risk of severe disease from H1N1, using monovalent vaccines including Pandemrix, if trivalent seasonal vaccine is not available. It also noted that no regulatory action had been taken by the European Medicines Evaluation Agency and that Pandemrix remains on the list of WHO-prequalified vaccines.

The WG noted that further information on the association between narcolepsy and receipt of Pandemrix vaccine would not be available until later in the year and that any recommendations about the use of oil in water adjuvanted seasonal influenza vaccines that the WG might include it is position paper would have to await the outcome of these pending studies and to be reported by GACVS.

9. Summary of action points and closure

- **Understanding of severity for informing recommendations**: Revisit again the evidence on burden of disease when pending papers become available. These papers on evidence will be shared by emails. An assessment containing all information available will be provided by the secretariat. Joe Breese will help the secretariat in putting it together.

- **Vaccine effectiveness**: Some consolidated evidence relevant to the topic needs to be scrutinized and should be made available for next meeting. It will include studies on efficacy and effectiveness. Cost effectiveness studies will be limited to seasonal influenza vaccine. For young children effectiveness on seasonal and pandemic vaccines will likely be similar. This issue will be discussed in the next face to face meeting.

- **For both of the above items, particular emphasis should be put on the collection of disease burden data relevant to children <2 years of age**.

- **Next meetings to be held**:
  a. Preparatory teleconference before next face to face meeting to be held in July 2011
  b. Face to face meeting: by end of August of beginning of September 2011. This meeting will be in preparation for the meeting to be held the second week of November. Two other meetings that might generate important information for the group will be held between June and July, the first one on maternal immunization and later the GAP-II meeting.

- **What to report back to SAGE in April?**
  a. Disease burden in the key target groups
  b. Conceptual matrix, needed research and further timelines and work plan
  c. Feedback on the discussions on the nature and use of the pandemic vaccine stockpile
  d. Information needed with respect to future policy recommendations for all influenza vaccines

- **Minutes of the meeting will be available by end of Feb together with the complete set of slides**

- **As documents (papers, reports, studies, etc) become available the will be circulated among the Influenza WG members**.

- **SharePoint**: A virtual space will be created in order to share all relevant documents, i.e. minutes, slide presentations and relevant information/publications.
- For SAGE report: include the minutes of this meeting. Other relevant reports such as the burden of disease paper, or documents needed in yellow book need to be ready by March 16th.
- Narcolepsy and Pandemrix: just as part of the report for this group. Not extra action needs to be taken.
Appendix 1 Agenda

Appendix 2 Conceptual matrix

Appendix 3 List of participants

Working group members:
Professor Jon S. Abramson
Dr William Ampofo (Apologies)
Dr Joseph S. Bresee
Dr Janet Englund
Dr Randeep Guleria
Dr Yu Hongjie (Apologies)
Professor Elizabeth Miller (Chair)
Dr Michael Pfleiderer
Professor Art Reingold
Professor David Salisbury
Professor Barry D. Schoub,
Professor Claire-Anne Siegrist

WHO Secretariat
Dr Philippe Duclos
Dr Joachim Hombach
Dr Marie-Paule Kieny
Dr Pem Namgyal
Dr Cuauhemoc Ruiz-Matus
Dr Nahoko Shindo
Dr John S. Tam
Dr Claudia Vivas Torrealba (rapporteur)
Dr David Wood
## Agenda

**Day 1, Monday, 14 February 2011, Room C202**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Welcome and opening remarks</td>
<td>Chair: Liz Miller</td>
</tr>
<tr>
<td></td>
<td>Rapporteur: Claudia Vivas</td>
<td>Rapporteur: Claudia Vivas</td>
</tr>
<tr>
<td>09:10</td>
<td>Review of previous meeting, action items and needed reports/statements for SAGE</td>
<td>Philippe Duclos</td>
</tr>
<tr>
<td>09:30</td>
<td>Update on the report to the WHA as a request from WHA63.19</td>
<td>Nahoko Shindo</td>
</tr>
<tr>
<td>09:45</td>
<td>Presentation of the conceptual matrix</td>
<td>John Tam</td>
</tr>
<tr>
<td>10:00</td>
<td>Discussion on needed research associated with the conceptual matrix and the development of a Research Agenda (SAGE recommendation)</td>
<td>Led: Chair</td>
</tr>
<tr>
<td>10:45</td>
<td>Refreshment Break</td>
<td></td>
</tr>
<tr>
<td>11:15</td>
<td>Discussion on future timelines and work plans associated with the conceptual matrix</td>
<td>Led: Chair</td>
</tr>
<tr>
<td>12:30</td>
<td>Lunch Break</td>
<td></td>
</tr>
<tr>
<td>13:30</td>
<td>Review of disease severity and burden in key target groups</td>
<td>Nahoko Shindo</td>
</tr>
<tr>
<td>14:00</td>
<td>Review of global disease burden</td>
<td>Marc-Alain Widdowson (TC)</td>
</tr>
<tr>
<td>14:30</td>
<td>Discussion on knowledge gaps and future actions for disease burden analysis in key target groups</td>
<td>Led: Joe Bresee</td>
</tr>
<tr>
<td>15:30</td>
<td>Refreshment Break</td>
<td></td>
</tr>
<tr>
<td>16:00</td>
<td>Discussion on report to SAGE on disease burden analysis</td>
<td>Led: Chair</td>
</tr>
<tr>
<td>16:30</td>
<td>Preliminary findings: 2009 Survey for the global mapping on the use of seasonal influenza vaccine II</td>
<td>Claudia Vivas</td>
</tr>
<tr>
<td>16:50</td>
<td>Summary of day 1 activities</td>
<td>John Tam</td>
</tr>
<tr>
<td>17:30</td>
<td>Cocktail</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Leader</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>08:30-09:00</td>
<td>Background and WHO conceptual directions for H5N1 stockpile</td>
<td>TBD</td>
</tr>
<tr>
<td>09:00-11:00</td>
<td>Review the needed information and strategy in relation with stockpile and the use of pandemic vaccines</td>
<td>Chair</td>
</tr>
<tr>
<td>11:00-11:30</td>
<td>Refreshment Break</td>
<td></td>
</tr>
<tr>
<td>11:30-12:15</td>
<td>H1N1 vaccine safety review</td>
<td>David Wood</td>
</tr>
<tr>
<td>12:15-12:45</td>
<td>Discussions on 2011 workplan of the SAGE WG and Summary report to SAGE on 5 April 2011</td>
<td>Chair</td>
</tr>
<tr>
<td>12:45-13:00</td>
<td>Summary of action points and closure</td>
<td>Chair</td>
</tr>
</tbody>
</table>
SAGE Working Group on Influenza Vaccine and Immunization: Conceptual Matrix for information required for recommendations

Questions to populate the matrix
• What data exists? At this stage as discussed, what would be needed is not an exhaustive list but indication of availability of data and critical pieces of info.
• What data are needed?
• What are the gaps?
• What infrastructure or technology could address these issues in the future?
• What info is being collected and when will it become available?
• What activity is needed to identify and/or compile the data?

<table>
<thead>
<tr>
<th>Key Issue</th>
<th>Children (&lt; 2 years?)</th>
<th>Elderly</th>
<th>Pregnant Women</th>
<th>High Risk Groups</th>
<th>Health care workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Performance (efficacy, effectiveness, safety) broken down for different vaccines i.e. LAIV, traditional, adjuvanted</td>
<td>Limited data exist on TVF for the elderly and efficacy is less than that for children. Systematic lit review required to understand knowledge gaps especially for LAIV and adjuvanted vaccines.</td>
<td>Data may exist for pandemic H1N1 vaccine and being made available gradually but little is known for seasonal vaccine. Requires systemic lit review.</td>
<td>(GIP) Literature review of efficacy of vaccination for severe immunocompromised underway, report 28Feb11. Lit review required for other risk groups such as patients with chronic diseases.</td>
<td>(GIP) Literature review of efficacy of vaccination of HCW in preventing nosocomial infection and spread in patients underway, report 28Feb11</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Extensive lit review required for cost effectiveness analysis for all age and risk groups. Information gaps likely exist and additional cost effectiveness studies will be required for specific groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Operational Issues

**HSN1 Vaccine:**
1. Clearly H5 vaccine stockpile strategy (virtual vs. physical) and selection criteria for acceptance of vaccines into the stockpile.  
2. Collect information on existing country-specific H5 vaccine pre-purchase plans, stockpiles, and expiration dates.  
3. Planning on the provision for storage, rapid fill, and finish facilities for H5 vaccine and adjuvant.  
4. Define priority groups for H5 vaccine and estimate size of priority groups identified nationally, regionally, and globally.  
5. Development of deployment and communication strategies, and initiate ethical discussion for H5 stockpile deployment.  
6. Identify strategy for rapid detection, assessment, and investigation of adverse events.  
7. Identify methods for assessment of effectiveness when the vaccine is deployed.  
8. Monitor research on heterotypic ‘priming’ (possible use of stockpile in the event that H5 pandemic strain differs from stockpiled H5 vaccine strain).  
9. Monitor research on development of new vaccines for H5 (LAIV etc.).

**Pandemic Vaccine:**
1. Review of lessons learnt from pandemic (H1N1) 2009 vaccination activities.  
2. Review of vaccine deployment/delivery procedures for current H1N1 pandemic vaccine particularly for low income countries.  

**Seasonal Vaccine:**
1. Survey of seasonal vaccine policy and pandemic vaccine preparedness for high, medium, and low income countries.  
2. Review seasonal vaccine production capacity in high vs. mid and low income countries, and coverage goals.  
3. Regulatory requirements, similarities, differences among high and low income countries.  
4. Possible harmonization of regulatory requirements among agencies including WHO prequalification standards for pandemic and seasonal vaccines among epidemiologically/geographical similar countries.  
5. Identify optimal strategies for each of the risk groups for annual vaccination programmes.  
6. Investigate the effect of herd immunity on influenza control.  
7. Review of data on transmission of influenza within family members and develop strategy on family vaccination programme that includes all ages.  
8. Evaluate studies that examine effective mechanism of communication for increasing the use of influenza vaccine.  
9. Monitor research that addresses the correlates of protection against influenza in humans.  
10. Monitor progress on research associated with needle free vaccination for seasonal influenza.  
11. Monitor research on more stable vaccine formulations that require less stringent conditions for storage and delivery.

---

*EPIA: The European Paediatric Influenza Analysis Project, Eur J Pediatr, 2010*
OPEN-ENDED WORKING GROUP OF MEMBER STATES ON PANDEMIC INFLUENZA PREPAREDNESS: SHARING OF INFLUENZA VIRUSES AND ACCESS TO VACCINES AND OTHER BENEFITS

TECHNICAL STUDIES UNDER RESOLUTION WHA63.1

Final document

CONTENTS

<table>
<thead>
<tr>
<th>Executive summary</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Background</td>
<td>5</td>
</tr>
<tr>
<td>II. Method of work, approach to the technical studies and assumptions</td>
<td>6</td>
</tr>
<tr>
<td>III. Laboratory and surveillance capacity-building</td>
<td>7</td>
</tr>
<tr>
<td>IV. Expanding global influenza vaccine production capacity</td>
<td>18</td>
</tr>
<tr>
<td>V. Access, affordability and effective deployment</td>
<td>43</td>
</tr>
<tr>
<td>VI. Sustainable financing, solidarity mechanisms and other approaches</td>
<td>71</td>
</tr>
</tbody>
</table>

Annexes

| Annex A1. Laboratory and surveillance capacity-building | 87    |
| Annex A2. Expanding global influenza vaccine production capacity | 102   |
| Annex A3. Access, affordability and effective deployment | 112   |
| Annex A4. Financing mechanisms: case studies            | 121   |
EXECUTIVE SUMMARY

This document is a response to a request from the World Health Assembly in the context of the Open-Ended Working Group on Pandemic Influenza Preparedness. It provides Member States with technical information to assist them in reaching final agreement on the Framework for the sharing of influenza viruses and access to vaccines and other benefits. The study covers three technical areas of importance for increasing global preparedness for pandemic influenza: (i) laboratory and surveillance capacities of countries, (ii) global influenza vaccine production capacity and (iii) access to vaccines and other necessary pandemic supplies by countries without such access. With a common approach, the current state of global capacity is reviewed for each technical area, gaps in those capacities are identified, and targets to reduce the gaps are proposed. Options and associated costs for achieving the targets are then presented. The final section of the study addresses sustainable financing mechanisms to meet the estimated costs. By identifying gaps and assessing the costs for reducing those gaps, concrete funding needs emerge, allowing a realistic assessment of financing requirements over time.

Parts of the study, covering laboratory and surveillance capacity, vaccine production and access to vaccines, were presented to Member States in December 2010 as Preliminary Findings. The entire study has now been edited, resulting in certain editorial and typographical changes in the text and footnotes; however, no substantive changes have been made to the Preliminary Findings that were available in December 2010 or to the supporting evidence.

As indicated in the Preliminary Findings, two new sections have now been added: a discussion of antiviral medicines and diagnostic tests. Likewise the section on financing mechanisms was updated with data on antiviral medicines. Annexes for each section are presented in the last section of this document.

Summary of findings

1. Laboratory and surveillance capacity-building

Globally, influenza-specific laboratory and surveillance capacity in many developing countries needs to be strengthened. Low capacity is most frequently found in three WHO regions: the African, Eastern Mediterranean and South-East Asia regions. Over the next five years, increasing surveillance and laboratory capacity in several countries in these regions will require specific, targeted activities. Depending on the number of countries in which work is carried out, the total estimated one-time start-up cost will range from US$ 10.4 million to US$ 44.9 million, and the annual cost thereafter will be US$ 32.2–101 million per year.

2. Expanding global influenza vaccine production capacity

The global production capacity of pandemic influenza vaccine is currently approximately 876 million doses per year. It is based on demand and on the capacity to produce seasonal influenza vaccine. If there are no interventions, production is anticipated to increase to approximately 1.8 billion doses per year in 2015, due mainly to investments by multinational companies and the governments of high-income countries.

Many complementary strategies may be used to increase global production capacity and global access to pandemic vaccines. A coordinated approach could result in increased pandemic vaccine production, which would significantly increase access to such vaccines by countries that currently do not have access. The strategies that could be considered include increasing the uptake of seasonal vaccine (estimated at US$ 280 million to US$ 3700 million); shifting to higher yield technologies, such as the production of live attenuated vaccine (estimated at US$ 450 million) and use of adjuvants (estimated...
at US$ 230 million to US$ 420 million); and maintaining or building new vaccine production capacity (estimated at US$ 125 million to US$ 490 million).

3. Increasing access, affordability and effective deployment of vaccines, antiviral agents, diagnostics and other materials for pandemic preparedness and response

**Vaccines**

One constraint to real-time access to pandemic influenza vaccines by countries without access is a lack of supply, because of pre-purchase agreements held by other countries. The main mechanism to address this constraint is to establish pre-purchase agreements on behalf of countries that do not have access, either by expanding existing country agreements or through new agreements. The estimated costs of this option generally include a reservation fee (estimated at US$ 0.5/dose), to be paid annually to the manufacturer, and purchase and deployment of vaccine at the time of a pandemic (estimated at US$ 4.2/dose). Both costs will vary according to the number of doses reserved. On the basis of the target groups identified by the WHO Strategic Advisory Group of Experts on immunization, three potential groups of people were identified who should be targeted for vaccination (ranging from 8 million to 334 million people); the costs were forecasted from current information on prices. The costs of pre-purchase agreements range from US$ 10 million to US$ 335 million for reserve fees and an estimated US$ 70 million to US$ 2795 million at the time of purchase.

**Antiviral medicines**

In contrast to vaccines, antiviral drugs for pandemic influenza could be made available at the start of a pandemic. Seasonal demand for influenza antiviral drugs, is, however, usually low, especially in lower income countries; therefore, stocks of antiviral medicines may not be immediately available. Both price and availability are determined by market conditions in higher-income countries. WHO has highlighted two options:

- procurement and maintenance of an antiviral agent stockpile to meet immediate needs at the time of the emergence of a pandemic and
- establishment of agreements with manufacturers and concomitant financing to purchase antiviral medicines to sustain the public health response throughout a pandemic.

As for vaccines, the cost of these options will vary with the number of countries, populations and treatment courses (estimated range of US$ 82 million to US$ 763 million).

**Diagnostic reagents and test kits**

In a pandemic, diagnostic tests are used mainly to identify and confirm outbreaks of pandemic influenza and to guide clinical decisions on treatment. The network of National Influenza Centre laboratories and Collaborating Centres in the WHO Global Influenza Surveillance Network represents the main mechanism by which countries identify outbreaks and monitor influenza activity in their countries and regions. Some laboratories in the Network provide critical reagents and set standards under their WHO terms of reference. The costs associated with this activity are included in the regular recurrent costs of WHO Collaborating Centres.

In the clinical setting, some tests are conducted with so-called “rapid point of care diagnostic kits” for influenza. These tests have the advantage that they can be performed without a laboratory; however, they must be purchased commercially, their price varies, they generally have low sensitivity, and they provide less specific information than laboratory tests.

**Sustainable financing, solidarity mechanisms and other approaches**
To the extent possible, the estimated costs were broken down into “units” to allow development of implementable “packages” and estimated yearly financial requirements. With this approach, “packages” of activities and their estimated costs were formulated, comprising elements from each of the three technical areas (laboratory and surveillance capacity, vaccine production capacity, and access). Costs were estimated for 5- and 10-year periods. Existing financing mechanisms and tools are described, and some are applied to show their potential use in financing these activities. Various types of financing will be needed to suit various implementation and funding needs. A separate document provides further details of potential financing mechanisms for concrete packages of benefits.

Full document available at:

**TECHNICAL STUDIES UNDER RESOLUTION WHA63.1**


Also available:

**PANDEMIC INFLUENZA PREPAREDNESS: OPTIONS FOR SUSTAINABLE FINANCING OF BENEFIT SHARING**

Vaccines against tick-borne encephalitis

WHO Position Paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and since 2006 they are reviewed and endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on Vaccines and Immunization. The position papers are designed for use mainly by national public health officials and immunization programme managers. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, the scientific media, and the public.

This is the first WHO position paper on vaccines against tick-borne encephalitis. Footnotes provide a limited number of core references; their respective abstracts as well as a more comprehensive list of references are found at http://www.who.int/immunization/documents/positionpapers/en/index.html.

Grading tables assessing the quality of scientific evidence for a few key conclusions are also available at this link and are referenced in the position paper.

Background

Epidemiology

Tick-borne encephalitis virus (TBEV) is an important cause of viral infections of the central nervous system in eastern, central, and northern European countries and in Russia. The endemic areas of tick-borne encephalitis (TBE) cover the southern part of the non-tropical Eurasian forest belt extending from north-eastern France to the Japanese Hokkaido Island (Suss J 2008; Suss J et al 2010). Approximately 10,000-12,000 clinical cases of TBE are reported each year, but this figure is believed to significantly underestimate the actual total number. Even in the most affected areas, TBE is usually limited to certain sylvan foci. Some countries, such as Germany, are defining at risk-areas at district level based on the reported number of clinical cases.

Currently, the highest incidences of clinical TBE are reported from the Baltic states, Slovenia, and from Russia. For example, in 2009, national incidences per 100 000 inhabitants were

---

1 References will be provided as footnotes in the final version
10.40, 7.50, and 6.89, respectively, for Estonia, Latvia, and Lithuania, and 9.90 for Slovenia (Stefanoff P et al 2011). In 2006, the average incidence of TBE in the Russian Federation was 2.44 per 100 000 population, but in the Siberian Federal Area, morbidity was more than 5 times higher - in some Siberian areas 10 times higher - than the national average. Similarly, in the Primorskiy Territory of the Far Eastern Federal Area, morbidity reached 3.38 per 100 000 population. High incidences of TBE were reported also from the North-Western Federal Area with 3.77 per 100 000 and 2.65 per 100 000, respectively, in the Pskov and Novgorod Provinces (Oniscenko GG et al 2007). Other countries that have reported TBE cases within their territories, or are considered at risk due to focally high TBEV prevalence in ticks, include Albania, Austria, Belarus, Bosnia, Bulgaria, Croatia, Denmark, Finland, Germany, Greece, Hungary, Italy, Mongolia, Norway, Poland, Romania, Serbia, Slovakia, Slovenia, South Korea, Sweden, Switzerland, Turkey, and Ukraine (Stefanoff P et al 2011; Suss J 2008).

TBE may represent an increasing problem as the disease is now reported from previously non-endemic areas of for example Scandinavia, Switzerland, Lithuania, Germany, and several regions of Russia (Oniscenko GG et al 2007; Suss J et al 2008). Also, TBE endemic zones are apparently expanding in altitude from below 800 m above sea level to about 1,500 m, as recently reported from Austria and Slovakia (Holzmann H et al 2009; Lukan M et al, 2010).

Three subtypes of the tick-borne encephalitis virus (TBEV) cause human disease (Ecker M et al, 1999; Fauquet CM et al 2005): The European subtype is prevalent in western, northern, central and eastern parts of Europe, and in South Korea; the Far-Eastern subtype occurs in eastern parts of Russia, in Japan and China, and the Siberian subtype in all parts of Russia (predominates in the Asian parts of Russia). All three sub-types co-circulate in the Baltic, the European part of Russia, and in Siberia (Demina et al 2010; Yun et al 2009; Golovljova I et al 2004).

Most TBEV infections result from tick bites acquired through outdoor activities in forested areas, although about one third of confirmed TBE cases may not recall any tick exposure preceding their illness (Kaiser R 1999). Ticks become active at temperatures above 8º C and a relative humidity of 70-80%. The seasonal incidence of TBE coincides with increased tick exposure during spring, summer and fall (Gritsun TS et al 2003).

The European subtype of TBE is transmitted primarily by *Ixodes ricinus*, and the Far Eastern and Siberian subtypes mainly by *Ixodes persulcatus*. The percentage of TBEV-infected ticks varies considerably with time and location; 1-3 % of the ticks were found to carry the virus in endemic areas of Austria and Southern Germany, 1.7% in Lithuania, and 14.3% in a heavily affected location in Switzerland (Süss J et al, 1999; Han X et al 2005; Casati et al 2006). In 2006, surveillance of the tick populations in highly endemic areas of the Russian Federation showed rates of TBEV infection that frequently exceeded 10%; in the Penza Province 29.2% of the ticks were TBEV-infected (Onischenko GG et al, 2007). However, the incidence of TBE among inhabitants of an area depends on a variety of factors and is not directly correlated to the prevalence of TBEV in the local tick population (Süss J et al 2006, Stefanoff P et al 2010).
Larvae, nymphs, and adult ticks become infected when ingesting blood from viremic animals, particularly small rodents, and can subsequently infect vertebrate species including humans, during the next blood meal. In addition, ticks may acquire TBEV transovarially or through co-feeding.

More than 100 different species of animals including foxes, voles, deer, dogs, sheep, monkeys and horses can be infected by TBEV and some of these species act as a reservoir for this virus (Barrett P et al 2008). Occasionally, infected cows, goats or sheep may pass the virus in unpasteurized milk or milk products and infect humans through the alimentary route (Holzmann H et al 2009). Person-to-person transmission of TBEV has not been described.

Attempts at eliminating the disease through chemical extermination of the tick population were unsuccessful or were discontinued for ecological reasons; the protective impact of impregnated clothing or the use of repellents have been at best short-lived (Hoffmann G, 1978). However, when staying out-door in endemic areas the risk of exposure to TBEV can be reduced through appropriate clothing and daily inspection of the skin for possible ticks to be removed. The risk of TBEV infection is negligible for persons who remain in urban or non-forested areas and who do not consume unpasteurized dairy products.

The virus, pathogenesis, and etiological diagnosis
TBEV is a member of the genus Flavivirus of the Flaviviridae family, which comprises about 70 viruses including dengue viruses (DV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), West-Nile virus (WNV) and also tick-borne viruses other than TBEV such as Kyasanur Forest disease virus (KFDV), Omsk hemorrhagic fever virus (OHFV), and Powassan virus (POW). The TBEV virion consists of a single-stranded RNA molecule enclosed by the core membrane and the envelope (E) protein. The E-protein contains the antigenic determinants responsible for haemagglutination and neutralization and induces protective immunity in the host. The three genetically and antigenically closely related subtypes of TBEV (Western, Far-Eastern, and Siberian) are not subject to significant antigenic variation (Holzmann H et al 1992; Ecker M et al 1999).

Following the bite of an infected tick, TBEV first replicates in the local dermal cells, subsequently in the regional lymph nodes and the reticuloendothelial system. The virus crosses the blood-brain barrier after infection of the capillary endothelium. In fatal cases, characteristic neuropathologic changes include polioencephalomyelitis which is accentuated in the spinal cord, brain stem and cerebellum (Gelpi E et al 2006).

The etiological diagnosis of TBE requires laboratory confirmation, as the clinical manifestations are relatively non-specific. During the initial viremic phase of the disease, TBEV may be detected by polymerase chain reaction (PCR) tests (Saksida A et al 2005) or recovered through inoculation into suitable cell-cultures or suckling mice. During the second, neurological stage, TBEV can in rare cases be detected in the cerebrospinal fluid or brain. Antibodies against TBEV are normally detectable at the time of neurological symptoms and serodiagnosis is based on a variety of methods including enzyme-linked immunosorbent assays (ELISA), tests for neutralizing antibodies (NT), and haemagglutination inhibition
techniques (HI). In cases of previous exposure to other flaviviruses (e.g. DV, YFV JEV, WNV, KFDV, OHV, or POW, including vaccination against YF or JE), tests for TBEV-specific IgG may show false positive results due to cross-reacting antibodies (Calisher et al 1989). In those cases, the use of a highly specific neutralization assay is required for determination of immunity (Sonnenberg K et al, 2004; Holzmann H 2003).

**The disease**

The incubation period lasting 2-28 days (most commonly 7-14 days) is followed by 1-8 days of nonspecific signs and symptoms such as fatigue, headache, aches of the back and limbs, nausea, and general malaise, usually combined with fever of 38°C, or more. TBE may run a mono- or a biphasic course: after an asymptomatic interval of 1-20 days about one third of clinical cases experience a second phase of the disease characterized by fever frequently exceeding 40°C and signs of central nervous system (CNS) involvement, such as meningitis, encephalitis (notably cerebellar ataxia), myelitis, or radiculitis. Encephalitic patients may develop stupor, pyramidal tract dysfunction as well as paralyses that frequently involve muscles of the shoulder region. In up to 40% of encephalitic cases TBE results in permanent central nervous sequelae (Kaiser R et al, 1999) including various neuropsychiatric and cognitive complaints characteristic of the postencephalitic syndrome (Haglund M et al 1996). There is no specific treatment for TBE.

Clinical observations have suggested an association between severity of TBE and the involved viral subtype, whereby the Far-Eastern variety seems to cause more severe disease than its European counterpart, and the Siberian subtype to occupy an intermediate position. Case-fatality rates (CFRs) of ≥20%, 6-8%, and 1-2%, respectively, have been reported for the Far Eastern, the Siberian, and the European subtypes (for references, see Gritsun TS et al 2003). However, CFRs are difficult to compare; recent unpublished estimates in Russia for these subtypes were 12%, 2%, and 1%, respectively (Platonov A et al, 2011). Subtype-associated differences in terms of age preference and disease manifestation are also reported. Thus, compared with the European subtype the Far-Eastern variety of TBEV seems to be characterized by more gradual onset and by affecting children more severely than adults (Barrett PN et al 2008). With the Western TBEV, the CFR seems higher and sequelae more common in the adult and elderly population than observed in younger individuals (Kunze U et al, 2005). Fatal haemorrhagic fever has been associated with the Far-Eastern subtype of the TBEV (Ternovoi VA et al, 2003) whereas rare cases of chronic TBE, characterized by slow progression of the disease for ≥6 months, have been reported mainly with the Siberian subtype (Pogodina VV et al 2004).

Different criteria for patient selection and access to medical services as well as differences of age-specific exposure could account for part of these subtype associated discrepancies.
TBE vaccines

The first vaccine against TBEV was developed in 1937 in the Soviet Union where outbreaks of TBE (then called Russian Spring and Summer Encephalitis) were of considerable public health concern. The first generation mouse-brain derived viral vaccine was efficacious, but resulted in frequent adverse events. Modern, less reactogenic TBE vaccines are based on formalin inactivated strains of TBEV produced in cell cultures. Currently, four different TBE vaccines are licensed: FSME-Immune® and Encepur® are manufactured in Austria and Germany, respectively, and are based on European strains of the virus whereas TBE vaccine Moscow (TBE-Moscow) and EnceVir® are manufactured in Russia based on Far Eastern strains.

Although numerous observational studies, in particular on the Western vaccines, testify to their safety and effectiveness, no randomized, controlled trials have been conducted to demonstrate the efficacy of these vaccines in protecting against clinical TBE. Given their excellent public health record, randomized controlled trials of effectiveness of these vaccines would now be considered unethical.

Immunogenicity is assessed using methods such as ELISA, NT, or HI. Presence of circulating TBEV-antibodies at or above locally agreed concentrations (e.g. an NT titer of ≥10) is commonly considered as surrogate markers of protection against TBE (Holzmann H et al 1996). However, systematic clinical studies to substantiate this assumption are not available. Data on the immunogenicity of different TBE vaccines are not directly comparable, since the manufacturers use different tests and independent head to head comparisons are rare.

Western TBE vaccines

The Western TBE vaccines are marketed as FSME-IMMUN® (new formulation post 2001) and Encepur adults®; their respective pediatric formulations are FSME-IMMUN(Junior)® and Encepur-K®. Children are defined as 1-15 years old with FSME-IMMUN (Junior)®, and as 1-11 years old with Encepur-K®.

FSME-IMMUN® (new) is based on the Neudörfl strain of the European TBEV subtype, Human albumin is used as stabilizer. The antigen content per dose is 2.4 μg for adults and 1.2 μg for children. Encepur® is based on the K23 strain of TBEV. Sucrose is used as stabilizer. The antigen content is 1.5 μg per dose for adults and 0.75 μg for children 1-11 years old. Both vaccines are produced according to WHO’s Good Manufacturing Practice guidelines (TRS No 889, 1999). They are produced on chick embryonic fibroblast cells, inactivated by formaldehyde, and use aluminium hydroxide as adjuvant. The vaccines do not contain polygeline or thiomersal, but traces of formaldehyde, protamine sulfate, gentamicin, and neomycin may be found in the final products. Both vaccines have a shelf-life of 24 months when stored at 2°C to 8°C. They are supplied in prefilled syringes for intramuscular administration, each syringe containing 0.5 ml for adults and 0.25 ml for children.
According to the manufacturers, both FSME-IMMUN® and Encepur® require 3 doses for a complete primary course of immunization. For the “conventional” vaccination schedules the dose intervals are 1-3 months between doses one and two, and 9-12 months between doses two and three. For the “accelerated” schedule of FSME-IMMUN®, the recommendation is vaccination on days 0 and 14, and a third dose after 6-12 months whereas for Encepur® the recommended “rapid” schedule entails vaccination on days 0, 7, and 21, followed by a fourth dose 12 to 18 months later. With both vaccines the manufacturers recommend a booster 3 years after completion of the primary series and subsequent boosters at intervals of 5 years (3 year intervals for individuals aged >60 years).

To identify the most suitable schedule for Encepur adults® and Encepur children®, respectively, two randomised, controlled studies were conducted that compared the immune responses (by ELISA and NT) obtained by 4 different schedules; one study included 398 individuals aged ≥12 years (Schøndorf I et al 2007a), the other 294 children aged 1 to 11 years (Schøndorf I et al 2007 b). Both studies concluded that the rapid immunization schedule prescribing vaccination on days 0, 7 and 21 compared favorably with vaccination on days 0, 28 and 300; days 0, 21 and 300; and days 0, 14 and 300, respectively, both in terms of fast induction of an immune response and stable NT titers for at least 300 days. Similar studies are not available for FSME-IMMUN®.

Vaccine immunogenicity and effectiveness

With both Encepur® and FSME-IMMUN® several studies have been published on the immunogenicity following primary immunization (Zent O et al 2003; Schoendorf I et al 2007a and 2007b; Wittermann C et al 2009; Ehrlich HJ et al 2003; Loew-Baselli A et al 2006; Pöllabauer EM et al 2006 a and b). A recent Cochrane review (Demicheli et al, 2009) summarized seroconversion data obtained from 11 vaccine trials including 4 RCTs of currently licensed Western vaccines (Encepur children, Encepur Adults, and FSME-IMMUN® "new"). A total of 5063 children and adults were included in these 4 trials, and with each of the vaccines, seroconversion by ELISA, HI, or NT were obtained in 92%-100% of the respective vaccinees. Similar high immunogenicity was achieved both with conventional (days 0, 28, and 300) and rapid (days 0,7 and 21) immunization schedules. In a subsequent RCT, >95% of the enrolled 334 children achieved neutralization titres ≥10 following 2 doses of Encepur Children or FSME-IMMUN® Junior (Wittermann C et al. 2009).

Little information is available on immunogenicity and effectiveness of TBE vaccines in cases when the recommended immunization intervals were grossly extended. A recent study on the persistence of immune memory in individuals who had not followed the regular schedule for TBE vaccination (Schosser R et al 2009). In the majority of cases, evidence of immunological priming as reflected by an anamnestic antibody response to TBE antigen, persisted irrespective of the time elapsed since the last vaccination (i.e. up to 20 years), even in individuals who had previously received only one TBE-vaccination, and in cases who were sero-negative prior to the booster. This finding suggests that extended intervals between the first two or three vaccinations is not a critical parameter for the success of subsequent immunizations. Further support for this conclusion is provided by an earlier study showing that the field effectiveness of Western TBE vaccines was around 95% even in irregularly
vaccinated subjects (Heinz et al, 2007). On the other hand, the demonstration of immunological priming alone is likely to an insufficient surrogate marker for protection in the case of TBE (Stiasny et al 2009).

Vaccine breakthroughs are rare, but they do occur, particularly in elderly individuals (Stiasny et al 2009, Andersson et al 2010). Thus, 25 breakthrough cases were reported in Austria between 2002-2008, 8 of whom vaccinated according to the regular vaccination scheme, and during the period 2000-2008, 27 break-through cases were described in Sweden, of whom 21 had received ≥ 2 doses according to schedule.

Studies on field-effectiveness in Austria for the years 1994-2001 showed protection rates against clinical TBE of 96.4% -100% following two doses and 96% - 98.7% following three doses of FSME-IMMUN® (Kunz C, 2003). These studies were based extensive post-licensure surveillance and the assumption that the whole Austrian population is at risk of infection. In similar studies covering the period 2000-2006, the overall effectiveness of the vaccine was about 99% in those with a documented history of at least three vaccinations within the recommended schedule (Heinz FX et al 2007). The Austrian experience shows that with current vaccines, high vaccination coverage can lead to a dramatic decline of the incidence of TBE.

**Duration of protection and the need for booster doses**

Longitudinal studies show that the annual decline in geometric mean titres (GMT) of neutralizing antibody is less following the primary series plus at least one booster than following the primary series only and also that in general, immunity following at least one booster dose lasts longer than the previously expected 60 months (Paulke-Korinek et al, 2009, Rendi-Wagner, 2007, Rendi-Wagner et al, 2004; Rendi-Wagner P et al, 2006; Loew-Baselli A et al, 2009; Wittermann C et al 2009, Plentz A et al 2009).

Similar rates of decline were observed irrespective of age, but those aged ≥60 years were more likely than younger individuals to become seronegative because they achieve lower antibody titers following boosters (Hainz et al 2004; Loew-Baselli et al, 2009, Paulke-Korinek et al, 2009, Rendi-Wagner et al, 2004b, Rendi-Wagner et al, 2007, Weinberger B et al 2010). In particular, those who started their primary course only at the age of ≥60 years showed reduced ability to respond to recall antigens. On the other hand, elderly persons who received primary TBE immunization when they were young responded to boosting similar to young people (Weinberger B et al, 2010).

Data from Austria indicate that in more than 90% of vaccinees, a TBE booster induce protective antibody levels that remain stable for at least 6 years and that the occasional break-through infections occur independent of time since last immunization (Paulke-Korinek et al 2009). Subsequent data from Austria show that in >90% of vaccinees protective antibody titers persist for at least 8 years following last booster immunization (WHO Background document).

As extended booster intervals will reduce costs and improve compliance, recommendations for TBE vaccine boosters are under revision in several countries. Currently, Switzerland
recommends 10 year intervals between the primary series and the first booster, as well as between subsequent booster doses (Bull BAG 2006; Nr. 13: 225-231).

Safety of Encepur® and FSME-IMMUN®

With pre-2001 formulations of these vaccines, adverse events were relatively frequent. Current formulations of FSME-IMMUN® and Encepur® represent considerable improvements in this regard and these vaccines are considered very safe (Zent O et al, 2005a). The above mentioned Cochrane review (Demicheli et al, 2009) summarized also safety data obtained from the 4 RCTs on Encepur children, Encepur Adults, and FSME-IMMUN "new". A total of 5063 children and adults were included in these trials. Although adverse events were commonly reported (transient redness and pain at the site of injection in up to 45% of the cases and fever in up to 5-6%), none of these events were serious or life threatening. In a single-blind, multi-center, randomized, controlled, phase III clinical study comparing the immunogenicity and safety of FSME-IMMUN Junior® and Encepur Children® in 303 children aged 1-11 years, systemic reaction rates were few and similar between the vaccines (Pöllabauer EM et al et al 2010).

Adverse events following booster doses of TBE vaccine were investigated in adults aged 18-67 years whose primary series had consisted of two doses of either FSME-IMMUN® or Encepur adults® and a third vaccination with FSME-IMMUN®. Adverse events associated with the booster given 3 years later were predominantly mild and occurred with a low frequency (Loew-Baselli A et al 2009). In another study, a second Encepur® booster 3 years after the first booster vaccination was well tolerated by all vaccinees (Beran J et al 2004).

Post-marketing studies confirm the absence of severe adverse events following administration of these vaccines. Thus, in 2002 an independent postmarketing sentinel study reported 0,413% adverse events following 25,905 vaccinations (Encepur® and FSME-IMMUN®); mild to moderate fever (<40°C), local reactions, and pain at the injection site were the most common complaints (Weinzettel et al., 2007). Similarly, post marketing surveillance following the distribution of more than five million vaccine doses did not disclose any potential safety risk (Zent O 2005). More recently, The safety of FSME-IMMUN® and Encepur® were compared also in a post licensure, randomized, controlled, single-blind, multi-centre trial that included a total of 334 children (Wittermann et al 2009). Both vaccines were well tolerated, with comparable safety profiles; no vaccine-related serious adverse events were reported. There are no reports indicating impaired immunogenicity or safety when Western TBE vaccines are administered simultaneously with other vaccines, for example in travelers.

Russian TBE vaccines

The TBE vaccine Moscow (TBE-Moscow) was approved for use in adults in 1982 and in 1999, following further improvement of the purification process, approved also for children ≥3 years of age. Since 1982, more than 25 million people in Russia and neighboring countries have received this vaccine (Vorob’eva MS et al, 2007).
TBE-Moscow is based on the Sofjin strain of the Far Eastern TBEV subtype. Following passages in mouse brain the virus is further propagated in primary chicken embryo cells. Harvested virus is inactivated by formalin, filtrated, concentrated, treated with the excipient protamine sulfate, stabilized through the addition of human albumin and gelatin, and finally lyophilized. The concentration of viral protein per dose is 0.50-0.75 μg, and immunogenicity is adjusted to preset standards. Before use, lyophilized vaccine is dissolved in fluid containing the adjuvant aluminum hydroxide. EnceVir® was licensed in the Russian Federation in 2001. This vaccine is based on the TBEV-Fe strain 205. The development steps of EnceVir® are nearly identical with those used for the production of the TBE-Moscow vaccine; the concentration of viral protein per dose is 2.0-2.5 μg, aluminum hydroxide is used as adjuvant, but EnceVir® is not lyophilized.

The manufacturing process of both TBE vaccine Moscow and EnceVir® follows WHO’s Manufacturing requirements (TRS No 889, 1999) and is controlled by the national Russian authorities (Vorob’eva MS et al, 2007). When stored at 2-8°C, the shelf life is 2 years for EnceVir® and 3 years for TBE vaccine Moscow. Both vaccines are stable for 2 days at 9-25°C.

The Russian vaccines are not licensed for children below 3 years of age. Above this age, all vaccinees receive 0.5 mL of either vaccine administered intramuscularly. According to the manufacturers, the standard primary immunization schedule consists of two doses given at an interval of 1-7 months. For EnceVir, a rapid schedule for emergency situations prescribes 5-7 days between the first two doses. Both schedules require a booster 12 months after the second dose, and further booster doses are recommended at 3-year intervals.

Immunogenicity and effectiveness
The immunogenicity (defined by HI) of TBE vaccine Moscow and FSME-IMMUN® was compared in children aged 7-17 years. Four weeks after the second vaccine dose, 91.5% of those receiving TBE vaccine Moscow and 98.7% of the FSME-IMMUN® recipients had seroconverted. Comparative immunogenicity studies of TBE vaccine Moscow and EnceVir® vaccines were carried out in 2001-2002 (Gorbunov et al, 2002, Krasilnikov 2002). Using HI tests, the immune response following two doses of either TBE-Moscow or EnceVir® was assessed in 200 adults, of whom half the number received the second dose after 2 months, the other half after 5 months. With TBE-Moscow antibody titers ≥1:80 were detected in 84% and 93% of subjects, respectively; with EnceVir® the corresponding results were 82% and 89%. Similarly, in 2003, the Russian National Regulatory Authority conducted a comparative evaluation of the TBE-Moscow and EnceVir® vaccines in 325 children and adolescents (Pavlova LI et al 2003). The participants were stratified into three age groups (3-6 years, 7-14 years and 15-18 years). After two doses of the respective vaccine administered 2 months apart, TBE-Moscow showed ≥4-fold increase of HI-antibody titres in 96%, 93% and 89% of the vaccinees, respectively, whereas the corresponding results with EnceVir® were 84%, 97% and 92%.
A recent study involving a total of 290 adults compared the immunogenicity of TBE-Moscow, EnceVir®, and the two Western vaccines FSME-IMMUN® (new) and Encepur® adults (Leonova GN et al 2009). Immunogenicity was measured 2-5 months and 2 years following the administration of 3 doses of the respective vaccine. All vaccines induced neutralizing antibody against the Far Eastern subtype strain P-73. With TBE-Moscow, antibody was detected in 100% and in 94% of the vaccinees after 2-5 months and two years, respectively. With EnceVir® the corresponding figures were 88% and 84%, with FSME-IMMUN® 88.2% and 78.1%, and with Encepur® 100% and 100%.

A mass immunization programme that was initiated in 1996 in the Sverdlovsk Region, Russia demonstrated high effectiveness of TBE. By 2005, 2.7 million people had received three doses of TBE vaccine, in most cases TBE-Moscow (Pogodina et al, 2006; Romanenko at al 2007). Vaccination coverage increased from 35% at the beginning of the programme to 55% in 2000 and to 72% in 2006. In this region, the incidence of TBE cases per 100 000 inhabitants decreased from 42.1 in 1996 to 9.7 in 2000 and to 5.1 in 2006. The number of cases was reduced in all age groups. Comparison of the number of TBE cases in vaccinated and non vaccinated groups suggested that vaccine effectiveness increased from 62% in 2000 to 89% in 2006. In part, this increase may be a consequence of more stringent diagnostic criteria (Romanenko et al, 2007). Following routine immunization of children in the Russian Krasnoyarsk Region, the incidence of TBE decreased from 48.5/100 000 in 1999 to 6.1/100 000 in 2003 (Borodina TN et al 2004).

Protracted surveillance following the three primary doses of EnceVir® showed persistence of high antibody levels during at least 3 years (Il’ichenko et al 2009). In the Sverdlovsk Region, the incidence of TBE breakthrough cases in fully immunized persons was in 2006 calculated at 1.5/100 000 (incidence of TBE in non-vaccinated individuals 13.0/100 000). Both Russian and Western vaccines were used, but TBE-Moscow accounted for about 80% of all TBE-vaccinations in this area (Romanenko VV et al, 2007). With the Russian vaccines there are currently no details available on the induction and persistence of immunity in elderly persons.

**Safety of TBE vaccine Moscow and EnceVir®**

Large-scale, randomized, controlled safety trials of these vaccines have not been published so far. Small-scale studies on systemic and local adverse events suggest a moderate reactogenicity profile with no significant differences between the two vaccines. In 2002-2003, the Tarasevich State Institute for Standardization and Control of Medical Biological Products assessed the local and systemic reactogenicity of TBE-Moscow and EnceVir® in a trial that included 325 children and 400 adults (Pavlova LI et al 2003). No severe adverse events were recorded. Both vaccines were found to be moderately reactogenic without statistically significant differences between the two. Similar conclusions on the safety of TBE-Moscow were reached in other studies (Pavlova et al 1999, Krasilnikov et al, 2002). Furthermore, post-marketing surveillance of EnceVir® did not reveal any severe adverse events (Il’ichenko TE et al 2009) and no vaccine-associated residual complications have been reported to the national control authorities (MichailovI, personal communication 2010; Romanenko VV et al 2007). There are no indications of impaired immunogenicity or safety when the Russian TBE
vaccines are administered simultaneously with other vaccines, for example in travelers. There are presently no reports available to us on the immunogenicity and safety of Russian TBE vaccines when administered simultaneously with other vaccines.

**Cross-protection by current TBE-vaccines**

There is limited clinical evidence that the two Western TBE vaccines induce protective immunity not only against the homologous subtype, but also against the Far Eastern and Siberian subtypes of the virus. The genetic and antigenic similarity between these subtypes, as well as evidences from non-clinical studies, makes such cross protection likely, however. Immunization of adults with Encepur® induced antibodies with high neutralizing capacity against strains of both the Western and the Far Eastern subtypes of TBEV (Leonova GN et al, 2007). Similarly, all four TBE vaccines induce neutralizing antibodies against Far eastern subtype virus (Leonova 2009). Furthermore, a recent study using FSME IMMUN® post immunization sera showed identical neutralization titers against the European, Siberian, and Far Eastern TBE virus (Orlinger KK et al, 2011). Further support for cross-protective immunity is provided by preclinical studies showing that immunization of mice with vaccine of the European subtype protected against lethal challenges with a variety of eastern TBEV isolates (Holzmann H et al, 1992; Hayasaka D et al, 2001).

Several studies suggest that existing TBE vaccines can be used interchangeably (Broker M 2006; Leonova et al 2009, Wittermann et al 2009; Loew-Baselli et al 2006).

**Contraindications and precautions**

Although currently licensed TBE vaccines are produced in chicken embryo cells, mild allergy to egg protein are not considered a contraindication.

The induction of protective immunity may be inadequate in individuals undergoing immunosuppressive therapy. In such cases, the antibody response should be assessed and, if necessary, an additional dose of TBE vaccine be administered. In general, TBE vaccination should be postponed during acute feverish infection (temperature >38.5°C) and should be administered to pregnant or nursing women only after a careful risk-benefit analysis.

Persons who have been exposed to flaviviruses other than TBEV may develop flavivirus cross-reactive antibodies that not only could interfere with serological tests (Holzmann H, 1996). Given that TBE-immunization programmes are likely to be organized in settings where TBEV and related flaviviruses co-exist, the possible implications of exposure to cross-reacting antigens should be further explored scientifically.

**Post-exposure prophylaxis**

Based on the assumption that vaccination after a tick bite is unlikely to induce immunity in time before possible onset of disease and considering the theoretical risk of antibody-dependent enhancement, no post-exposure prophylaxis is currently recommended after a tick bite in non-vaccinated patients (Bröker M et al, 2008).
In Western Europe, the injection of immune globulins containing high concentrations of antibodies against TBEV showed no beneficial effect when used for post-exposure prophylaxis and this approach is no longer recommended (Arras et al 1996). In contrast, a recent review of Russian experiences in this field indicates some protective effect of early post-exposure administration using Russian immunoglobulin preparations (Pen’efskaya et al, 2010).

**Cost-effectiveness of TBE vaccination**

Where TBE is prevalent, the disease causes high costs both at the individual and societal levels, in particular due to its frequent long-term neurological sequelae (Donoso Mantke et al., 2008, Kaiser, 1999, Kaiser, 2008). The immunization campaigns in Austria 1991-2000 were estimated to save an equivalent of US$ 80 million by reducing TBE-associated patient care, loss of productivity, and premature retirement (Schwarz B, 1993). In Sweden, the cost-effectiveness ratio for immunisation was estimated to be 1:68, if hypothetically 75% of cases were averted by vaccination of 42% of the Stockholm population (Haglund M et al 1996).

Cost-effectiveness calculations are critically dependent on how well the target group can be defined.

**WHO policy on the use of TBE vaccine**

Immunization offers the most effective protection against TBE (see Grading table I: immunogenicity/protective immunity). The two TBE vaccines that are manufactured in Western Europe are considered safe and efficacious for individuals ≥1 year of age. Favorable safety and efficacy profiles for individuals ≥3 years of age are reported also for the two Russian TBE vaccines, although for the latter products the published safety and effectiveness data are more limited (see Grading table II: safety). Current TBE vaccines seem to protect against all TBEV subtypes circulating in endemic areas of Asia and Europe (see Grading table III: cross protection within subtypes).

As the incidence of TBE may vary considerably between and even within geographic regions, public immunization strategies should be based on careful risk assessment even at district level and be appropriate to the local endemic situation. Therefore, establishing case reporting of TBE is essential before deciding on the most appropriate preventive measures. Similarly, health authorities are encouraged to conduct a cost-effectiveness analysis before possibly recommending programmatic TBE vaccination.

In areas that are highly endemic for TBE (average pre-vaccination incidence of clinical TBE ≥5/100 000/year), implying a high individual risk of infection for the entire population, WHO recommends to offer TBE vaccination for all age groups either through regular immunization programmes or immunization campaigns. Where a large
percentage of children is likely to be exposed to TBEV infected ticks, inclusion of TBE vaccination into the national or regional immunization programmes should be considered. Routine TBE vaccination of children is likely to result in high coverage and to facilitate monitoring the immunization status of individual vaccinees.

As the disease tends to be most serious and the immune response following primary immunization tends to be relatively low in individuals >60 years of age, elderly people at risk of infection constitute an important target group for TBE immunization.

Where the pre-vaccination incidence of TBE is moderate (>1 to <5/100,000/year, or low (annual average over a 5-year period of about 1/100 000) and/or is limited to particular geographic locations or certain out-door activities, TBE immunisation should be targeted at individuals of the most affected locations and those at highest risk of exposure according to live-style and occupation. This may include travelers from non-endemic to endemic areas.

TBE vaccination requires a primary series consisting of 3 doses and for those at continued risk, one or more booster doses. However, the duration of protection is poorly defined and the scientific evidence for the manufacturers’ choice of the primary immunization schedules is relatively weak. Within the considerable range of acceptable dose intervals, programme managers should select the most rational schedule according to the respective national, regional or district immunization programmes.

With the Western vaccines an interval of 1-3 months is recommended between the first two doses, and 5-12 months between the second and third doses. When rapid protection is required, for example for travelers to TBE endemic areas, the interval between the first two doses may be reduced to 1-2 weeks. The first booster dose should be given 3-5 years after the primary series. WHO recommends that the intervals of subsequent boosters are extended from the current 3-5 years to 10 years in children and adults. However, for those having received their primary immunization beyond the age of 60 years, boosting every 3-5 years appears prudent (see Grading table IV: duration of protection).

With the Russian vaccines, the recommend intervals are 1-7 months between the first two doses, and 6-12 months between the second and third doses. Booster doses are recommended every 3 years for those at continued risk of TBEV exposure. The currently recommended booster interval should be practiced until more data have been generated on the duration of protection induced by Russian TBE vaccines.

Regardless of duration of the delay, interrupted schedules should be resumed without repeating previous doses.

Although there is no experience to suggest any interference between existing TBE vaccines and simultaneously administered vaccines, the issue of potential immunological interactions needs to be addressed by appropriate studies. In addition,
more information is needed on the immune response to TBE vaccine in individuals who have received previous YF or JE immunization.

Post-exposure TBE vaccination following a tick-bite is not recommended.

Administration of specific immunoglobulin for passive post-exposure prophylaxis is not recommended in Western Europe but is sometimes practiced in Russia.

Standardized case definitions and reporting requirements across endemic countries are greatly needed to better define the burden of disease, to develop evidence-based vaccination recommendations, and to measure the impact of vaccination. This also entails endorsement of standard diagnostic procedures for patients with suspected TBE and well as standardized measurement and follow-up processes to identify long-term sequelae after TBE. Similarly, standardized reagents are needed to allow comparison of test results across laboratories.

In all endemic areas information on the disease, its vector and transmission patterns as well as on available prophylactic measures should be readily available, for example in schools, doctors’ offices and in tourist information leaflets.

**Literature** (in WER, the 40-50 finally selected references will occur as footnotes)


Bundesamt für Gesundheit, Schweiz:Bull BAG 2006; Nr. 13: 225-231


Gorbunov MA et al. [Results of clinical evaluation of EnceVir vaccine against tick-borne encephalitis], *Epidemiology and Vaccinoprophilaxis*, 2002, v5, 49. [Article in Russian].

Grading table of scientific evidence: Table I immunogenicity/protective immunity, with key references.

Grading table of scientific evidence: Table II safety, with key references.

Grading table of scientific evidence: Table III cross protection between serotypes, with key references.


Il'ichenko TE et al. [Organization of Public Health], *Siberian Journal of Medicine*, 2009, 2: 50-55. [Article in Russian].


Pavlova BG et al. [Immunization of children and adolescents with inactivated vaccines against tick-borne encephalitis]. *Biopreparations*, 2003, 1: 24-28. [Article in Russian]

Pavlova LI et al. [A cultured concentrated inactivated vaccine against tick-borne encephalitis studied during the immunization of children and adolescents]. *Zh Mikrobiol Epidemiol Immunobiologiya*, 1999, 6:50-53. [Article in Russian].


Pen'evskaia NA et al. [Efficiency of use of immunoglobulin preparations for the postexposure prevention of tick-borne encephalitis in Russia (a review of semi-centennial experience)]. *Med Parazitol (Mosk)*, 2010, 1:53-9.[Article in Russian]


Romanenko VV et al. [Experience in implementing the mass immunization program against tick-borne encephalitis in the Sverdlovsk Region]. *Vopr Virusol.*, 2007, 6: 22-25.[Article in Russian]


Schosser R et al. Seropositivity before and seroprotection after a booster vaccination with FSME-IMMUN® adults in subjects with a time interval of > 4,5 years since the last TBE vaccination. In: *International Jena Symposium on tick borne diseases*, Weimar, 2009.


Schwarz B. [Health economics of early summer meningoencephalitis in Austria. Effects of a vaccination campaign 1981 to 1990], *Wiener Medizinische Wochenschrift*, 1993, 143: 551-555.[Article in German]


Vorob'eva MS et al. [Vaccines, immunoglobulins, and test systems for the prevention and diagnosis of tick-borne encephalitis]. *Vopr Virusol.*, 2007, 52:30-36. [Article in Russian]

Vorob'eva MS et al. [Comparative study of inactivated cultured vaccines against tick-borne encephalitis manufactured in Russia and in Austria by the "Immuno" firm]. *Vopr Virusol.*, 1996, 41: 221-224. [Article in Russian]


Table I: Does a primary series of the currently available TBE vaccines protect children and adults of all ages against clinical TBE for 3 years?

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors decreasing confidence</td>
<td>Limitation in study design</td>
<td>None serious&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Inconsistency</td>
<td>None serious</td>
</tr>
<tr>
<td></td>
<td>Indirectness</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Imprecision</td>
<td>None serious</td>
</tr>
<tr>
<td></td>
<td>Publication bias</td>
<td>None serious</td>
</tr>
<tr>
<td>Factors increasing confidence</td>
<td>Large effect</td>
<td>Very large effect&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dose-response</td>
<td>Evidence of dose-response&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Antagonistic bias and confounding</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Final Score</td>
<td>6 (Maximum score is 4)</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Findings

<table>
<thead>
<tr>
<th>Quality</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are very confident that the true effect lies close to that of the estimate of effect on health outcome.</td>
<td></td>
</tr>
<tr>
<td>There is strong evidence that a primary series of the currently available TBE vaccines protects children and adults of all ages against clinical TBE for 3 years.</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> There are no trials on vaccine efficacy against clinical TBE; indirect evidence of protection is provided by trials using immunogenicity (in this case mainly induction of neutralizing antibodies) as an endpoint. These 7 RCTs show strong antibody induction (high seroconversion rates) following TBE vaccination. In addition, observational studies regularly demonstrate the strong immunogenicity of currently available TBE vaccines. Four observational studies which were followed up for 3 years showed persistence of neutralizing antibodies throughout this period; <sup>2</sup> four of the 7 RCTs suffer from inappropriate randomization and/or lack of concealment; no serious limitation in study design for the remaining 3; <sup>3</sup> Immunogenicity rather than clinical protection is used as an endpoint. There is a lack of a standardized serological correlate of protection; <sup>4</sup> Very high seroconversion rates demonstrated in RCTs and observational studies. Where measured, observational studies consistently indicate high levels of protection for at least 3 years; <sup>5</sup> Increasing reduction of clinical TBE with increasing immunization coverage observed through observational studies.
Randomised, controlled trials (RCTs) on immunogenicity

A recent Cochrane review (Demicheli et al, 2009) summarized seroconversion data obtained from 11 vaccine trials including 4 RCTs of currently licensed Western vaccines (Encepur children, Encepur Adults, and FSME-IMMUN® "new"). In these 4 trials a total of 5063 children and adults were followed up serologically for 6-12 months; all vaccinees reached seroconversion rates of 92%-100% by ELISA, HI, or NT (Ehrlich 2003; Loew-Baselli 2006; Schoendorf 2007; Schöndorf 2007). Similar high immunogenicity was achieved both with conventional (days 0, 28, and 300) and rapid (days 0, 7 and 21) immunization schedules. In a subsequent RCT, >95% of the enrolled 334 children achieved neutralization titres 1 10 following 2 doses of Encepur Children or FSME-IMMUN® Junior (Wittermann C et al. 2009).

Two additional RCTs pertain to the Russian vaccines TBE-Moscow and EnceVir®. A recent randomized study compared the immunogenicity in adults of TBE-Moscow, EnceVir®, and the two Western vaccines FSME-IMMUN® (new) and Encepur® adults (Leonova GN et al 2009). Immunogenicity was measured 2-5 months and 2 years following the administration of 3 doses of the respective vaccine. All vaccines induced neutralizing antibody against the Far Eastern subtype strain P-73. With TBE-Moscow, antibody was detected in 100% and in 94% of the vaccinees after 2-5 months and two years, respectively. With EnceVir® the corresponding figures were 88% and 84%, with FSME-IMMUN® 88.2% and 78.1%, and with Encepur® 100% and 100%. A single-blind, multi-center, randomized, controlled, phase III clinical study compared the immunogenicity and safety of FSME-IMMUN® Junior and Encepur® Children in 303 children aged 1-11 years. With FSME-IMMUN® Junior, the seropositivity rates as determined by NT 28 days after the second vaccination were 100.0% in all three age groups (1–2, 3–6 and 7–11 years). The corresponding rates with Encepur® Children were 100.0% in subjects aged 1–2 years, 95.5% in children aged 3–6 years and 97.6% in those aged 7–11 years (Pöllabauer EM et al 2010).

Observational studies on immunogenicity

Data on the immunogenicity of Encepur® from 8 clinical trials and post-marketing studies (database 7,500 subjects) showed that following primary immunization all subjects seroconverted or showed a fourfold increase in anti-TBEV antibodies (Zent O et al 2005). The seroconversion rate (ELISA) of FSME-IMMUN was 98.5-100% after primary immunization of 412 children aged 1-15 years (pediatric dose); 96% in 64 vaccinees 12-15 year old (also pediatric dose), and 98.2% in 57 vaccinees aged 16-35 years (adult dose) (Pöllabauer et al 2010).

In 2001-2002, two studies in Russia involving 200 adults showed that with TBE-Moscow, antibody titers 1:80 were detected in 84% and 93%, and with EnceVir® in 82% and 89% of the vaccinees, following two doses, 2 or 5 months apart (Gorbunov et al, 2002; Krasilnikov et al. 2002). Similarly, an evaluation involving 325 individuals stratified into the age groups 3-6 years, 7-14 years and 15-18 years, showed 4-fold increase of HI-antibody titres in 96%, 93% and 89%, respectively, using the TBE-Moscow vaccine, as compared to 84%, 97% and 92% with EnceVir® (Pavlova LI et al 2003).

Little information is available on immunogenicity and effectiveness of TBE vaccines in cases when the recommended immunization intervals were grossly extended. However, a recent study (Schosser R et al 2009) concluded that even the first TBE immunization mounts long lasting immune memory in 94% of vaccinated subjects.

Although vaccine breakthroughs do occur, they are rare (Sitasny et al 2009; Andersson CR et al 2009). Direct assessments of the break-through rate require RCTs against clinical outcome measures, which are currently unavailable.

Observational studies on persistence of neutralizing antibodies ! 3 years after primary TBE-immunization

After the primary 3-dose immunization with FSME-IMMUN®, Vene S et al (2007) found persistence of neutralizing antibody activity in 89-95% of 535 adult vaccinees before the first booster (due after 3 years). Loew-Baselli et al (2009) showed that following a primary series of 2 doses of Encepur® and one dose of FSME-IMMUN®, initial seropositivity rates by NT were 100%, decreasing to 96.8% in the first two years and to 95.4% after 3 years. With Encepur Adult®, neutralizing TBE antibodies (geometric mean titers) remained on a high level prior to the first booster (Zent et al 2003). Protracted surveillance following the three primary doses of EnceVir® demonstrated maintenance of high antibody levels during at least 3 years (Il’ichenko et al 2009).

References

Randomised, controlled trials (RCTs) on immunogenicity


Leonova GN, Pavlenko EV. Characterization of neutralizing antibodies to Far Eastern of tick-borne encephalitis virus subtype and the antibody avidity for four tick-borne encephalitis vaccines in human. Vaccine. 2009 May 11;27(21):2899-904.


Observational studies on immunogenicity


Gorbunov MA, Pavlova LI, Vorob’eva MS, Raschepkina MN, Stronin OB, 2002. [Results of clinical evaluation of EncoVir vaccine against tick-borne encephalitis], Epidemi. Vaccinoprophil, v5, 49


Pavlova LI, Gorbunov MA, Vorob’eva MS, Karavanov AS, Grachev VP, Ladyshenskaia IP, Rasdhchehpina MN, Meñnikova LN, Lebedeva TM, Meñnikov NA, Gusmanova AG, Deviatkov Mt, Rozanova EV, Mukachev MA. [A cultured concentrated inactivated vaccine against tick-borne encephalitis studied during the immunization of children and adolescents]. Zh Mikrobiol Epidemiol Immunobiol. 1999 Nov-Dec;(6):50-3.[Article in Russian]


Romanenko VV, Esiunina MS, Kiliachina AS. [Experience in implementing the mass immunization program against tick-borne encephalitis in the Sverdlovsk Region]. Vopr Virusol. 2007 Nov-Dec;52(6):22-5.[Article in Russian]


Observational studies on persistence of neutralizing antibodies ≥3 years after primary TBE-immunization

Il'ichenko TE, Bilalova GP, Stavitskaya NX, Solanik RG, Bistritskaya LD, Krasilnikov IV, 2009. [Organization of Public Health], Siberian Journal of Medicine, (Russia) 2, 50-55. (No summary in English).


Table II. Are the currently available TBE vaccines responsible for serious adverse vaccine reactions?

<table>
<thead>
<tr>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Studies/Starting Score</td>
<td></td>
</tr>
<tr>
<td>5 RCTs</td>
<td>4</td>
</tr>
<tr>
<td>Limitation in study design</td>
<td>None serious</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>None serious</td>
</tr>
<tr>
<td>Indirectness</td>
<td>None serious</td>
</tr>
<tr>
<td>Imprecision</td>
<td>Serious</td>
</tr>
<tr>
<td>Publication bias</td>
<td>None serious</td>
</tr>
<tr>
<td>Large effect</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Antagonistic bias and confounding</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Final Score</td>
<td>3</td>
</tr>
</tbody>
</table>

Quality Assessment

Factors decreasing confidence

- Limitation in study design: None serious
- Inconsistency: None serious
- Indirectness: None serious
- Imprecision: Serious
- Publication bias: None serious

Factors increasing confidence

- Large effect: Not applicable
- Dose-response: Not applicable
- Antagonistic bias and confounding: Not applicable

Final Score: 3

Summary of Findings

Quality

We are moderately confident in the estimate of effect on health outcome: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Conclusion

Current TBE vaccines are not causally associated with serious adverse vaccine reactions.

1 All RCTs on western vaccines. For Russian vaccines, only two observational studies are available. These are referenced below, but not included in the table. Clinical studies (RCTs as well as observational) consistently describe current TBE vaccines as moderately reactogenic, but so far, none has been causally linked to severe adverse events. In addition, post-market surveillance did not identify any report of serious vaccine-associated adverse events. 2 The RCTs suffer from inappropriate randomization and/or lack of concealment. Yet no serious adverse event were detected in either groups and hence this is not seen a critical limitation with respect to serious events. 3 Trials are of limited size, so that very rare adverse events could have been missed.

A recent Cochrane review (Demicheli et al, 2009) summarized seroconversion data obtained from 11 vaccine trials including 4 RCTs of currently licensed Western vaccines (Encepur children, Encepur Adults, and FSME-IMMUN® "new"). (Ehrlich 2003; Loew-Baselli 2006; Schoendorf 2007a; Schöndorf 2007b). In these 4 trials a total of 5063 children and adults were included. Although adverse events were commonly reported (transient redness and pain at the site of injection in up to 45% of the cases and fever in up to 5-6%), none of these events were considered as serious. An RCT recently conducted by Pollabauer EM et al (2010) compared safety between Encepur Children® and FSME-IMMUN Junior®. Systemic reaction rates were low and similar between the vaccines.

With TBE-Moscow and EnceVir® small-scale observational studies on systemic and local adverse events suggest a moderate reactogenicity profile with no significant differences between the two vaccines. The local and systemic reactogenicity of these Russian vaccines were assessed in a trial that included 325 children and 400 adults (Pavlova Li et al 2003). No severe adverse events were recorded. Similar conclusions on the safety of TBE-Moscow were reached in other studies (Pavlova et al 1999, Krasilnikov et al, 2002). Furthermore, passive
post-marketing surveillance of EnceVir® did not reveal any serious adverse events (Il’ichenko TE et al 2009).

During the period 2001-2009 about 42 million doses of FSME-IMMUN® and 30 million doses of Encepur® have been produced. Since 1982, approximately 25 million people have been immunized with TBE-Moscow (current version of the vaccine used since 1999); the corresponding figure for EnceVir (in use since 2001) is not available.

References


Il’ichenko TE, Bilalova GP, Stavitskaya NX, Solanik RG, Bistritskaya LD, Krasilnikov IV, 2009. [Organization of Public Health], Siberian Journal of Medicine, (Russia) 2, 50-55. (No summary in English).


Pavlova LI, Gorbunov MA, Vorob’eva MS, Karavanov AS, Grachev VP, Ladyshenskaia IP, Rashchepkina MN, Mel’nikova NA, Gusmanova AG, Deviatkov Ml, Rozanova EV, Mukachev MA. [A cultured concentrated inactivated vaccine against tick-borne encephalitis studied during the immunization of children and adolescents]. Zh Mikrobiol Epide miol Immunobiol. 1999 Nov-Dec;(6):50-3.[Article in Russian]


Table III. Do currently available TBE vaccines protect against clinical TBE with all 3 TBE virus subgroups (European, Far-Eastern, and Siberian)?

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Studies/Starting Score</td>
<td>5 observational</td>
<td>2</td>
</tr>
<tr>
<td>Limitation in study design</td>
<td>Serious 1</td>
<td>-1</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>None serious</td>
<td>0</td>
</tr>
<tr>
<td>Indirectness</td>
<td>Serious 1</td>
<td>-1</td>
</tr>
<tr>
<td>Imprecision</td>
<td>None Serious</td>
<td>0</td>
</tr>
<tr>
<td>Publication bias</td>
<td>None serious</td>
<td>0</td>
</tr>
<tr>
<td>Large effect</td>
<td>Very large effect 1</td>
<td>+2</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Not applicable</td>
<td>0</td>
</tr>
<tr>
<td>Antagonistic bias and confounding</td>
<td>Not applicable</td>
<td>0</td>
</tr>
<tr>
<td>Final Score</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

**Summary of Findings**

**Quality**

Our confidence in the estimate of the effect on the health outcome is limited: The true effect maybe substantially different from the estimate of the effect.

**Conclusion**

Currently available TBE vaccines protect against clinical TBE with all 3 TBEV subgroups (European, Far-Eastern, and Siberian).

1 Small number of strains tested. 2 Evidence based on in vivo as well as in vitro trials and serological studies, but no direct evidence from RCTs using clinical TBE as endpoint. 3 High protection rates observed and consistent conclusions of studies in animal models as well as in humans.

Evidence that the two Western TBE vaccines induce protective immunity not only against the homologous subtype, but also against the Far Eastern and Siberian subtypes of the virus, is provided by preclinical studies in mice. Thus, Holzmann H et al, 1992 found no statistically significant difference in the degree of protection when mice were immunized with European prototype vaccine virus and subsequently challenged with three selected Asian isolates and one isolate from the European part of the USSR. In vivo (mice) as well as in vitro studies by Hayasaka D et al (2002) showed that FSME-IMMUN® induced antibody that effectively neutralize Siberian, Far-Eastern, as well as European subtypes of TBEV. Leonova GN et al 2007 concluded that Encepur®/Adult induced a pronounced humoral immune response towards the genetically and antigenically heterogeneous P-69, P-202, and P-73 strains of the Far Eastern TBEV subtype.

In 2009, Leonova GN et al compared the immunogenicity in adults of TBE-Moscow, EnceVir®, and the two Western vaccines FSME-IMMUN® and Encepur® adults. Immunogenicity was measured 2-5 months and 2 years following the administration of 3 doses of the respective vaccine. All vaccines induced neutralizing antibody against the Far Eastern TBEV subtype.

This document is a draft
Eastern subtype strain P-73. With TBE-Moscow, antibody was detected in 100% and in 94% of the vaccinees after 2-5 months and two years, respectively. With EnceVir® the corresponding figures were 88% and 84%, with FSME-IMMUN® 88.2% and 78.1%, and with Encepur® 100% and 100%.

Recently, Orlinger KK et al (2011) showed that a tick-borne encephalitis vaccine based on the European prototype strain induces broadly reactive cross-neutralizing antibodies in humans against the European, Siberian, and Far Eastern TBE virus.

References


Leonova GN, Pavlenko EV. Characterization of neutralizing antibodies to Far Eastern of tick-borne encephalitis virus subtype and the antibody avidity for four tick-borne encephalitis vaccines in human. Vaccine. 2009 May 11;27(21):2899-904.


Table IV. Is protection against clinical TBE waning >3-5 years after one booster in individuals <60 years of age who previously received primary TBE immunization?

(Assessment based on Western TBE-vaccines only)

<table>
<thead>
<tr>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Studies/Starting Score</td>
<td>5 observational¹</td>
</tr>
<tr>
<td>Limitation in study design</td>
<td>None serious</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>None serious</td>
</tr>
<tr>
<td>Indirectness</td>
<td>Serious²</td>
</tr>
<tr>
<td>Imprecision</td>
<td>None serious</td>
</tr>
<tr>
<td>Publication bias</td>
<td>None serious</td>
</tr>
<tr>
<td>Large effect</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Antagonistic bias and confounding</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Final Score</td>
<td>1</td>
</tr>
</tbody>
</table>

Summary of Findings

Quality

We have very little confidence in the estimate of the effect on the health outcome. The true effect is likely to be substantially different from the estimate of effect.

Conclusion

There is no evidence of waning protection > 3-5 years after a booster following the primary series. Available evidence suggests that following a booster dose of TBE-vaccine, protection against clinical TBE persists for at least 6-8 years.

¹There are no trials on vaccine efficacy against clinical TBE; indirect evidence of protection is provided by trials using immunogenicity (in this case mainly induction of neutralizing antibodies) as an endpoint. Regardless of which of the two Western TBE vaccine that is used, all long-term serological studies show very low rates of waning of neutralizing antibody titres during the first 3-5 years following the booster. Also, where observation periods of up to 6-8 years have been achieved, neutralizing antibody titres suggesting protective immunity against TBE persist in the vast majority of vaccinees. Although on rare occasions break-through infections occur, (mostly in individuals aged >60 years), the incidence of break-through infections does not increase with time since last vaccination. Immunogenicity rather than clinical protection is used as an endpoint. There is lack of a standardized serological correlate of protection.

²Immunogenicity rather than clinical protection is used as an endpoint. There is lack of a standardized serological correlate of protection.

Studies on duration of protection following TBE vaccination.

A total of 222 adults 19-51 years of age were followed up serologically for 3 and 5 years after their first booster dose (Encepur® Adults). High antibody titres were recorded throughout the follow-up period. Neutralization test (NT) titres ! 10 were noted in 99% of subjects 3 and 5 years after the first booster vaccination (Plentz A et al 2009). Paulke-Korinek et al (2009) in a 6-year follow up study of 195 vaccinees who had previously received primary TBE vaccination (Encepur® Adults) and at least one booster, all remained seropositive (NT titres ! 1:2) throughout the observation period. In the age group <60 years, 94% had NT titres considered to be protective (! 1:10) six years after the last vaccine dose (86% in subjects aged ! 60 years). Rendi-Wagner (2007) found NT titres ! 10 in 96% (187/195) of the Encepur® Adults- vaccinated subjects at year 2, and 97% (232/240) at year 3 post-booster. An analysis by Wittermann C et al (2009), showed that 275 of 278 (99%) and all 190 (100%) of

This document is a draft
Encepur® Children recipients who completed the follow-up at 3 and 5 years, respectively, had NT titres ! 10. A longitudinal study in Sweden by Vene S et al (2007) showed that after the 3 primary doses of FSME-IMMUN®, neutralizing antibody titers of 1:15 persisted in 77% of the vaccinees before administration of the first booster dose, and in 89-95% of 535 adult vaccinees before administration of the second and third boosters (about 3 year intervals between doses).

Recent data indicate that in more than 90% of vaccinees, the primary series of TBE vaccination plus one TBE booster induce neutralizing antibody levels that remain stable for at least 8 years and that the occasional break-through infections occurs independent of time since last immunization (WHO Background paper).

Breakthrough infections in vaccinated individuals are rare, but do occur, particularly in elderly individuals (Stiasny et al 2009, Andersson et al 2010). Thus, 25 breakthrough cases were reported in Austria between 2002-2008, 8 of whom vaccinated according to the regular vaccination scheme, and during the period 2000-2008, 27 break-through cases were described in Sweden, of whom 21 had received 2 doses according to schedule. (Neither study tries to assess the incidence of break-through infections among vaccinated individuals).

References


WHO Background document on TBE vaccines, 2011.
# Background paper on Meningococcal Vaccines

**SAGE Working Group**

## Table of Contents

I. Background on the disease, routes of transmission, risk factors and treatment
- Pathophysiology
- Routes of transmission
- Signs and symptoms
- Risk Factors
- Diagnosis
- Prevention (Chemoprophylaxis and Vaccines)
- Treatment

II. Epidemiology
- Definition of epidemics and endemic situations
- Epidemiology of invasive meningococcal disease at country level
- Serogroups, Serotypes
- Carriage
- Duration of protection of natural disease/ acquisition of natural immunity
- Age specific attack rates
- Use of vaccines
- Replacement disease

III. Immunology, safety and effectiveness of meningococcal vaccines
- Correlates of protection against meningococcal disease
- Field effectiveness of vaccines
- Duration of immunity
- Herd protection
- Polysaccharide meningococcal vaccines
- Conjugate meningococcal vaccines
- MenC Conjugate vaccine
- Quadrivalent meningococcal conjugate vaccines
- MenA conjugate vaccine
- MenB OMV vaccines

IV. Cost effectiveness of vaccine and cost of disease
- Cost effectiveness of vaccines in Africa
- Cost of disease and impact on health systems in Africa
- Cost effectiveness of Men C conjugate vaccine

---
V. Fractional doses
  • Immunology.....................................................................................................32
  • Feasibility.........................................................................................................32

VI. Research needs on immunization against meningococcal disease..................34

VII. Recommendations............................................................................................36

VIII. References.......................................................................................................38
I. Background on the disease, routes of transmission, treatment and risk factor

*Neisseria meningitidis* is one of the leading causes of bacterial meningitis globally. It is a gram negative diplococcus that causes disease only in humans. Strains that cause invasive meningococcal disease (IMD) are classified into serogroups based on the type of polysaccharide capsule expressed, and these virulent strains are different from those that reside harmlessly in the nasopharynx resulting in an asymptomatic carrier state. A number of virulence factors have a role in the pathogenesis of the disease including lipoooligosaccharide and surface adhesive proteins along with the polysaccharide capsule.

Colonization of the upper respiratory mucosal surfaces by *N. meningitidis* is the first step in establishing a human carrier state and a precursor to invasive meningococcal disease. Meningococcal transmission among humans occurs largely through respiratory droplets and salivary secretions. In a small proportion of carriers, meningococci overcome host defenses, penetrate the mucosa, and gain access to the blood stream causing systemic disease including meningitis. A combination of bacterial virulence and host susceptibility factors, may alter the colonization state and ultimately lead to meningococcal disease.(1)

Although 12 meningococcal serogroups have been described (A, B, C, 29E, H, I, K, L, Y, W-135, X and Z), the majority of disease is caused by organisms expressing one of six capsule types namely A, B, C, X, Y and W-135.(2) Serogroup W-135 is responsible for recent worldwide outbreaks associated with pilgrims returning from the Hajj. An increase in the incidence of disease due to serotype X has been reported in Africa. Capsule switching between serogroups has reportedly arisen in several geographic areas through *in vivo* recombination during co-carriage, and further evolution and adaptation occurs through import of DNA from other commensal pathogens and phages. (3, 4)

Pathophysiology

The first step in the disease process is attachment of the organism through pili to non-ciliated columnar epithelial cells of the nasopharynx. These pili are classified as ‘major adhesins’ and are expressed in abundance on the bacterial surface. These surface structures have the ability to undergo structural/antigenic variation through import of DNA in order to evade immune detection. This phenomenon occurs frequently in *N. meningitidis* as it is naturally competent to readily take up DNA from the microorganisms in its environment.
Following attachment, meningococci proliferate on the surface of endothelial cells and form small micro-colonies. Close adherence of the organism (mediated by bacterial surface opacity proteins Opa/Opc) to host cells results in recruitment of additional factors with extension of pseudopods that internalize the meningococci (Figure 1). Meningococci are able to replicate inside epithelial cells as they can utilize intracellular iron. The organisms may then transcytose further into the tissues and enter the bloodstream. Translocation across the blood-meningeal barrier, proliferation in the central nervous system (CNS) and meningitis may also occur. However, detectible bacteremia is not required for meningitis to develop, although the vasculature is considered the primary route to the brain.(1)

Once access to the bloodstream is acquired, multiplication of the organism is rapid. In the blood, meningococci produce a strong inflammatory response with activation of the complement and coagulation cascades. A key inducer of cellular inflammatory responses, Lipooligosaccharide (LOS), is essential in causing meningococcal sepsis. LOS-induced secretion of various cytokines (e.g., IL-6 and TNF-α), as well as chemokines, ROS (reactive oxygen species) and NO (nitric oxide), leads to endothelial damage and capillary leakage, with necrosis of peripheral tissues and multiple organ failure (Figure 2). LOS levels correlate with mortality rates seen in meningococcal disease.
Resistance to complement-mediated lysis and opsonic and non-opsonic phagocytosis is determined by the expression of the capsule and LPS. This enhances survival both in the blood and the CNS and thus isolates from the blood or CSF are invariably capsulate. Meningococci also have the means to interact with several regulators of the complement pathways which could lead to increased bacterial survival(5).

In summary, the key components in meningococcal survival in the blood are the capsule and LOS. Proteinaceous adhesins play important roles in entry to and exit from the vasculature and may also modulate immune responses.

**Routes of transmission:**

Classically, *N. meningitidis* was known to spread from human to human through droplets or direct physical contact such as intimate kissing. Most cases arise following transmission from an asymptomatic carrier; nasopharyngeal carriage rates of between 10 and 35% have been reported in healthy adults. However cases have been reported which indicate that the nasopharynx is not the only primary site of infection. The pathogen has been isolated from atypical sites such as the mucous membranes of endocervix, conjunctiva, urethra and anus, implicating orogenital sex and vertical transmission as other possible modes of transmission.(6-9)
Signs and Symptoms

Meningococcal disease usually occurs 1–4 days after acquisition of the pathogen but can occur up to 14 days after colonisation. Signs and symptoms of meningococcal disease in infants and young children include fever, poor feeding, irritability, lethargy, nausea, vomiting, diarrhea, photophobia and convulsions. The most characteristic feature of meningococcal septicemia is a hemorrhagic (i.e. petechial or purpuric) rash that does not blanch under pressure. Additional signs in children and adults include neck rigidity, myalgia, swollen joints, mental status changes and ataxia.

Invasive disease can also result in localized infection in other sites including arthritis, myocarditis, pericarditis and endophthalmitis.

Risk factors

Known risk factors for invasive meningococcal disease include smoking or environmental tobacco smoke, crowding, asplenia, HIV infection and travel to epidemic areas. (10) Host genetic factors that predispose to infection include deficiencies in terminal complement components and mannose binding lectin. Other host genetic factors that modify susceptibility and outcome are being discovered, such as polymorphisms in SERPINE1 (plasminogen activator inhibitor) and Surfactant Protein A and D, which influence vulnerability and mortality. (11-14)

Meningococcal disease can affect persons of all ages, but higher rates of invasive disease in developed countries are seen in infants and children less than 4 years of age, adolescents, military recruits, and groups where crowding and new exposures occur such as college students living in dormitories(15). Factors that influence the spread and severity of meningococcal disease include smoking, low humidity, dust and respiratory co-infections.(16, 17) These factors may damage the integrity of the nasopharyngeal mucosa. Sub-Saharan outbreaks coinciding with the dry season highlight the potential role of humidity in damaging the mucosa and producing irritant coughing that aids transmission. In countries with a temperate climate, susceptibility to meningococcal disease is highest in the winter when absolute humidity is low(18, 19).

Diagnosis

The gold standard of diagnosis is isolation of *N. meningitidis* from sterile body fluid (blood or CSF) or purpural lesion scraping. Since *N. meningitidis* can be a component of normal nasopharyngeal flora, isolation from this site is not helpful diagnostically. Diagnosis relies on culturing the organism on a chocolate agar plate. However, after parenteral antibiotics are started the isolation rate of meningococci from blood cultures drops from 50% to less than 5% and the likeliness of CSF being positive by culture or microscopy are also reduced. In these situations, PCR, when available, can complement standard laboratory procedures and confirm the diagnosis as its sensitivity is not affected by therapy initiation.(20) Further testing to differentiate the species includes testing for oxidase (all clinically relevant *Neisseria* show a positive reaction) and the carbohydrates maltose, sucrose, and glucose test in which *N. meningitidis* will oxidize the glucose and maltose. Where laboratory facilities are limited and rapid diagnosis is essential,
the latex agglutination test may be used. Although less sensitive than PCR it has a high specificity along with ease of performance. (21)

Prevention

Clearance antibiotics: Close contacts of a patient with IMD are at increased risk for secondary disease; the attack rate amongst household contacts is 500 to 800 times higher than the general population. Clearance antibiotics are effective in protecting close contacts, and should be started ideally within 24 hours of identification of the index case. Close contacts would include household contacts, child care and preschool contacts and others with direct, prolonged contact with IMD patient secretions. Effective clearance antibiotics including rifampin, ciprofloxacin, ceftriaxone or azithromycin should ideally be started within 24 hours of identification of the index case. Although resistance to these drugs has been identified, most strains of *N. meningitidis* remain sensitive. (22-26)

Rifampin is the drug of choice for children; however a single IM dose of ceftriaxone is as effective as rifampin in eradication of serogroup A, while also has the added advantage of being administered as a single does and is safe in pregnancy. Rifampin is contraindicated during pregnancy.

Vaccination: Capsule based vaccines against several serogroups have been available for over 20 years. However, although purified capsular antigens elicit protective antibody responses, they do not induce long-term memory, are less effective in young children who are at the highest risk of disease, and do not induce sustained herd immunity. To overcome this deficiency, conjugate vaccines have been introduced. Strain specificity is based on the meningococcal capsule or protein vaccines based on meningococcal outer membrane vesicles (Serogroup B).

Vaccination during an outbreak:

When an outbreak is caused by a serogroup against which an effective vaccine exists, polysaccharide and conjugate vaccines have both been used effectively for outbreak control. In some countries, it is routine to offer the vaccine to all close contacts of the patient to prevent late secondary cases not prevented by clearance antibiotics.(27)

Vaccination for routine use:

Conjugated meningococcal vaccines are used in several developed countries for routine use. The countries that have seen the largest impact have implemented both mass catch-up campaigns in broad age groups and added meningococcal vaccines against locally prevalent serogroups in their infant immunization programs. Other countries only use this vaccine in adolescents and people with high risk of meningococcal disease (military recruits, travelers to areas where meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *N. meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency)(28-31)
Treatment

Septicaemic shock and raised intracranial pressure in severe meningitis cases are particular concerns in the management of suspected cases of meningococcal disease. (32, 33) Short course long-acting chloramphenicol is used for the treatment of epidemic meningococcal meningitis in sub-Saharan Africa. A randomized non-inferiority trial in Niger showed that ceftriaxone provides an alternative treatment for epidemic meningococcal meningitis due to its efficacy, ease of use, and low cost. Cefotaxime and ceftriaxone show a high degree of in vitro activity against moderately penicillin-susceptible meningococci. (34, 35) Empiric therapy with cefotaxime or ceftriaxone should be started while confirmation of diagnosis is sought. Once the diagnosis is confirmed the treatment can be changed to IV Penicillin G (250000-300000 U/kg/day, divided every 4-6 hours). Alternatively, Ceftriaxone may be used for the entire duration of therapy owing to its easy dosing and reports of development of varying degrees of resistance to Penicillin in several countries. (36-38)

Epidemiological data is critical to tracking the spread of less susceptible strains of \textit{N meningitidis} and to providing guidance in the empirical selection of antimicrobial agents for treatment. Isolates with decreased susceptibility to penicillin have been identified sporadically from several regions of the United States and widely from Spain, Italy, Turkey and parts of Africa. (36-40) Resistant meningococcal isolates for which the minimum inhibitory concentration to penicillin is more than 1 µg/mL are rare. Most reported isolates are moderately susceptible, with a minimum inhibitory concentration to penicillin of between 0.12 µg/mL and 1.0 µg/mL. Treatment with high-dose penicillin is effective against moderately susceptible strains. (41) In Australia, the percentage of isolates susceptible to penicillin had dropped from a high of 45% to 26% by 2000. (42) In certain developing countries like Vietnam where penicillin resistance is high, IM Chloramphenicol is the standard treatment for \textit{Neisseria Meningitidis}, but emerging resistance against this drug is a cause for concern. (43) In Africa, a gene study conducted in CDC’s Epidemic Investigation laboratories on 33 serogroup A isolates, collected from 9 countries from1963-1998 showed full sensitivity to both Chloramphenicol and penicillin. In addition to supportive measures such as fluid resuscitation, inotropic and ventilator support may be used where required. Isolation and droplet precautions of the hospitalized patient are necessary until 24 hours after initiation of effective antibacterial therapy. Detailed guideline for diagnosing and managing meningitis have recently been published. (44)

Rifampin and ciprofloxacin are the main antibiotics used for chemoprophylaxis. Resistance to ciprofloxacin it is rare, however, in 2007 and 2008, the first ciprofloxacin-resistant strains of \textit{N meningitidis}-causing disease were detected in certain areas of the United States. Low level resistance (MICs0.12–0.25mg/L) exists in Australia, France, Spain and Argentina, Hong Kong and China. (45) Fluoroquinolone resistance is also increasing in India, however the study here found 100% susceptibility to penicillin, azithromycin, ceftriaxone and chloramphenicol. (46) Resistance to rifampin, is also rare. One report from USA had 2 isolates which were resistant. (47) Other such case reports exist but are very few.
II. Epidemiology

Definition of epidemics and endemic situations:
The African meningitis belt originally characterized by Lapeysonnie in 1963 and modified in 1987, is a region in Sub-Saharan Africa, which stretches from Senegal in the west to Ethiopia in the east. (48, 49) This region has the highest incidence of meningococcal disease in the world and frequent epidemics constitute a major public health burden. Case fatality rates of meningitis in the meningitis belt range from 10-50%, and 10-20% of the survivors suffer permanent brain damage(50). The meningitis belt region consists of 300 million people and is characterized by particular climatic features and social habits. The dry season from December to June, is characterized by dry winds and cold nights, and is the period with the highest incidence of epidemics. The WHO definition of a meningococcal disease epidemic used in this paper, specifically for the meningitis belt, is >100 cases/100,000 population/year.

Other countries have not experienced epidemics at the level seen in the African meningitis belt. These countries may be classified according to the level of endemic disease present as high, moderate, low endemicity (Figure 3). This classification does not derive from any standardized definitions; rather it is based on country-specific epidemiological data. It may be used as a guide to direct prevention/immunization efforts by identifying regions that would benefit the most from induction of herd protection and where a vaccine intervention would be most cost-effective.

Fig. 3: Grouping countries according to IMD attack rates for best allocation of resources

- Epidemic is defined as >100 cases/100,000 population within a large region or the entire country
High endemic rate is defined as >10 cases/100,000 population per year in a country or large region.

Moderate endemic rate is defined as 2-10 cases/100,000 population per year in a country or large region.

Low endemic rate is defined as <2 case/100,000 population per year in a country or large region.

There is no global standardised definition of IMD outbreak outside the meningitis belt. For the purpose of this paper and its affiliated recommendations, we define outbreak as an increase in IMD cases in a defined population above what is expected by place and time.(51)

**Epidemiology of invasive meningococcal disease at country level**

Data on incidence of meningococcal disease is presented below in Tables 1-3. Countries are grouped into priority regions according to the definitions above, using national and published data from the last 20 years. Countries not listed in the table have insufficient published data available regarding epidemiology of IMD and the priority would be for establishing surveillance in these countries.

Table 1. Countries with high endemic rates and/or >=1 epidemic over the last 20 years

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence/100,000 population</th>
<th>Predominant strain</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>1999-2008</td>
<td>3.5-14.33</td>
<td>B</td>
<td>(52-54)</td>
<td></td>
</tr>
<tr>
<td>European Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrafique</td>
<td></td>
<td>3.3-19.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td></td>
<td>2.6-12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niger</td>
<td></td>
<td>7.8-90.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td>0.7-52.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD Congo</td>
<td></td>
<td>7.3-23.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chad</td>
<td></td>
<td>9.6-15.9</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Togo</td>
<td></td>
<td>6-13.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td></td>
<td>0-108</td>
<td></td>
<td>(56, 57)</td>
<td>Epidemic in 1997</td>
</tr>
<tr>
<td>Gambia</td>
<td></td>
<td>4-165</td>
<td></td>
<td></td>
<td>Epidemic in 1997</td>
</tr>
<tr>
<td>Benin</td>
<td></td>
<td>6-57</td>
<td></td>
<td>(57, 58)</td>
<td>Attack rate during 2001 epidemic up to 250 per</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td>0-104</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Year Range</td>
<td>Cases</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>---------</td>
<td>--------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea</td>
<td>0-17</td>
<td></td>
<td>(55) Epidemic in 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Côte d'Ivoire</td>
<td>0-6</td>
<td></td>
<td>(60) Epidemic in 2006, 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>1990</td>
<td>267</td>
<td>X in large outbreaks (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td>0-133</td>
<td></td>
<td>* (62) Epidemic in 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burundi</td>
<td>Upto 1605</td>
<td>A</td>
<td>Epidemic in 1991-92, 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mauritania</td>
<td>1980-1999</td>
<td>0-14</td>
<td>(57) Incidence &gt;50 in 1983</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td>0-53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td>0-28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>0-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Namibia</td>
<td>4-165</td>
<td></td>
<td>Epidemic in 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>0-18</td>
<td></td>
<td>(60) Epidemic in 2006-07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>A, W-135</td>
<td></td>
<td>225 cases in month after 2000 Hajj season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of the Americas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uruguay</td>
<td>2001</td>
<td>B</td>
<td>(64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>1991-2000</td>
<td>B</td>
<td>(65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data not available
Table 2. Countries with moderate endemic rates

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence/100,000 population</th>
<th>Predominant strain</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>1994-2007</td>
<td>0.8-8.9</td>
<td>B, C</td>
<td>(66)</td>
<td>2 peaks in 2000 and 2006</td>
</tr>
<tr>
<td>Belgium</td>
<td>1990-2008</td>
<td>3.69 (pre-vaccine) 0.8 (post-vaccine)</td>
<td>B, C</td>
<td>(67)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>1999-2006</td>
<td>3.74(pre-vaccine) 1.3(post-vaccine)</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td>1999-2006</td>
<td>7.58(pre-vaccine) 1.3(post-vaccine)</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1999-2008</td>
<td>1.2-3.5</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxemburg</td>
<td>1999-2008</td>
<td>0.4-1.5</td>
<td>*</td>
<td>(52)</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>1999-2008</td>
<td>0.65-2.39</td>
<td>C</td>
<td></td>
<td>A conjugate vaccine for group C introduced in 2001 in pediatric population, dramatic drop in C cases by 2004 (68)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1999-2008</td>
<td>4.51(pre-vaccine) 1.1(post-vaccine)</td>
<td>B, C</td>
<td>(54, 69)</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1999-2008</td>
<td>1.02-2.43</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1992-2008</td>
<td>0.74-4.6</td>
<td>B</td>
<td>(70)</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>2000-08</td>
<td>0.55-2.08</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>1997-2006</td>
<td>0.3-2.2</td>
<td>*</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>1997-2007</td>
<td>1.7-2.7</td>
<td>*</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1999-2008</td>
<td>5.39(pre-vaccine) 2.1(post-vaccine)</td>
<td>B, C</td>
<td>(52)</td>
<td></td>
</tr>
<tr>
<td><strong>African Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>2000-05</td>
<td>0.8-4</td>
<td>B in Western Cape</td>
<td>(71)</td>
<td>High rates in 2005 from one province. W-135 endemic, emerging &amp; more severe than A in northern Provinces</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuba</td>
<td>1998-2003</td>
<td>3.4-8.5(pre-vaccine) &lt;1(post-vaccine)</td>
<td>B</td>
<td>(72)</td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>1998-2006</td>
<td>0.7-2.4</td>
<td>B</td>
<td>(64)</td>
<td>Pediatric population</td>
</tr>
<tr>
<td>Brazil</td>
<td>1998-2006</td>
<td>1-4.5</td>
<td>B, now C</td>
<td>(64)</td>
<td>Epidemics in 1970s, peak incidence 179</td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>1995-2006</td>
<td>3.5-7.9(pre-vaccine) 1.4(post-vaccine)</td>
<td>B</td>
<td>(73)</td>
<td></td>
</tr>
</tbody>
</table>

* Data not available
Table 3. Countries with low endemic rates

<table>
<thead>
<tr>
<th>Countries with low endemic rates (&lt;2 case/100,000 population per year in a country or large region)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>European Region</strong></td>
</tr>
<tr>
<td>Austria</td>
</tr>
<tr>
<td>Bulgaria</td>
</tr>
<tr>
<td>Cyprus</td>
</tr>
<tr>
<td>Czech Republic</td>
</tr>
<tr>
<td>Estonia</td>
</tr>
<tr>
<td>Finland</td>
</tr>
<tr>
<td>France</td>
</tr>
<tr>
<td>Italy</td>
</tr>
<tr>
<td>Slovenia</td>
</tr>
<tr>
<td>Sweden</td>
</tr>
<tr>
<td>Poland</td>
</tr>
<tr>
<td>Germany</td>
</tr>
<tr>
<td>Hungary</td>
</tr>
<tr>
<td>Latvia</td>
</tr>
<tr>
<td>Slovakia</td>
</tr>
<tr>
<td>Serbia</td>
</tr>
<tr>
<td>Albania</td>
</tr>
<tr>
<td>Croatia</td>
</tr>
<tr>
<td><strong>African Region</strong></td>
</tr>
<tr>
<td>Mauritius</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
</tr>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>Mexico</td>
</tr>
<tr>
<td>Venezuela</td>
</tr>
<tr>
<td>Columbia</td>
</tr>
<tr>
<td>Chile</td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
</tr>
<tr>
<td>Japan</td>
</tr>
<tr>
<td>Malaysia</td>
</tr>
<tr>
<td>China</td>
</tr>
</tbody>
</table>
### South East Asia Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>Serogroup</th>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>1994-99</td>
<td>*</td>
<td>(83)</td>
<td>36 cases from 13 govt. hospitals in 5 years</td>
</tr>
<tr>
<td>Korea</td>
<td>2002-03</td>
<td>* Y</td>
<td>(84)</td>
<td>11 cases in this year</td>
</tr>
</tbody>
</table>

### Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>Serogroup</th>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egypt</td>
<td>1990-96</td>
<td>* A,B</td>
<td>(85)</td>
<td>3000 cases in 1990 down to 670 in 1996, vaccine introduced in 1992</td>
</tr>
<tr>
<td>Iran</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>150 to 500 cases per year</td>
</tr>
<tr>
<td>Iraq</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>3000-5000 cases per year</td>
</tr>
<tr>
<td>Jordan</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>30-60 cases per year</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>5-10 cases per year</td>
</tr>
<tr>
<td>Morocco</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>200-800 cases per year</td>
</tr>
<tr>
<td>Oman</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>10-30 cases per year</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1990-96</td>
<td>*</td>
<td>(86)</td>
<td>5000-6000 cases per year</td>
</tr>
<tr>
<td>Qatar</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>0-1 case per year</td>
</tr>
<tr>
<td>Syria</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>200-500 cases per year</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>300-450 cases per year</td>
</tr>
<tr>
<td>UAE</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>40-70 cases per year</td>
</tr>
<tr>
<td>Yemen</td>
<td>1990-96</td>
<td>*</td>
<td></td>
<td>400-600 cases per year</td>
</tr>
</tbody>
</table>

*Rates not available*
Serogroups/Serotypes

*N. meningitidis* is classified into 13 serogroups based on the immunogenicity and structure of the polysaccharide capsule. Further classification into serosubtype, serotype and immunotype is based on class 1 outer membrane proteins (PorA), class 2 or 3 (PorB) outer membrane proteins and lipopoly[oligo]saccharide structure, respectively. (1) Figure 4 below shows commonly found and predominant serogroups in different regions of the world.

Predominant strains are highlighted in bold text.

Carriage

Strains of Neisseria commonly reside in the human nasopharynx asymptptomatically. Studies put carriage rates in healthy adults at between 10 and 35% depending on populations sampled, and sampling sites and techniques. (87, 88) Higher carriage rates have been found in some confined populations like university students and army recruits. (89-91) (92)

Although carriage is a necessary step for the development of invasive disease, the transition from carriage to invasive disease is rare owing to differences in the genetic composition and capsule
structure of pathogenic and non-pathogenic strains (even within the same serogroup) as well as host susceptibility factors. Isolates from carriers may be capsulated or may not have a capsule, whereas blood and CSF isolates invariably have a capsule. Moreover, 10-14 days post acquisition of the pathogen, invasive disease becomes highly unlikely. This can be related to the appearance in serum of antibodies against the bacteria within two weeks after nasopharyngeal colonization. (1, 2, 93) Carriage studies may be helpful in understanding transmission dynamics but are not useful to predict the course of an epidemic.

Outbreaks following the Hajj (muslim pilgrimage to Mecca, Saudi Arabia) in 1987 and 2001 are good examples of widespread transmission of *N. meningitidis* leading to disease outbreaks in multiple countries. (94, 95) In 1987, there was an outbreak with serogroup A, and in 2001 serogroup W-135 was shown to be the causative agent of meningococcal epidemic in several countries following Hajj. A number of carriage studies were conducted on returning pilgrims in 2001 to assess the risk to close contacts. A study in Singapore on returning pilgrims estimated 15% of them to be carrying W135 and 55% of them to still be carriers 6 months later. These people transmitted the pathogen to 8% of their unvaccinated household contacts within the first few weeks of return, but no late transmissions were reported. Other countries showed significantly lower carriage among travelers and lower risk among household contacts. This pathogen was carried back to regions as far apart as China and Latin America, and is now the third most predominant serogroup in Brazil and Argentina. Serogroup W-135 caused an epidemic in Burkina Faso in 2002. Studies done in the region showed that the subtype of W-135 (ST-11) was identical to the one isolated during the Hajj epidemic; however, very closely related strains had been found in multiple countries including previously Africa. (96-99)

**Duration of protection against natural disease/acquisition of natural immunity**

In the neonate, immunity to systemic meningococcal infection is associated with the passive transfer of IgG antibodies from mother to fetus, although transplacental transport of antibodies is suboptimal in preterm infants. (100, 101) Many studies have been conducted to evaluate the best measure of immunity after carriage or vaccination. Current expert consensus suggests that hallmark of immunity to meningococcal disease is a Serum Bactericidal Antibody (SBA) activity which is a measure of antibody-mediated, complement-dependent killing. (99) A cardinal study by Goldshneider et al in 1970 showed that the bactericidal activity that develops in response to carriage is not limited to the strain that is being carried, but can also extend to heterologous strains of pathogenic meningococci (groups A, B, C) and subsequent development of specific IgG, IgM and IgA. (102-104) This response may last several months after the carried strains can no longer be detected. However, it is not clear whether natural immunization leads to immunological memory. Also, although specific immunity is generally protective, this immunity is not absolute; meningococcemia can occur in individuals with preexisting antibody titers that are considered protective. (105)
Age-specific attack rates

In most countries with epidemiological the age distribution of meningococcal disease demonstrates two peaks. The highest incidence is in infants less than one year of age, and a secondary rise in incidence occurs in adolescents and young adults. Fifteen years of data from Niger shows that under-5 year olds were more affected during epidemics when compared to non-epidemic years. However, some studies have suggested a shift towards older age groups during epidemics. Figures 5-8 below depict age specific attack rates for selected countries. Figure 10 shows the correlation between the peak in infancy and low serum bactericidal antibody titers and increasing titers in adulthood with decreasing incidence of disease.

Fig. 5: Age specific incidence in the United States from 2000-2009. Source: Active Bacterial Core Surveillance

Figure 7. Age specific incidence and case-fatality ratio of laboratory confirmed meningococcal infection, Europe, 2006. Source: European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS)
Figure 8. Proportion of meningitis cases due to specific organisms during 11 inter-epidemic years in Niamey, Niger. (1981-1994) (106)

Fig. 9: Changing epidemiology of pyogenic meningitis in India. (108)
Fig. 10: Relationship of incidence of disease and Serum Bactericidal Antibodies with age for serogroup B (108)

Use of vaccines

Currently available meningococcal vaccines include both polysaccharide vaccines and polysaccharide-protein conjugate vaccines based on the meningococcal capsule. For serogroup B, development has included protein vaccines based on meningococcal outer membrane vesicles; more recently a range of conserved proteins including fHBP and nadA have been used as vaccine components.

Table 4. Comparison of the immune response to polysaccharide and conjugate vaccines.(109)

<table>
<thead>
<tr>
<th></th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>Adults</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Young children</td>
<td>Poor</td>
</tr>
<tr>
<td>Quality of antibodies</td>
<td>Avidity</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Bactericidal activity</td>
<td>Low</td>
</tr>
<tr>
<td>Response to booster</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Induction of immunologic memory</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>Reduction of colonisation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Protection</td>
<td>Short</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Polysaccharide vaccines have high serogroup specificity, but show poor immunogenicity in infancy (except for MenA) (Table 4). Hypo-responsiveness (as defined by impaired serum anticapsular antibody responses to subsequent injections of vaccine after the initial dose) to Men C polysaccharide in infancy has been shown, especially if doses are repeated more than once. There is also an age dependent decline in antibody levels after vaccination. (110-113) Polysaccharide and conjugate vaccines for serogroup A, C, W135 and Y are already available for purchase. Strain-specific serogroup B outer membrane vesicle vaccines are licensed and used in several countries but are not widely available.

Conjugate vaccines have had a profound effect on incidence of meningococcal disease in countries where they have been introduced by mass campaigns followed by routine infant immunization, even benefitting unvaccinated individuals through the induction of herd protection. Table 5 lists these countries and their current immunization schedules for meningococcal vaccines.

**Table 5.** Countries that have introduced meningococcal vaccines in using mass immunization and/or routine immunization programs

<table>
<thead>
<tr>
<th>Country</th>
<th>Source</th>
<th>Vaccine</th>
<th>Year introduced</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (Burkina Faso, Niger, Mali)</td>
<td>MVP</td>
<td>MenAfriVac™</td>
<td>2010</td>
<td>Mass vaccination of 1-29 year old with a single dose</td>
</tr>
<tr>
<td>Canada</td>
<td>(114)</td>
<td>NACI MenC conjugate Menactra approved in 2006,</td>
<td>2002</td>
<td>Most provinces use the MenC conjugate at 12 months while a few use the quadrivalent conjugate based on local epidemiology and/or children &gt;2 years with primary antibody deficiencies</td>
</tr>
<tr>
<td>China</td>
<td>(82)</td>
<td>MenA polysaccharide MenA/C polysaccharide</td>
<td>1982</td>
<td>Vaccine at 6 and 18 months</td>
</tr>
<tr>
<td>Cuba</td>
<td>(115)</td>
<td>VA-MENGOC-BC</td>
<td>1991</td>
<td>Introduced into National Infant Immunization Program after epidemic incidence levels in 1980s</td>
</tr>
<tr>
<td>Egypt</td>
<td>(85)</td>
<td>A/C Polysaccharide</td>
<td>1992</td>
<td>School based vaccination program</td>
</tr>
<tr>
<td>Iceland</td>
<td>(116)</td>
<td>MenC conjugate</td>
<td>2002</td>
<td>6 and 8 months of age</td>
</tr>
<tr>
<td>Netherland ns.</td>
<td>(69, 117)</td>
<td>MenC conjugate</td>
<td>2002-3</td>
<td>Single dose at 12 or 14 months</td>
</tr>
</tbody>
</table>

(110-113)
Belgium
Australia

<table>
<thead>
<tr>
<th>Country</th>
<th>Company/Conjugate</th>
<th>Year</th>
<th>Age</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand</td>
<td>MeNZB IMAC MenC conjugate</td>
<td>2004</td>
<td>Mass immunization for everyone aged between 6 months and 20 years. MeNZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>MenC conjugate</td>
<td>2001</td>
<td>3, 5 and 15 months of age</td>
<td>Up to 18 years</td>
</tr>
<tr>
<td>Spain, Ireland</td>
<td></td>
<td>2000-2001</td>
<td>Part of routine immunization at 2, 4 and 6 months of age (now 4, 6 months and second year of life in Ireland)</td>
<td>Up to 19 years in Spain (most regions) Up to 23 years (Ireland)</td>
</tr>
<tr>
<td>UK</td>
<td>MenC (NeisVac-C, Meningitec, Menjugate)</td>
<td>1999</td>
<td>Part of primary immunisation schedule at 2, 3 and 4 months of age. From 2006 at 2, 4, 12 months of age</td>
<td>Up to 18 years of age (1999-2000), up to 25 years (2001)</td>
</tr>
<tr>
<td>USA</td>
<td>MCV4 (Menactra)/Menveo/MPSV4 acceptable alternative</td>
<td>2005</td>
<td>Primary dose at age 11-12 years with a booster dose at age 16, people at increased risk as mentioned above Booster dose at 5 years</td>
<td>Adolescents aged 13-18</td>
</tr>
</tbody>
</table>

In England and Wales, after the introduction of MCC in 1999, the impact on serogroup C disease has been sustained with the lowest recorded incidence (0.02 cases per 100,000 population) in the 2008-2009, although protection (SBA titers) has not been long lasting. This impact on disease epidemiology has been attributed to the development of herd protection due to reduced carriage. Similar results have been shown in Canada (114) and Australia. (124) Induction of long term humoral memory development is another potential advantage of vaccination, although in practice the response has not been as significant as that induced by conjugate vaccines against other diseases. (125, 126) Nonetheless, studies have also shown that antibody responses are higher after booster doses than in vaccine-naive adults making a case for a multiple dose regimen against \textit{N. meningitides}. (127, 128)

**Replacement Disease**

\textit{N. meningitidis} has been shown to switch capsules. For example, the ST11/ET37 strain had been identified in both serogroup B and W135. (129, 130) Moreover, meningococci of different serogroups, B and C, but with identical serotype and electrophoretic type were detected in the Czech Republic, Canada, and the Pacific Northwest, which raised the possibility that genetic
exchange between epidemic and endemic strains may be more common than previously suspected. (131-134)

Despite these concerns, current evidence does not show significant replacement disease after the introduction of meningococcal vaccines. Extensive carriage studies and surveillance after introduction of MenC in the UK in 1999 have found no evidence of capsule replacement following mass immunization with MenC conjugate vaccines from 1988-2005 (135). This time period extended from the pre-vaccination era to 5 years after mass vaccination with MenC. The results were supported by studies conducted in other countries, including Spain and Italy, which showed that the presence of the hyper-virulent strains of different serogroups but same electrophoretic subtype was either insignificant post vaccination or occurred even without mass vaccination. (136, 137) A study done in Spain to analyze the possible impact of two vaccination campaigns (with A/C polysaccharide in 1997 and MenC conjugate from 2000-2008) showed that the overall diversity of the meningococcal population, measured by the frequency of STs and clonal complexes, numbers of alleles, polymorphic sites, and index of association, remained relatively constant throughout the study period. (138)
III. Immunology, Safety and Effectiveness of Meningococcal Vaccines

Correlates of protection against meningococcal disease

Due to the relatively low incidence of meningococcal disease, pre-licensure clinical effectiveness studies are not feasible. Meningococcal vaccines are licensed based on evidence of an immune response in subjects receiving vaccine using serum bactericidal activity (SBA) as the immunologic correlate of protection.

Goldschneider et al., demonstrated that SBA levels correlates with protection against serogroup C meningococcal disease using human complement (hSBA). Titers of 1:4 were shown to confer protection against disease. hSBA has since been considered the gold standard correlate of protection (139, 140). As it is difficult to obtaining immunologic naïve samples of human complement, baby rabbit complement is more frequently used in the assays. Because meningococci are more susceptible to lysis by rabbit complement, correlates of protection were re-evaluated to identify serologic titers that could be used as proxies for effective protection. Subsequent studies have shown rSBA titers (serogroup C) of ≥1:8 reliably predicted protection in humans (141-144). While the SBA titers indicating protection were established based on serogroup C disease, they are generally accepted as correlates of protection for other serogroups.

Field effectiveness of vaccines

Post-licensure field effectiveness studies are critical to evaluate the true impact of a vaccination program, and to inform decisions about future vaccination strategies. All of the vaccines discussed below induce strong immunogenic responses (SBA titers) when evaluated one month after vaccination. It is the intersection of the properties of a vaccine, the specific vaccination strategy, program coverage, and disease epidemiology that determine how well a vaccine works in the field. For example, polysaccharide vaccine is highly effective against serogroup C outbreaks in military barracks when given prior to the start of basic training because these outbreaks occur shortly after the start of basic training, vaccination coverage is likely 100%, and antibody titers are still high. However, polysaccharide vaccines are less effective at producing long term control against serogroup A outbreaks in Africa because they are less immunogenic in young children, do not provide long-term protection, and there are no benefits of herd protection. A study done in 1985 to detect age-specific differences in duration of clinical protection after vaccination with MenA polysaccharide vaccine showed that a single dose does not yield lasting protection in children aged less than 4 years. (145)

Duration of immunity

When using meningococcal vaccines to prevent or halt disease outbreaks, short-term protection is sufficient. However, routine vaccination programs against meningococcal disease require vaccines that provide long-term protection or high levels of herd protection in order to reduce disease burden. Meningococcal conjugate vaccines were developed because polysaccharide vaccines had a limited duration of protection, especially in infants and young children. The
ability of conjugate vaccines to induce a T-cell immune response, with benefits including immunologic memory and impact on nasopharyngeal carriage, makes them better vaccines to use for long-term protection against meningococcal disease.

There are three characteristics of conjugate vaccines that are important for establishing long term control against a bacterial pathogen: circulating antibody, a memory response, and herd protection (146). SBA titers decline after vaccination with all meningococcal vaccines, although this is more pronounced in infants and young children and the rate of antibody decline may vary based on the characteristics of each vaccine. However, if the initial response to a vaccine induces higher SBA titers, the antibody titers may be protective for longer even if the rate of declining titers is the same as other vaccines.

Immunologic memory means there are circulating memory cells that can result in a strong and rapid immunologic response to the next antigen exposure (either the pathogen or through vaccination). In one study of 4 year old children, following conjugate vaccination initially at 2, 3 and 4 months of age, rSBA titers increased 1000 fold (GMT levels) and geometric mean avidity index was 1.33 fold higher one month following a booster vaccine dose (147-152). We do not have enough experience yet to truly understand the duration of protection from OMV and other serogroup B meningococcal vaccines that do not include polysaccharide as an antigen.

**Herd protection**

Herd protection is an important component of long-term community protection against meningococcal disease. MenC conjugate vaccines induced herd protection when used in the UK with reduced nasopharyngeal carriage and decreased transmission to non-vaccinated populations (153). The UK achieved high coverage in children aged 0-18 years very rapidly. A majority of serogroup C disease was caused by a single clone which caused high rates of disease for several years prior to vaccination. Even though antibody titers in a large portion of the population have now declined, there is almost no serogroup C disease in the UK and it appears that the indirect benefits of herd protection are a major contributor to long-term decrease in disease incidence in the UK.

Whether different meningococcal vaccine programs will see the same benefit of herd protection likely depends on the coverage of the program and the vaccination strategy used. In the United States, quadrivalent meningococcal conjugate vaccine was introduced in 2005 and added to the routine schedule only for adolescents aged 11-18 years. Five years after introduction vaccination coverage is only 52% (NIS). While the incidence of disease in the US has decreased in those who have been vaccinated, there is little evidence of wide scale herd protection with this vaccine program. High vaccination coverage in the age group that likely transmits the organism (older adolescents) is a key factor for achieving herd protection. In Netherlands, one dose of conjugate vaccine in the second year of life has significantly reduced the incidence of Men C disease and a similar pattern has been seen in Australia where after an initial campaign included all children and young adults, routine immunization now occurs at 12 months of age (69). It remains to be seen whether MenB vaccines in development will impact nasopharyngeal carriage.
Polysaccharide Meningococcal Vaccines

There are several combinations of polysaccharide vaccines used globally, including bivalent (A,C), trivalent (A,C,W-135) and quadrivalent (A,C, Y, W-135) vaccines. The first polysaccharide vaccines were developed at Walter Reed Army Institute and implemented in military recruits to prevent recurrent outbreaks among young soldiers (140, 154). Polysaccharide meningococcal vaccines are immunogenic and safe. They are highly effective in closed populations of adults at high risk for disease including military recruits and household contacts of affected individuals (155-157) and in outbreak control.(158) Serogroup A vaccine has also been used effectively during outbreaks in Africa (159-161).

Although a few countries had a routine vaccination program with polysaccharide vaccines prior to conjugate vaccines (Syria, Saudi Arabia), they have been used typically to protect persons at increased risk for disease, e.g. following splenectomy or travellers to the Hajj, or in reactive vaccination campaigns in response to outbreaks in developed countries and especially in the African Meningitis Belt.

Conjugate meningococcal vaccines

Meningococcal conjugate vaccines were introduced in 1999 with initial introduction of MenC conjugate vaccines in the UK. Since then, quadrivalent (A,C,Y,W-135) and monovalent MenA vaccines have been licensed in certain countries (Table 6). Multiple countries have since introduced conjugate vaccines into their routine vaccination schedules. Conjugate vaccines use a carrier protein to present the polysaccharide antigen to the immune system, inducing a T-cell immune response. Ten years of experience in countries with adequate surveillance systems have shown conjugate vaccines to be safe and effective, with large reductions in meningococcal disease burden as a result of vaccine introduction in countries with adequate surveillance systems. However, questions remain regarding long-term effectiveness of conjugate vaccines and how to optimize routine vaccination programs.

Table 6. Meningococcal Conjugate Vaccine Products

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Serogroups</th>
<th>Protein Conjugate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menevo™</td>
<td>Novartis Vaccines</td>
<td>A, C, Y, W-135</td>
<td>Diphtheria cross reactive material 197 (CRM197)</td>
<td>(162, 163)</td>
</tr>
<tr>
<td>Menactra™</td>
<td>Sanofi Pasteur</td>
<td>A, C, Y, W-135</td>
<td>Diphtheria toxoid</td>
<td>(30, 164, 165)</td>
</tr>
<tr>
<td>Meningitec™</td>
<td>Wyeth Vaccines</td>
<td>C</td>
<td>CRM197</td>
<td>(166)</td>
</tr>
<tr>
<td>Menjugate®</td>
<td>Novartis Vaccines</td>
<td>C</td>
<td>CRM197</td>
<td>(167, 168)</td>
</tr>
<tr>
<td>NeisVac-C™</td>
<td>Baxter Bioscience</td>
<td>C</td>
<td>Tetanus toxoid</td>
<td>(169)</td>
</tr>
<tr>
<td>MenAfriVac™</td>
<td>Serum Institute of India</td>
<td>A</td>
<td>Tetanus toxoid</td>
<td>(170, 171)</td>
</tr>
</tbody>
</table>

Page 225
MenC conjugate vaccines

Meningococcal C conjugate (MCC) vaccine was first licensed in the UK without pre-licensure Phase III clinical trials. Several vaccine products are now licensed, conjugated to either tetanus toxoid or Crm-197. Multiple studies have since evaluated the safety and immunogenicity of MCC vaccination in several countries. Studies in healthy adults show a significant rise in geometric mean titers (GMT) from under 40 to 700-3000 one month after vaccination (149, 172). Similar results have been seen in healthy adolescents (173). At least five studies found MCC to be safe, with no major adverse reactions and only minor local reactions (150, 174-177). Immunogenicity studies have shown MCC to be immunogenic in infants as well as adults; prior to moving the third dose to 12 months of age in the UK, Borrow, et al. found only 8-12% of children completing a 3 dose series in infancy to have rSBA titers ≥1:8 at 4 years of age, with GMTs similar to pre-vaccination levels (178). In a phase 4 clinical trial of 250 children in the UK, rSBA titers were tested 6 years after the primary MCC series. Age at priming ranged from 2 months to 6 years. Only 25% (CI 20%-30%) of all children had protective titers ≥1:8 (179).

Recent data from the United Kingdom indicate that the memory response may not be rapid enough to protect against meningococcal disease if a booster is provided following close contact. After initial priming with monovalent MenC conjugate vaccine, a memory response after a booster dose is not measurable until 5 to 7 days later.(143) The incubation period of meningococcal disease is usually less than 3 days. Therefore, while a memory response may protect some individuals from disease or ameliorate disease severity, already present circulating antibody may be a more important indicator of direct long-term protection against meningococcal disease.

Antibody responses were similar when MCC was co-administered simultaneously with routine infant immunizations (180-182). Further studies have shown that a two dose series at 3 and 5 months yields equivalent immunity (148, 181, 183).

Quadrivalent meningococcal conjugate vaccines

In 2005, the first quadrivalent meningococcal conjugate vaccine (A,C,W,Y) conjugated to diphtheria toxin was licensed by the US Food and Drug Administration. A second MenACWY vaccine conjugated to Crm-197 was licensed in 2010. In pre-licensure clinical studies, both vaccines were found to be safe and immunogenic. In the United States these vaccines are licensed for ages 2-54 years, with studies evaluating multiple dose series in infants and toddlers having just been completed.

MenA conjugate vaccine

While meningococcal conjugate vaccines have the attributes needed to eliminate epidemic meningitis is Africa, including eliminating carriage of the organism, previous monovalent and quadrivalent meningococcal conjugate vaccines used in developed countries are too costly for widespread and sustainable use in the African Meningitis Belt. The Meningitis Vaccine Project
was started in 2001 as a collaboration with multiple partners, including WHO and PATH, to bring an affordable conjugate vaccine targeting serogroup A to the African Meningitis Belt.

In 2010, Meningococcal A conjugate vaccine (MenAfriVac), manufactured by the India Serum Institute, was licensed and prequalified by WHO for use. In Sept. 2010, MenAfriVac was introduced in mass vaccine campaigns in Burkina Faso, Mali, and Niger. All persons age 1-29 years were vaccinated in the districts included in the campaigns. This vaccine has been shown to be highly immunogenic and the safety profile is comparable to the safety profile of polysaccharide vaccine (184). One year after vaccination, the proportion of subjects who were responders was the same as the proportion 28 days after vaccination (83%). Infants also have strong responses to a 3 dose primary series with MenAfriVac. The vaccine effectiveness and impact on disease burden these vaccines will have is being monitored closely.

Vaccine effectiveness (VE) varies by conjugate vaccine and how the program was implemented, but is clearly higher in older children and adolescents compared to young children, with studies reporting VE as high as 97% for MenC vaccine in teenagers. Short term VE was high (83%) in those receiving immunization but declined with time, particularly in those vaccinated in infancy or pre-school age. Estimates of VE over time in those vaccinated in infancy fell from 95% in the first year to 31% by the fourth year after vaccination. (123, 185-187). In the United States, initial VE estimates of 75% have been found with MenACWY vaccine in adolescents. (162) Analyses of vaccine failures have found evidence of priming but low SBA activity in many of those vaccinated. Aukland, et al. have reported 53 cases of vaccine failure, largely in healthy children who had received a primary vaccination series in infancy. All cases mounted an anamnestic immune response (188).

Another measure of the effectiveness of the meningococcal conjugate vaccination programs is its herd effects. Two years after introduction of MCC vaccine in the UK, the serogroup C carriage rate was reduced by 81% (189). Attack rates among unvaccinated children and adults in the UK declined by 67% in the 4 years following vaccine introduction. Between 1998 and 2009, the incidence of serogroup C disease in persons over 25 years dropped from 0.55 / 100,000 persons to 0.02 / 100,000 persons in the UK; and the number of cases in infants under 3 months of age dropped from 13 in 1998 to 1 in 2009 (123). These effects were seen despite a declining seroprevalence of protective antibodies among vaccination cohorts as early as 18 months after the last scheduled dose of vaccine (190).

Implementation of meningococcal conjugate vaccination programs in countries across Europe, North America and Australia, have all documented a reduction in serogroup C incidence. In the UK, incidence has decreased by 97% since 1998. The number of deaths from serogroup C disease declined from 78 in 1998 to 1 in 2009 (191). In Canada, incidence declined 65% five years after implementation. Ontario saw a 16% reduction per year in serogroup C disease among persons ≥20 years of age from 2000-2006 after introducing a MCC vaccination program in adolescents and infants (114). No such reduction was seen in other serogroups that were not included in the vaccine (78). Dramatic reductions in disease incidence have also been recorded in Australia, Netherlands, Spain, and Greece (68, 69, 192, 193). Since quadrivalent vaccine was introduced in the United States, overall incidence of meningococcal disease has declined by
64.1%. This decline in incidence was seen in infants too young to be vaccinated and persons over 20 years, again indicating possible herd effects (194) although as the decline was also seen in other serogroups, including serogroup B, some of this change may be due to cyclic variation.

**MenB OMV vaccines**

While progress towards reducing meningococcal disease globally has been made with meningococcal conjugate vaccines for serogroups A, C, Y and W-135, vaccines to protect broadly against serogroup B disease have presented a challenge because the B polysaccharide is not immunogenic and other potential antigen targets are highly diverse. Serogroup B vaccines have been developed for specific outbreak strains using the outer membrane vesicles (OMV) specific to that strain, including vaccines to target disease in New Zealand and Cuba (195, 196). These vaccines are immunogenic, but require multiple doses, especially in young infants, and efficacy appears to have a short duration of protection (197). Efforts to find novel vaccine antigens to protect against serogroup B disease have identified several protein surface antigens. Two vaccines that target these antigens are currently under investigation in clinical trials. These vaccines may have the potential to protect not only against serogroup B disease but against other serogroups as well. Preliminary data from these vaccines are promising, but the role these vaccines will play in controlling meningococcal disease remains to be determined.

**IV. Cost effectiveness of vaccine and cost of disease**

Data on the cost of vaccine and financial burden of disease is available from Africa and some developed countries where a vaccine has been introduced. Limited data on meningococcal carriage and incidence is available from other countries, especially in Asia, and thus cost effectiveness cannot currently be accurately determined for these countries.

**Cost effectiveness of vaccines in Africa**

In early 2000, the need for an affordable and highly immunogenic conjugate vaccine against Men A was highlighted jointly by a WHO expert group and African public health professionals. (170) In June 2001, the Bill and Melinda Gates Foundation agreed to fund the Meningococcal Vaccine Program, which is a 10 year partnership between WHO and PATH with the goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of conjugate meningococcal vaccines. This contributed to the development of MenAfriVac™ vaccine (PsA-TT) by Serum Institute of India, which is a Men A polysaccharide (PsA) conjugated to a protein carrier, tetanus toxoid (TT). This vaccine obtained marketing authorization in India in 2009 and WHO prequalification certification in June 2010. GAVI has committed to fund a one-time vaccination campaign, but indicated that the expense of booster doses or incorporation of the MenAfriVac into EPI programs must be borne by the public health systems of participating countries.
Cost of disease and impact on health systems in Africa

One study in Burkina Faso found that the cost per household of a case of meningococcal disease in Sub-Saharan Africa is US$ 90 and an additional US$154 if sequelae of the disease occur. The urban cost is more than 200% higher than the rural cost. An idea of the overall burden of disease can be gauged from the total cost of the 2006-2007 outbreak, which was US$ 9.4 million, 7.1M borne by the public health system and 2.3M borne by households which comprised 34% of the GDP capita (198). The Meningitis Vaccine Project has the potential to:

- Prevent 123,000 deaths by 2018
- Prevent permanent disability in 287,000 children and adults
- Prevent 11 million DALYs lost
- Save approximately $99.7 million in medical costs for diagnosis and treatment

For Africa, a model was developed by Parent du Chatelet in 2001 in Senegal, which compared two vaccination strategies: vaccination with men A+C polysaccharide vaccine when epidemic thresholds are exceeded and alternatively mass preventive vaccination before outbreaks occurred. The model predicted prevention of 59% of the cases using a pre-emptive strategy compared to 49% for the emergency reactive strategy. The cost per case prevented was US$59 for the preventive strategy and US$133 for the reactive strategy, and the preventive strategy saved US$0.20 per inhabitant. Preventive meningococcal vaccination through mass campaigns prevented more disease at a lower cost, provided that the occurrence of an epidemic could be predicted within 3 years and that the vaccination coverage rates for the preventive and reactive strategies were > 70% and < 94%, respectively. (199) This model recommended mass preventive vaccination, especially for areas with poor surveillance systems.

Cost effectiveness of Men C conjugate vaccine

Six countries undertook economic evaluations around the introduction of MCC vaccines (Australia, Canada (Quebec), The Netherlands, UK, Portugal and Switzerland). All recommended that one dose in the second year of life was more cost-effective than a three-dose infant schedule (200).

Further development of the dynamic model was undertaken after vaccine introduction to predict the impact of the meningococcal vaccination program and its cost effectiveness in the UK. Various factors feed into this dynamic model, including the high transmissibility of the disease, the role of carriage/colonization and possibility of recurrent colonization with different serotypes, interaction between related bacteria, and the differing risks of colonization and disease at different ages. The model accurately reflected the trends of meningococcal disease in the UK when it was applied retrospectively to the actual experience in the UK from 1998 to 2004. It was also able to predict the significant herd protection that is being seen with the use of this vaccine. The UK model was also used to investigate the impact of vaccine schedules in the UK and Spain. (201) The catch-up campaign differed between Spain, where the upper age limit was 6 years in most autonomous regions, and the UK where a broader age range (up to 25 years of age) was
targeted. The latter approach was more effective in reducing disease, because both the direct and indirect effects were larger. Consistent with the observed results, the model predicted that herd protection effects for the Spanish strategy would be small (since 0-5 year olds rarely carry meningococci) and that by targeting teenagers, who are the most common carriers of meningococci, much greater herd protection could be achieved.

The major application of this model is in selecting the most cost effective modification that could be made in the meningococcal immunization program. Models can be used to inform decisions around introduction of meningococcal vaccines. These models must be adapted to the local epidemiology including serogroup distribution, age specific attack rates and nasopharyngeal carriage.
V. Fractional doses

Immunology

In recent years there has been concern that in the event of a large scale epidemic, the supply of the meningococcal vaccines may not be enough to match the demand. Thus, a trial was conducted to test the hypothesis that fractional doses of ACWY meningococcal polysaccharide vaccine confer for each serotype in the vaccine an immunogenic response, which is non-inferior to the full dose licensed vaccine(s) in the population targeted during mass vaccination campaigns in Africa. The objective of the trial was to measure the immunogenicity of each component of a dose corresponding to 1/5\textsuperscript{th} and 1/10\textsuperscript{th} of the amount of the current licensed vaccine. This was a randomised, single-blind, non-inferiority trial, in which healthy subjects aged 2 to 20 years in Uganda were enrolled. The study subjects were divided into three groups, with one group receiving a normal dose of the ACWY polysaccharide vaccine, a second group receiving 1/5\textsuperscript{th} of the normal dose and the third group receiving 1/10\textsuperscript{th} of the normal dose. An rSBA titer of $\geq 1:128$ was considered to be a marker of immunity. A non inferiority margin of 10\% between “full dose” and each study arm was selected.

The intent to treat and per protocol analysis included all participants, irrespective of the baseline seropositivity status. However, a sub group analysis was also done on subjects who were not immune to the particular meningococcal serotype at baseline, i.e. before the vaccine administration (SBA $< 1:128$). In the non-immune population, the immunogenicity of the 1/5\textsuperscript{th} dose for serogroups A, W135 and Y was non-inferior compared to full dose. In the ITT and PP analysis, the immunogenicity of 1/5\textsuperscript{th} dose for serogroups W135 and Y was non-inferior compared to full dose. The immunogenicity of 1/5\textsuperscript{th} dose was inferior to full dose for serogroup C. With the 1/10\textsuperscript{th} dose, the antibody titers generated were lower compared to 1/5\textsuperscript{th} dose, however, it was still non-inferior to full dose for serogroups W135 and Y.

In the event of an acute shortage of meningococcal vaccines during an epidemic, 1/5\textsuperscript{th} or 1/10\textsuperscript{th} of the normal dose of ACWY polysaccharide vaccine can be considered depending on the serogroup causing the epidemic. However, since the absolute titers generated by the fractionated doses are lower compared to the full dose, the duration of protection provided by the fractionated doses is likely to be shorter than the full dose.

Feasibility

The International Coordinating Group, a collaboration between MSF, WHO, Red Cross and UNICEF, maintains a bank of meningococcal vaccines for public health emergencies. For the next year, there are approximately 10 million doses of Men AC/Men ACW vaccine and 3 million...
doses of Men A conjugate vaccine in storage. At the time when 1/5th dose was considered, the vaccine supply situation was much tighter. Now in addition to the vaccine stock pile, there are 10-15 million doses available in the marketplace as well. Hence there are around 25 million doses available in total for 2010/11. The WHO is currently satisfied with the supply for dealing with the next epidemic.
VI. Research needs on immunization against meningococcal disease

- Surveillance research needs

1. Epidemiological data on burden on invasive meningococcal disease is lacking from some parts of the world, especially Asia. Primary data on disease incidence is needed in these countries. In many countries where data exists, it remains suboptimal with especially limited laboratory confirmation.

2. Although no significant evidence of replacement disease has yet been seen, the possibility still exists. However, replacement disease should be differentiated from unmasking of secular trends that may be seen following improved surveillance and decrease in the vaccine prevalent serogroups. Timely surveillance and monitoring using molecular epidemiology tools can prevent outbreaks from unexpected strains.

3. Increased surveillance for IMD and meningococcal carriage in the times following Hajj is recommended in all countries, especially in countries from where a large number of people participate in this event.

4. Impact of meningococcal vaccines in the HIV positive population should be specifically studied.

5. Duration and breadth of protection, as well as effect on carriage/herd protection needs to be evaluated in countries (especially the meningitis belt countries) which have introduced meningococcal vaccines in their routine immunization program. Such studies should guide/validate need for booster doses and cost effectiveness of a certain immunization routine.

- Vaccine research needs

6. Consideration should be given to making a single vaccine formulation which combines meningococcal vaccines with the existing pentavalent vaccines. Another consideration is to make a single ‘meningitis vaccine formulation’ which combines *S. pneumoniae, H. influenza type b* and *N. meningitidis.*

7. Comparative immunogenicity of multivalent, bivalent, and monovalent conjugate meningococcal vaccines should be compared against each serogroup in order to make informed decision about the choice of vaccine to be used in a particular setting.
8. Fractionated doses of polysaccharide vaccines have been effective. Similar studies on conjugate vaccines can answer the question of whether it would be feasible to use the fractionated doses of quadrivalent conjugate vaccines on a mass scale in relevant countries.

9. Newly developed MenB vaccines using multiple conserved proteins conjugated with OMVs are promising. Data on safety and immunogenicity in infants, children and adults has been demonstrated for the Novartis vaccine; however persistence of antibodies and evidence of broad protection still needs to be evaluated. (202, 203) Studies to address these are highly recommended.
Recommendations

1. For all countries, knowledge of meningococcal disease burden is critical to making appropriate use of its vaccine. All countries considering the use of meningococcal vaccines should develop the surveillance infrastructure for meningococcal disease. This infrastructure should include both clinical case detection as well as laboratory capacity to diagnose and characterize *N. meningitidis*.

2. The ongoing MenAfricVac roll out plan should be used to strengthen the routine EPI program as well as the meningococcal disease surveillance infrastructure in these countries.

3. In countries where mass vaccination of 1-29 years old is being conducted under the MenAfriVac roll out plan, it is recommended that after the campaign, MenAfriVac be administered as part of the routine vaccination of young children in order to ensure continued protection. Currently MenAfriVac is only licensed in children older than one year of age, however studies to demonstrate its safety and immunogenicity in infants are at advanced stage. It is therefore recommended that after the campaign, MenAfriVac be given to all children 1-2 years of age on routine basis in these countries. This recommended age may be revised if MenAfriVac gets approved for use in younger infants.

4. Impact of the MenAfriVac vaccination campaign on the immunization and health care system, should be measured in African meningitis belt, using the tools under development and recommended by SAGE.

5. Countries with high endemic rate of IMD (as classified in the background document) should use an appropriate meningococcal vaccine in their population. The recommended strategy for the vaccine use is initial mass vaccination of the population 1-29 years of age, followed by the inclusion of meningococcal vaccine in the routine vaccination programs for the infants. Continued surveillance of IMD should dictate the need and timing of repeat mass vaccination campaign.

6. Countries with intermediate endemic rates of IMD (as classified in the background document) may choose to use the appropriate meningococcal vaccine in their population. If so, similar approach to introducing meningococcal vaccines is recommended in these countries as has been described above for highly endemic countries.

7. The choice of vaccine for each country should depend on the serogroup(s) (or serosubtype in case of serogroup B) of *N. meningitidis* that are locally prevalent. In general, conjugate vaccines are preferred to polysaccharide vaccines due to their impact on decreasing nasopharyngeal carriage of *N. meningitidis* and their overall increased immunogenicity in children. Nonetheless, polysaccharide vaccines are also acceptable especially when individual level protection (as opposed to population level protection) is desired e.g. for the military recruits, during Hajj and during an outbreak.
8. Further research in the development and testing of protein based vaccines against serogroup B is highly encouraged, as these vaccines have the potential to be cross protective against all meningococcal serogroups.

9. During an outbreak, vaccine which covers the prevalent serogroup (or serosubtype in case of serogroup B), if available, should promptly be used in a mass vaccination campaign. While appropriate monovalent vaccines, when available, are recommended for such mass campaigns, multivalent vaccines potentially offer additional benefit in those countries that have a substantial amount of disease due to more than one serogroup if their immunogenicity against outbreak causing serogroup is as good as the monovalent vaccine and the price is in an acceptable range.
VII. References


51. Epidemiological Investigation of Outbreaks.


53. NDSC. Epidemiology of Meningococcal Disease in Ireland


86. WHO. Emerging and other Communicable Diseases, Surveillance and Control: Available from: http://www.who.int/emc


124. CDNA. Guidelines for the early clinical and public health management of meningococcal disease in Australia 2007.


48


The Meningitis Vaccine Project

F. Marc LaForce\textsuperscript{a,*}, Kader Konde\textsuperscript{b}, Simonetta Viviani\textsuperscript{a}, Marie-Pierre Préziosi\textsuperscript{b}

\textsuperscript{a} The Meningitis Vaccine Project, PATH, 13 Chemin du Levant, 01210 Ferney-Voltaire, France\textsuperscript{1}

\textsuperscript{b} The Meningitis Vaccine Project, World Health Organization, 13 Chemin du Levant, 01210 Ferney-Voltaire, France\textsuperscript{1}

Available online 7 May 2007

Abstract

Epidemic meningococcal meningitis is an important public health problem in sub-Saharan Africa. Current control measures rely on reactive immunizations with polysaccharide (PS) vaccines that do not induce herd immunity and are of limited effectiveness in those under 2 years of age. Conversely, polysaccharide conjugate vaccines are effective in infants and have consistently shown an important effect on decreasing carriage, two characteristics that facilitate disease control. In 2001 the Meningitis Vaccine Project (MVP) was created as a partnership between PATH and the World Health Organization (WHO) with the goal of eliminating meningococcal epidemics in Africa through the development, licensure, introduction, and widespread use of conjugate meningococcal vaccines. Since group A \textit{Neisseria meningitidis} (\textit{N. meningitidis}) is the dominant pathogen causing epidemic meningitis in Africa MVP is developing an affordable (US$ 0.40 per dose) meningococcal A (Men A) conjugate vaccine through an innovative international partnership that saw transfer of a conjugation and fermentation technology to a developing country vaccine manufacturer. A Phase 1 study of the vaccine in India has shown that the product is safe and immunogenic. Phase 2 studies have begun in Africa, and a large demonstration study of the conjugate vaccine is envisioned for 2008–2009. After extensive consultations with African public health officials a vaccine introduction plan has been developed that includes introduction of the Men A conjugate vaccine into standard Expanded Programme on Immunization (EPI) schedules but also emphasizes mass vaccination of 1–29 years old to induce herd immunity, a strategy that has been shown to be highly effective when the meningococcal C (Men C) conjugate vaccine was introduced in several European countries. The MVP model is a clear example of the usefulness of a “push mechanism” to finance the development of a needed vaccine for the developing world.

° 2007 Elsevier Ltd. All rights reserved.

Keywords: Meningococcal meningitis; Meningococcal conjugate vaccine; Public–private partnerships

1. Introduction

In 1963 Lapeyssonnie first described the African “meningitis belt,” a vast area that stretches from Senegal to Ethiopia with a 2005 estimated population of more than 300 million where major epidemics of meningococcal meningitis regularly occur [1]. He emphasized the striking periodicity of meningitis epidemics; they start at the beginning of the dry season in late December, peak towards the end of the dry season, and promptly stop with the first rains in May and June. The epidemic season is characterized climatically by the “harmattan,” a hot dry wind that generates a great deal of dust [2]. Most countries in the meningitis belt have had large outbreaks every 5–12 years since the 1940s, but over the last two decades the intervals between epidemics have become more irregular. Furthermore, the belt is expanding further south with meningitis epidemics reported in Burundi, Rwanda, Angola, and Zambia. In major African epidemics, incidence rates can soar to 500 cases per 100,000 population, but in smaller loci disease rates are often greater than 1%. Over the last decade over 700,000 cases in Africa have been reported, and in 1996 there were over 200,000 cases and over 20,000 deaths [3].

Despite antimicrobial therapy, about 10% of cases of meningitis die, typically within 24–48 h after the onset of symptoms. Another 10–20% of survivors are left with major neurologic sequelae such as mental retardation, hearing loss, and seizures [4]. Because about half of the cases during epidemics are working age adolescents and young adults the
disruption and chaos in the community are enormous, and epidemics can quickly evolve into a social, human, and economic disaster for an affected country.

2. Control measures for epidemic meningitis in sub-Saharan Africa

The current WHO approach for control of meningitis epidemics in sub-Saharan Africa is based on early detection of cases and emergency mass vaccination of the population at risk with meningococcal polysaccharide (PS) vaccines [5]. Meningococcal PS vaccines have been available for more than 20 years and have been shown to be effective in preventing disease in adults and older children. Nonetheless, meningococcal PS vaccines have important limitations; they have limited efficacy in infants and young children [6], do not decrease carriage, and do not confer herd immunity [7]. Two meningococcal PS vaccines are available for reactive campaigns in the African meningitis belt: a bivalent A/C PS vaccine for US$ 0.66 per dose, and a trivalent A/C/Y/W135 PS vaccine at about US$ 1.30 per dose. A tetravalent A/C/Y/W135 PS vaccine is licensed but its high cost precludes widespread use in Africa for epidemic control.

A successful reactive strategy depends on good surveillance, accurate bacteriologic diagnosis, availability of PS vaccine, and a logistic system capable of rapidly mounting immunization campaigns. Despite organizational and logistic improvements in recent years African public health officials have been frustrated with having to respond to meningococcal epidemics with strategies that are at best, moderately useful and at worst, ineffective.

3. Meningococcal conjugate vaccines

In the late 1980s, Schneerson et al. revolutionized the field of polysaccharide vaccines by developing conjugate polysaccharide vaccines [8]. By linking carbohydrate antigens from Hemophilus influenzae (Hib) to proteins they formulated a new vaccine that was much more immunogenic than its plain polysaccharide precursor. Plain polysaccharide vaccines are B cell-dependent antigens, they are not able to prime immunological memory and are poorly immunogenic in infants and young children, and their protection is short lasting. The coupling of polysaccharides to a carrier protein transforms PS into T cell-dependent antigens that are capable of priming immunological memory and are immunogenic in infants.

Pharmaceutical development of Hib conjugate vaccines followed, and introduction of these conjugate vaccines resulted in a dramatic reduction in cases of invasive Hib disease. Through the 1990s evidence mounted that the use of Hib conjugate vaccine also resulted in dramatic decrease of carriage and a strong herd immunity effect [9]. In addition to Hib conjugate vaccines, this technology has been used to develop conjugate PS vaccines against Streptococcus pneumoniae, N. meningitidis group C, and more recently against N. meningitidis A/C/W/Y.

During the 1990s the United Kingdom experienced an increasing number of cases of meningitis due to group C N. meningitidis. Vaccine manufacturers were asked to develop meningococcal C (Men C) conjugate vaccines, and in November 1999 Men C conjugate vaccines were introduced in the primary immunization schedule with doses at 2, 3, and 4 months, accompanied by a catch-up campaign of two doses for the 5–11 months age group, and a single vaccination for those aged 1–17 years (later extended to 24 years) [10]. An extensive postlicensure evaluation program documented that group C meningococcal conjugate vaccines were safe and had a dramatic impact on serogroup C disease [11]. The vaccine reduced group C nasopharyngeal carriage by 66% in adolescents and resulted in herd immunity with significant and sustained decrease in cases in those not vaccinated [12]. While the long-term effectiveness (beyond 10–15 years) of the meningococcal C conjugate vaccines remains to be seen, we now know that the Men C conjugate vaccines offered individual protection for vaccinees above 2 years for at least 7 years plus strong herd immunity that extended to all age groups for at least that long. A key point that has been learned from these exemplary post-introduction studies is that a single dose of conjugate vaccine in the age group most likely to transmit the organism (1–24 years) blocks colonization and induces herd immunity [13].

4. Developing a Men A conjugate vaccine for Africa: the Meningitis Vaccine Project

MVP grew out of a WHO-sponsored effort to improve the public health response to meningitis outbreaks in Africa after the devastating outbreak in 1996–1997. In early 2000, WHO asked a group of experts to review the epidemiology of meningococcal disease in sub-Saharan Africa, data from clinical trials of polysaccharide and conjugate meningococcal vaccines, and the costs to develop Men A conjugate vaccines for Africa. The expert group concluded that development of a meningococcal A or A/C conjugate vaccine was feasible and offered an attractive strategy for epidemic control and perhaps, elimination of meningococcal disease as a public health problem in Africa [14]. In April 2000, a group of international experts and delegates from African ministries of health endorsed the initiative, and in 2001 the Bill & Melinda Gates Foundation agreed to fund a partnership between WHO and PATH aimed at developing, testing, and licensing meningococcal conjugate vaccines for sub-Saharan Africa.

Throughout the Fall of 2001 and the Spring of 2002 MVP held extensive discussions with African public health officials who emphasized the key importance of a low vaccine price on the ability of African countries to purchase vaccine in a sustainable way. African leaders asked MVP to vigorously explore less expensive products. In view of these concerns,
MVP convened a series of meetings and consultations with WHO, PATH, and pharmaceutical consultants that resulted in an alternative model for the development of a monovalent group A meningococcal conjugate vaccine [15]. MVP would identify the following:

- suppliers of tetanus toxoid and group A polysaccharide, the two main components of the conjugate vaccine;
- a research laboratory that was willing to develop and transfer a conjugation technology;
- a vaccine manufacturer who could accept the technology transfer and was willing to make a conjugate vaccine that would cost less than US$ 0.50 per dose.

After extensive due diligence, MVP identified the following three partners:

- SynCo Bio Partners in Amsterdam, The Netherlands, for supply of meningococcal group A polysaccharide;
- the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration (CBER/FDA) in Bethesda, Maryland, for development of a conjugation technology for the polysaccharide-tetanus toxoid vaccine;
- the Serum Institute of India Limited (SIIL) in Pune, India, for supply of the tetanus toxoid and manufacturing the Men A conjugate vaccine.

The conjugation technology was transferred to SIIL in December 2003, and in 2004 SIIL prepared test lots and clinical batches of the study vaccine using the CBER/FDA technology. Animal testing, including toxicity, local tolerance, and immunogenicity of the study vaccine, was completed in 2004, and a Phase 1 clinical study of the Men A conjugate vaccine was completed in India in December 2005. Results of the Phase 1 study showed that the Men A conjugate was safe and immunogenic, and a full report describing these results is included in this supplement [16]. Phase 2 studies in Mali and the Gambia began in 2006, and Indian licensure of the vaccine is expected in 2008–2009. SIIL will produce at least 25 million of doses of the Men A conjugate vaccine annually, and the WHO Regional Office for Africa will be responsible for coordinating introduction of the Men A conjugate vaccine through country-wide mass immunization campaigns of people aged 1–29 years with a single dose of Men A conjugate vaccine, as well as a two-dose schedule in under ones (14 weeks and 9 months). The proposed strategy is expected to induce herd immunity. To document this important point extensive meningococcal carriage studies are planned during a country-wide demonstration study [17]. The enhanced community immunity against group A N. meningitidis will prevent epidemic and endemic disease due to this organism.

5. Future development

Making vaccines is neither easy nor cheap, and vaccine manufacturers must pay attention to profitability if they are to stay in business. Not surprisingly “Big Pharma” companies are more interested in vaccines that have potential markets in developed countries. Therefore, financing the development of new vaccines that are to be used almost exclusively in developing countries, like a Men A conjugate vaccine, is no simple matter. A “push” financing strategy to develop new vaccines involves the provision of financial resources to aid in the pharmaceutical development and clinical testing of products that by themselves would not be developed for commercial reasons. “Push” funds significantly lower the risk to a vaccine manufacturer, and in exchange, a negotiated price for the product may be possible. Achieving this goal immeasurably facilitates planning for the introduction of a product because the price is known up front. The development of the Men A conjugate vaccine is a good example of the usefulness of “push” whereby a needed conjugate vaccine that was of limited interest to large vaccine manufacturers is now being developed [15].

In addition, the vaccine manufacturing field has changed dramatically over the last 20 years. Developing country vaccine manufacturers – so-called emerging suppliers – now make and sell most of the basic Expanded Program on Immunization (EPI) vaccines (diphtheria/tetanus/pertussis, tetanus toxoid, measles, measles/rubella, BCG, and oral polio vaccine) that are used globally. Several of these new suppliers have continued to invest heavily to improve their plants, their quality control, and their clinical programs. WHO prequalification of these vaccines has offered a mechanism that not only establishes a quality standard but also guarantees these manufacturers access to UNICEF tenders. As a group these developing country vaccine manufacturers are interested in filling a niche—that is, making and selling affordable and needed vaccines for developing countries. The success of the Serum Institute of India Limited in being able to accept technology transfer and to produce a Men A conjugate vaccine that meets every international standard and yet remains affordable, offers an attractive model for the development of other needed vaccines. As developing country manufacturers (“emerging suppliers”) master conjugation technology, it will be easier to develop other conjugate vaccines. Because widespread use of conjugate vaccines has been shown to generate dramatic reductions in morbidity and mortality it is important that development timelines are shortened so that needed conjugate vaccines can be made available at prices that developing countries can afford to pay.

References


Serogroup B meningococcal vaccines—an unfinished story

Manish Sadarangani, Andrew J Pollard

Most invasive meningococcal disease in developed countries is caused by Neisseria meningitidis with a serogroup B capsule. However, despite availability of vaccines for other serogroups since the 1960s, no serogroup B vaccine exists. In this Review we look at the development of serogroup B vaccines over the past 40 years. Outer membrane vesicle vaccines have been successfully used to control geographically isolated epidemics, but most have not been highly immunogenic in young children or provided broad cross-protection from infections with other strains. Vaccines based on subcapsular antigens have recently produced promising results in early clinical trials, and the disease burden might be substantially reduced over the next few years.

Introduction

The first description of a disease with the characteristics of infection with Neisseria meningitidis was made by Gaspard Vieuxseux1 in Geneva, Switzerland, during a meningitis epidemic in 1805. Invasive meningococcal disease is now endemic worldwide and most cases are caused by five of the 13 meningococcal serogroups (A, B, C, Y, and W135). Serogroup B disease accounts for many cases in Europe, the Americas, and Australasia, where the incidence of invasive meningococcal disease ranges from less than one case per 100 000 per year to six cases per 100 000 per year,12 peaking in children between ages 6 months and 2 years.

Meningococci can be characterised by serological methods, on the basis of surface structures of the organism (figure 1),4 or by multilocus sequence typing (MLST)13 during surveillance and vaccine development. The latter uses DNA sequence data to identify variation in housekeeping genes, and assigns genetically related isolates into sequence types, and related sequence types into clonal complexes. Most serogroup B disease since the 1960s has been caused by isolates from sequence type 32 and sequence type 41/44-clonal complexes.14

Introductions of a serogroup C conjugate vaccine (MenC) into several countries since 1999 reduced the incidence of serogroup C disease ten-fold,15 and anACYW135 tetravalent conjugate vaccine has recently been introduced into the USA for adolescents (aged 11–18 years),16 although data are not yet available on its effectiveness. Because available vaccines can control A, C, Y, and W135 disease, serogroup B is the main cause of invasive meningococcal disease in most temperate countries, and accounts for 85–90% of cases in the UK.17–21 Until a safe and effective serogroup B vaccine is developed, invasive meningococcal disease will continue to cause substantial morbidity and mortality in children worldwide.

Immunity and surrogate markers of protection

Serogroup B disease has a low incidence in countries where it is endemic, so the large sample size needed for vaccine efficacy studies prohibits trials that use disease as an outcome. Surrogate markers of protection are therefore needed that can be measured in participants of the trials. The importance of so-called bactericidal substances in human blood in protecting against invasive meningococcal disease, and higher concentrations of such factors in adults compared with children, was first proposed in the early 1900s.21 In 1969, Irving Goldschneider and colleagues22 provided evidence that circulating antibody was the crucial substance, showing an inverse correlation between the incidence of disease and the prevalence of complement-dependent serum bactericidal antibody (figure 2). This finding led to accepted use of the serum bactericidal antibody assay as a surrogate marker of protection.

In the modern serum bactericidal antibody assay, N meningitidis target strains are killed in the presence of meningococcal-specific antibody (from postvaccination serum) and exogenous complement.23 For MenC, a serum bactericidal antibody titre of 1/16 or greater (with rabbit complement) correlated strongly with postlicensure vaccine effectiveness.24 For serogroup B disease the data are less secure, but the proportions of vaccine recipients...
with four-fold or greater rises in serum bactericidal antibody after vaccination or serum bactericidal antibody titres of 1/4 or greater, using human complement, have been correlated with clinical efficacy in trials of outer membrane vesicle vaccines.19,20 These cutoffs are therefore thought to be the protective threshold in assessment of experimental vaccines, and are required to support vaccine licensure.

Several limitations of the serum bactericidal antibody assay exist. There is substantial interlaboratory variation, particularly when measuring serum bactericidal antibody titre of 1/4 or greater and no consensus about representative target strains. Recent data suggest that rabbit complement factor H (fH) does not bind to N meningitidis, unlike human fH. Binding of fH to the bacterial surface downregulates complement activation, leading to higher titres of serum bactericidal antibody and overestimation of vaccine efficacy with rabbit complement.21 These data suggest that either human complement or exogenous human fH should be used in these assays, but there is difficulty in getting human complement sources for all test strains.

Evidence is increasing that alternative mechanisms are important in establishing protection against invasive meningococcal disease. First, the relation between incidence of disease and prevalence of serum bactericidal antibody described by Goldschneider and colleagues22 was not seen in more recent studies in the UK and Canada,23,24 where a decline in disease incidence throughout childhood was not associated with a change in the prevalence of serum bactericidal antibody. In the UK study, the second peak of disease in teenagers coincided with a paradoxical increase in the proportion with a serum bactericidal antibody titre of 1/4 or greater, and adults had a low risk of disease despite a much lower prevalence of serum bactericidal antibody activity.

Second, in a large study in Iceland, titres of serum bactericidal antibody gave an underestimate of vaccine efficacy.25 Third, disease in individuals with complement deficiency has a different age distribution, less severe clinical features, and involves unusual serogroups.26 Indeed, serogroup B disease has only occasionally been described in series of complement-deficient individuals with invasive meningococcal disease.

Alternative surrogate markers of protection include the opsonophagocytic assay8 and antibody avidity,9 but there are no data linking these with vaccine efficacy or even population protection. Protection in the absence of serum bactericidal antibodies is probably conferred by opsonophagocytosis.10 This protection is seen in complement factor C6-deficient rats, which permit opsonisation but not bacteriolysis. Both serum bactericidal antibody and opsonophagocytic activity have been elicited in animals and human beings after immunisation with serogroup B protein and lipopolysaccharide antigens. However, few data suggest that opsonophagocytic activity in the absence of serum bactericidal antibody can prevent or improve outcome from invasive meningococcal disease. The importance of antibody avidity and the ability of vaccines to stimulate avidity maturation have been shown for MenC, and vaccines against Streptococcus pneumoniae and Haemophilus influenzae type b.12 Serum bactericidal antibody titre and IgG concentration after vaccination with an outer membrane vesicle vaccine correlated poorly, possibly because only high avidity antibodies were bactericidal,13 and further investigation for serogroup B vaccines is warranted.

The serum bactericidal antibody assay continues to be widely used, but whether mechanisms of protection for new vaccine candidates will be the same as for polysaccharide and outer membrane vesicle vaccines is unknown. New vaccines might elicit different mechanisms of killing, and other immune responses might be important. However, serum bactericidal
antibody remains the only surrogate of protection for which there are any supportive data from human beings, although vaccine effectiveness will only be accurately evaluated during postmarketing surveillance.

Capsular polysaccharide vaccines
The serogroup B capsule is the most obvious candidate for a universal vaccine, but this has not elicited serum bactericidal antibody in humans being or animals or (table I). Some studies of complexes of the B polysaccharide and outer membrane proteins showed antibody responses to polysaccharide and protein components, but this has not been confirmed by other studies. When polysaccharide-specific antibodies are present, they are mostly the IgM class, not bactericidal, and therefore might not be protective. The most likely explanation for

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Strain</th>
<th>Components</th>
<th>Number of doses</th>
<th>Number of people</th>
<th>Age group</th>
<th>Proportion with serum bactericidal antibody titre against vaccine strain</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsular polysaccharide vaccines</td>
<td>USA (1972)</td>
<td>NA</td>
<td>B polysaccharide</td>
<td>1</td>
<td>113</td>
<td>Adults</td>
<td>0%</td>
</tr>
<tr>
<td>France (2000)</td>
<td>NA</td>
<td>N propionylated B polysaccharide</td>
<td>1</td>
<td>17</td>
<td>Adult men</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Outer membrane vesicle vaccines</td>
<td>South Africa (1983)</td>
<td>M958</td>
<td>Outer membrane protein and B polysaccharide</td>
<td>1</td>
<td>4400</td>
<td>4 months to 5 years</td>
<td>41% (titre 1.8 or greater)</td>
</tr>
<tr>
<td>Cuba (1991)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>106252</td>
<td>10-14 years</td>
<td>-</td>
<td>85%</td>
</tr>
<tr>
<td>Norway (1991)</td>
<td>447/84</td>
<td>Outer membrane vesicle</td>
<td>2</td>
<td>171800</td>
<td>14-16 years</td>
<td>97%</td>
<td>80%</td>
</tr>
<tr>
<td>Norway (1991)</td>
<td>447/84</td>
<td>Outer membrane vesicle</td>
<td>2 and 1</td>
<td>311</td>
<td>13-14 years</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Norway (1991)</td>
<td>447/84</td>
<td>Outer membrane vesicle</td>
<td>3 and 1</td>
<td>374</td>
<td>12-17 years</td>
<td>92%</td>
<td>90%</td>
</tr>
<tr>
<td>Sao Paulo, Brazil (1992)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>About 2.4 million in all three groups</td>
<td>-</td>
<td>-</td>
<td>74% (16-92)</td>
</tr>
<tr>
<td>Sao Paulo, Brazil (1992)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>24-47 months</td>
<td>43%</td>
<td>45%</td>
<td>47% (72 to 84)</td>
</tr>
<tr>
<td>Sao Paulo, Brazil (1992)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>3-23 months</td>
<td>13%</td>
<td>22%</td>
<td>-37% (-100 to 73)</td>
</tr>
<tr>
<td>Rio de Janeiro, Brazil (1992)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>6 months to 9 years</td>
<td>-</td>
<td>-</td>
<td>58% (31-74)</td>
</tr>
<tr>
<td>Rio de Janeiro, Brazil (1992)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>About 1.6 million in all four groups</td>
<td>-</td>
<td>-</td>
<td>70% (38-85)</td>
</tr>
<tr>
<td>Rio de Janeiro, Brazil (1995)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>24-47 months</td>
<td>-</td>
<td>-</td>
<td>42% (47 to 77)</td>
</tr>
<tr>
<td>Rio de Janeiro, Brazil (1995)</td>
<td>Cu385/83</td>
<td>Outer membrane vesicle, C polysaccharide, and 65-95 kDa envelope proteins</td>
<td>2</td>
<td>6-23 months</td>
<td>-</td>
<td>-</td>
<td>23% (-159 to 73)</td>
</tr>
<tr>
<td>Chile (1995)</td>
<td>85/95</td>
<td>Outer membrane protein and C polysaccharide</td>
<td>2</td>
<td>40811 in all three groups</td>
<td>1-21 years</td>
<td>-</td>
<td>51% (-11 to 80)</td>
</tr>
<tr>
<td>Chile (1995)</td>
<td>85/95</td>
<td>Outer membrane protein and C polysaccharide</td>
<td>2</td>
<td>5-21 years</td>
<td>-</td>
<td>-</td>
<td>69% (14-91)</td>
</tr>
<tr>
<td>Chile (1995)</td>
<td>85/95</td>
<td>Outer membrane protein and C polysaccharide</td>
<td>2</td>
<td>1-4 years</td>
<td>-</td>
<td>-</td>
<td>12%</td>
</tr>
<tr>
<td>New Zealand (2005)</td>
<td>N298/254</td>
<td>Outer membrane vesicle</td>
<td>3</td>
<td>75</td>
<td>Adults</td>
<td>96%</td>
<td>-</td>
</tr>
<tr>
<td>New Zealand (2005)</td>
<td>N298/254</td>
<td>Outer membrane vesicle</td>
<td>3</td>
<td>608</td>
<td>8-12 years</td>
<td>-</td>
<td>76%</td>
</tr>
<tr>
<td>New Zealand (2005)</td>
<td>N298/254</td>
<td>Outer membrane vesicle</td>
<td>3 or 4</td>
<td>325</td>
<td>16-24 months</td>
<td>75% (titre 1.8 or greater)</td>
<td>75% (100% after fourth dose)</td>
</tr>
<tr>
<td>New Zealand (2005)</td>
<td>N298/254</td>
<td>Outer membrane vesicle</td>
<td>3</td>
<td>294</td>
<td>6-8 months</td>
<td>74% (titre 1.8 or greater)</td>
<td>74%</td>
</tr>
<tr>
<td>New Zealand (2005)</td>
<td>N298/254</td>
<td>Outer membrane vesicle</td>
<td>3 or 4</td>
<td>375</td>
<td>6-8 weeks</td>
<td>54% (titre 1.8 or greater)</td>
<td>53% (69% after fourth dose)</td>
</tr>
<tr>
<td>Netherlands (2000)</td>
<td>H44/751</td>
<td>Monovalent PnA outer membrane vesicle</td>
<td>3</td>
<td>372</td>
<td>2-3 years</td>
<td>28-38%</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continues on next page)
this lack of immunogenicity is structural homology between the B polysaccharide and human tissue, leading to immunological tolerance. The key component of the serogroup B capsule is an a2-8-linked sialic acid homopolymer, which contains epitopes that are cross-reactive with the polystyriated form of the neural cell adhesion molecule. Any antiscapsular antibodies elicited could cross-react with host antigens and contribute to autoimmunity disease.

A modified polysaccharide in which the N-acetyl groups were replaced with N-propionyl groups, which were then conjugated with tetanus toxoid, elicited bactericidal antibodies in mice but not in humans beings (table 1). Although there was no evidence that this vaccine induced autoantibodies, worries remain about this possibility. Failure to derive a capsule-based vaccine and worries about autoimmunity have shifted focus to capsular antigens.

Outer membrane vesicle vaccines

Bacterial antibodies directed against subcapsular antigens develop after disease and carriage, suggesting that outer membrane proteins are candidates for vaccine development. The first outer membrane protein vaccines in the 1970s were immunogenic in animals but did not elicit serum bactericidal antibody in human beings, leading to the development of soluble protein vaccines in the form of outer membrane vesicles. In these preparations, some of the lipopolysaccharide is removed from outer membrane fragments by detergent, after which the detergent is removed and proteins in the vesicles solubilized. The vesicles are similar to outer membrane blebs naturally released by N meningitidis during culture and infection and contain lipopolysaccharide, outer membrane proteins, periplasmic proteins, and phospholipid (figure 3). Studies of early outer membrane vesicle vaccines during the late 1970s and early 1980s showed a four-fold or greater rise in serum bactericidal antibody in 70–85% of adults after a single dose, but children younger than 6 years had lower responses. Immunogenicities were enhanced with the addition of capsular polysaccharide or aluminium hydroxide, and the latter was included as an adjuvant in most subsequent outer membrane vesicle vaccines. A number of serogroup B outer membrane vesicle vaccines have since undergone efficacy trials (table 1). A Cuban outer membrane vesicle vaccine, which had an efficacy of 83%, was the first serogroup B vaccine to be highly efficacious. After a mass vaccination campaign, the incidence of invasive meningococcal disease in Cuba fell from a peak of 14-4 per 100000 people per year in 1983 to 0.8 per 100000 people per year in 1993–94, although it was already in decline before the introduction of the vaccine. Two subsequent case–control studies of this vaccine in Brazil were the first to estimate its efficiency in young children. The efficacy was 70–74% in children 4–9 years of age, but the vaccine was ineffective in younger children. Similar results were reported for an outer membrane protein vaccine in Chile. These studies also suggested that responses to outer membrane vesicle antigens were highly specific to the strain used in the vaccine (table 1).
Review

![Figure 3: Electron micrographs of Neisseria meningitidis (A) and outer membrane vesicles (B)](image)

*N meningitidis shown as a diplococcus (A); arrow denotes naturally occurring blebs of the outer membrane. Provided courtesy of David Ferguson and Gunneke Norheim, University of Oxford, Oxford, UK.*

vaccines were largely restricted to the vaccine strain, although older individuals seemed to have some crossprotective responses.

In Norway, an outer membrane vesicle vaccine based on an epidemic strain had an efficacy of 57% after two doses, which was deemed insufficient to justify a public vaccination campaign. There was substantial reduction of immunity over time with an efficacy of 87% in the first 10 months after vaccination, compared with only 30% after 21–29 months. Subsequent studies showed boosting of serum bactericidal antibody titres with additional doses, which also resulted in serum bactericidal antibody activity against strains of a different serosubtype, suggesting this strategy could induce broader protection. The Norwegian vaccine is being used to aid control of a serogroup B epidemic in Normandy, France, which started in 2003 and has had a high case-fatality rate (19%). A vaccination programme started in 2006 and data on its effect are awaited.

The second serogroup B meningococcal vaccine to be licensed after the Cuban vaccine was used in New Zealand. From 1991, New Zealand experienced an epidemic of invasive meningococcal disease, reaching a peak in 2001, predominantly caused by one serogroup B strain. After three doses of an outer membrane vesicle vaccine based on this strain, an increase in serum bactericidal antibody titre of four-fold or greater was seen in 53% of young infants (aged 6–8 weeks), 74%–76% of older children (aged 6 months to 12 years), and 96% of adults. A four-fold or greater increase and a postvaccination titre of 1/8 or greater (rather than 1/4 or greater) was needed for patients to be designated as seroresponders in these studies, which could result in these data underestimating population immunity. Again there was substantial waning of immunity over time with only 3–34% of children aged between 6 weeks and 24 months sustaining a response 4–16 months after the third dose. The proportion of seroresponders increased to 100% of toddlers (aged 16–24 months) and 69% of young infants after a fourth dose, which was given to a subset of participants.

The vaccine was rolled-out nationally in 2004, contributing to a decrease in number of cases, although the disease burden was already waning. The effectiveness of this vaccine, which depends on a number of variables in addition to vaccine efficacy at an individual level, has been estimated by two methods. A theoretical statistical model that included confounding variables such as age, ethnicity, socioeconomic status, and geographical region derived a vaccine effectiveness of 73% overall over 2 years. This number has been disputed because of lack of inclusion of overcrowding and other factors, and the failure to account for different disease confirmation rates. This model showed no benefit of the vaccine in infants. A cohort analysis estimated that the effectiveness of the vaccine was 80% in children aged between 6 months and 5 years, and 85% in those aged 6 months to 3 years. There was no evidence, however, of effectiveness in any age group 13–24 months after the third dose. This study did not consider the youngest infants, who have the highest rates of disease in New Zealand.

The vaccination programme was stopped in 2008 by the New Zealand Ministry of Health. The rationale for stopping the programme is not clear given the lack of long-term protection induced by this vaccine and the persistence of disease rates above pre-epidemic levels. Ongoing surveillance will establish the longer term effect of the vaccine campaign and its cessation, and provide important information for strategies to control future outbreaks.

The serum bactericidal antibody response induced by outer membrane vesicle vaccines is largely specific to the serosubtype, being predominantly directed against PorA. There are over 600 PorA variants, although only a few have been associated with most isolates that cause disease. To increase vaccine coverage, a hexavalent PorA outer membrane vesicle vaccine was developed in the Netherlands, consisting of two outer membrane vesicles each expressing three different PorA proteins (table 1). In phase 2 trials in children aged between 8 weeks and 8 years in the Netherlands and the UK, the proportion with significant serum bactericidal antibody responses was 16–100%, dependent on the PorA variant, with the most common serosubtype inducing the lowest response. By 32–42 months of age, serum bactericidal antibody titres of immunised infants had returned to titres found after the first dose, confirming the difficulty of achieving long-term protection. A nonavalent PorA outer membrane vesicle vaccine has been developed, adding a third outer membrane vesicle containing three further PorA proteins. This vaccine elicited serum bactericidal antibody in mice against most of the targeted PorA variants and is in clinical trials. The six PorA variants included in the hexavalent vaccine represent 60–70% of European meningococcal disease isolates overall, and use of the nonavalent vaccine would result in a slight increase in potential vaccine coverage to 70–80%.

An alternative approach to increase breadth of protection is combining outer membrane vesicles, and two such vaccines have been investigated.

For more on PorA variants see [http://www.neisseria.org](http://www.neisseria.org)
and adults, 42–87% of vaccine recipients achieved serum bactericidal antibody responses against homologous strains (ie, expressing the same PorA), with similar results for both vaccines (table 1). Minor outer membrane proteins and genetically modified lipopolysaccharides have also been manipulated in outer membrane vesicle vaccines. Outer membrane vesicles without PorA and with overexpression of the conserved proteins TbpA, Hsf, NspA, or Omp85 only induced a serum bactericidal antibody response in mice when combined. This suggests that a key density of bactericidal antibodies is needed on the bacterial surface to mediate bacteriolyis, which can be done either by a single major protein, such as PorA, or multiple minor outer membrane proteins. More recently, a vaccine combining outer membrane vesicles from three different genetically modified strains, each expressing two PorA variants and different detoxified lipopolysaccharide immunotypes, with overexpression of the outer membrane proteins fHbp, NaDA or Opc, elicited serum bactericidal antibody in mice and rabbits. All three sets of antigens were involved in the bactericidal response, and a phase 1 study is in progress.

Outer membrane vesicle vaccines are useful in the control of serogroup B outbreaks, but a number of hurdles remain. The conventional method of detergent extraction for removal of potentially toxic lipopolysaccharide from these vaccines might also remove other desirable surface antigens. This could be avoided using native outer membrane vesicles (extracted without detergent) derived from strains containing genetically modified lipopolysaccharide. The problem of serosubtype–restricted responses has yet to be overcome to produce a vaccine with wide coverage. Lack of persistence of immune responses suggests that multiple doses throughout childhood would be needed to maintain protection; this is already necessary with vaccines against tetanus and diphtheria, which have been acceptable for decades worldwide. Most outer membrane vesicle vaccines have shown limited efficacy in younger children, although estimated effectiveness of the New Zealand vaccine was higher than in previous studies.

Other vaccines in clinical trials
Several vaccines based on other subcapsular antigens are in development (table 1). One promising candidate, SCVMB, is based on three proteins—NaDA factor H binding protein (fHbp; also known as GNA1870 or LP2086), and neisserial heparin-binding antigen (NHBA, also known as GNA2132)—combined with the New Zealand outer membrane vesicle. The inclusion of multiple antigens reduces the risk of escape variants, which might readily happen with single antigen vaccines given the high rate of phase variation, recombination, and mutation in N. meningitidis. This vaccine was developed by use of so-called reverse vaccinology—570 new putative surface-exposed or secreted proteins were identified from the N. meningitidis genome sequence, and 350 of the encoded proteins were used to immunise mice. 29 proteins induced bactericidal antibodies and the most immunogenic were included in SCVMB. fHbp combined with GNA2091 and NHBA with GNA1030 are present as fusion proteins. Immune responses elicited by the fusion proteins were more potent than those induced by the individual antigens, and they also allow large-scale industrial manufacturing. Although GNA2091 and GNA1030 did induce protective immunity in mice, they elicited lower bactericidal activity than the other proteins and are not thought to be major vaccine antigens.

Serum from mice immunised with SCVMB (without the New Zealand outer membrane vesicle) killed 66 (78%) of 85 representative worldwide isolates, suggesting that this vaccine has the potential to provide broad coverage against serogroup B disease. In phase 2 studies of a vaccine including the outer membrane vesicle component, three doses resulted in serum bactericidal antibody titres of 1:4 or greater in 63–100% of young infants and 96–100% of children 6–8 months old against homologous strains. All target strains expressed one of the vaccine antigens, so no comment can be made about the breadth of protection based on these data. A phase 3 study in infants is in progress across Europe.

fHbp has also been studied as an independent vaccine candidate. Different classification systems have divided fHbp into either three variants (1, 2, and 3) or two subfamilies (A and B). A vaccine containing proteins of subfamilies A and B, which therefore has the potential for broad coverage, elicited serum bactericidal antibody responses in 22–100% of adults in a phase 1 trial in Australia, depending on dose and target strain. Data from completed phase 1 trials in toddlers and teenagers are awaited.

The genes encoding fHbp and NHBA seem to be present in all meningococci, whereas only 38–46% contain naDA. More recently, NaDA, fHbp, and NHBA have been subdivided into 14, 3, and 5 variants, respectively, and how broad the protection is against strains containing more genetically distant variants is unclear. Variant 1 (subfamily B) of fHbp is present in SCVMB and is the most common, but data from animal studies suggest that immune responses are restricted to strains expressing the variant.

fHbp is an outer membrane lipoprotein responsible for recruiting fH to the bacterial surface, resulting in dysregulation of the complement pathway and increased bacterial survival. fHbp also provides protection for bacteria against killing by the antimicrobial peptide LL37. Anti-fHbp antibodies might therefore mediate beneficial effects by multiple mechanisms. Inhibition of binding between fHbp and fH would increase bacterial susceptibility to killing via the alternative complement pathway, and directly elicit bactericidal activity via the classical pathway. One potential problem is that surface
expression of fHbp varies between meningococci, and isolates expressing low fHbp concentrations might not be targeted by anti-fHbp antibodies. Antisera from immunised mice killed bacteria expressing low concentrations of fHbp in studies with rabbit complement. Studies with human complement, however, found that monoclonal antibodies recognising different epitopes that were not bactericidal individually were bacteriolytic when combined. This synergy was thought to happen because the overall antibody density on the bacterial surface was sufficient to allow complement deposition and activation of the classic pathway. Whether this happens with antibodies generated in vivo is unknown.

fHbp consists of two domains of antiparallel β-strands connected by a five amino acid linker. Variable residues are in the surface-exposed part of the molecule, fully accessible to the immune system, and correspond to known antibody epitopes. These regions also seem to bind to fH, suggesting that vaccine-induced antibodies could block this interaction, even if they are not bactericidal. The bactericidal epitopes of variants 1 and 2 are only partly overlapping, suggesting that a recombinant protein containing epitopes from both could increase breadth of coverage. Moreover, recombinant chimeric fHbp molecules and outer membrane vesicles with overexpression of different fHbp variants did elicit bactericidal antibodies in mice against strains of meningococci expressing different variants of fHbp. A potential difficulty is that the high affinity binding between fHbp and fH might mask relevant epitopes during immunisation. Future vaccines might reduce fH binding sufficiently to allow exposure of all immunogenic epitopes to the immune system.

NadA aids meningococcal adhesion and invasion into epithelial cells, activates human monocytes or macrophages in vitro, and might have a role in stimulating the inflammatory cascade that happens during invasive meningococcal disease. Vaccines that elicit anti-NadA antibodies might have the added benefits of improving outcome from disease or inducing herd immunity via blocking of nasopharyngeal attachment.

NHBA is a surface-exposed lipoprotein that is a target of both meningococcal and human proteases and binds to heparin at an arginine-rich region, suggesting a possible role in serum resistance. The genes encoding GNA2091 and GNA1030 were found in all 95 meningococcal isolates in one collection, but they are thought to be accessory proteins in the SCVMB vaccine and there have been no studies describing their structure or function.

A potential problem with these outer membrane proteins as vaccine components is variation in expression between strains, which some studies have considered for fHbp. Furthermore, immunodominant surface structures such as PorA, which are exposed to the immune system in vivo, are under immune selection pressure and therefore show sequence variability. The conservation of NadA, fHbp, and NHBA might suggest that they are not naturally immunologically exposed (during colonising infection), and as such might not be as immunogenic as more variable outer membrane proteins.

Several other vaccines have been tested in clinical trials (table 1). The protein NepA is highly conserved across most strains of N meningitidis, but it did not induce bactericidal antibodies in human beings after promising mouse studies and is not being pursued. Transferrin-binding proteins elicited serum bactericidal antibody in mice and rabbits, and there have been trials in people, but data have not been published. Intranasal outer membrane vesicle vaccines have been tested in a way that mimics the natural immunising effect of colonisation, Nasal IgA concentrations did increase in most people vaccinated in phase 1 trials, but only 43–75% had significant serum bactericidal antibody responses. More data are needed, in particular to establish whether mucosal IgA has a role in protection against colonisation with virulent meningococci. Neisseria lactamica is a commensal carried in the nasopharynx of young children and has been implicated in the

### Table 2: Preclinical studies of serogroup B meningococcal vaccines

<table>
<thead>
<tr>
<th>Outer membrane vesicle vaccines</th>
<th>Serum bactericidal antibody in mice</th>
<th>Serum bactericidal antibody in rabbits</th>
<th>Passive protection in rats or mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrelevant PortA outer membrane vesicle (fHbp)</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Outer membrane vesicle with overexpression of fHbp</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Outer membrane vesicle with overexpression of fHbp, HsF, NepA, OpnBP57</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hexarelated PorA, trivalent lipopolysaccharide outer membrane vesicle with overexpression of fHbp, NadA, Oxy</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Outer membrane vesicle with overexpression of LbpA and LbpB</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Outer membrane vesicle with genetically detoxified lipopolysaccharide</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N lactamica outer membrane vesicle</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Outer membrane protein preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chimeric fHbp</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transferrin binding proteins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FepA (FbpB)</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>OpaA</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMB0506</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMB09218</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMB08373</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMB1163</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMB0938</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other vaccine candidates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule mimetics</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Lipopolysaccharide inner core</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Live attenuated N meningitidis</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
development of natural immunity to the meningococcus. A N. lactamica outer membrane vesicle vaccine was developed on the basis that it would avoid PorA-dependent strain restriction because it does not express PorA. No bactericidal responses were elicited after immunisation in mice or rabbits, and only 8–31% of adults (dependent on the target strain) showed a four-fold or greater rise in serum bactericidal antibody after three doses during a phase 1 trial. Antiserum from immunised rabbits, however, did mediate opsonophagocytosis, suggesting this as a mechanism for the protection against meningococcal bacteraemia seen in mice. With the limited data available at present for alternative assays to the serum bactericidal antibody, whether vaccines that do not induce serum bactericidal antibody could be licensed is unclear.

Vaccines in preclinical studies
Several approaches have provided promising data in animal models, in addition to those involving Hbp (table 2). Iron-regulated proteins (eg, FetA, LbpA, and LbpB) are upregulated in conditions where the concentration of iron is low, so the amount present in outer membrane vesicle vaccines is dependent on growth conditions during manufacture. FetA induced serum bactericidal antibody in rabbits, and an outer membrane vesicle vaccine with high expression of FetA is in development, aiming to overcome strain restriction by eliciting antibodies against both PorA and FetA. Other proposed candidates include outer membrane vesicles with overexpression of LbpA, purified LbpB, and recombinant Opa, which have all induced bactericidal antibodies in mice. Although these vaccines are immunogenic, antibodies are usually directed against variable regions of the outer membrane proteins and have limited cross-reactivity. The additional problem of variable expression on target bacteria must also be overcome if these vaccines are to be developed further. In addition to these antigens, analysis of meningococcal genome sequences, similar to the methods used during the development of SCVMB, has revealed five new putative surface proteins that have elicited bactericidal antibodies after immunisation of mice and which need further assessment.

Lipopolysaccharide has been implicated in the immune response to natural infection, but must be detoxified before inclusion in a vaccine. Meningococcal strains that have a disrupted lpxC gene produce the less toxic penta-acylated instead of the usual hexa-acylated lipopolysaccharide. These strains have been used in the preparation of native or partly detergent-extracted outer membrane vesicles, including the outer membrane vesicles with overexpressed Hbp and a vaccine based on outer membrane vesicles enriched with different immunotypes of genetically detoxified lipopolysaccharide. Both of these vaccines elicited bactericidal antibodies in mice, and avoid loss of antigens caused by the detergent used in conventional outer membrane vesicle production. Different approaches with lipopolysaccharide have shown that oligosaccharides conjugated to tetanus toxoid induced immunotype-specific serum bactericidal antibody in rabbits and the conserved lipopolysaccharide inner core elicited serum bactericidal antibody in mice. An alternative function of lipopolysaccharide could be as an adjuvant. Outer membrane vesicle vaccines without lipopolysaccharide resulted in lower immune responses, whereas an lpxC1 mutant lipopolysaccharide retained adjuvant activity similar to wild-type with reduced toxicity in mice; although more recent in-vitro studies using human dendritic cells suggested this adjuvant property of the mutant lipopolysaccharide might not happen in human beings.

From clinical trials to immunisation schedules
Multiple vaccines are at present competing for introduction into routine immunisation schedules. A successful serogroup B vaccine would, at the very least, have to show immunogenicity against some pathogenic strains using the serum bactericidal antibody assay. Induction of antibodies against different variants of included antigens would provide further supporting evidence that such a vaccine might be broadly protective. On the one hand, vaccines containing multiple antigens, such as SCVMB and some of the modified outer
Review

Search strategy and selection criteria

Data for this Review were identified by searches of Medline and PubMed, references from relevant articles, and the reports of health agencies of relevant countries. Search terms were "meningitis", "vaccination", "immunisation", "neisseria", "meningococcal", "cerebrospinal fluid”, "GNNs", "GNA1870", "LP2806", "factor H binding protein”, "fHbp", "GNA2103", "NadA", "germ-derived neisserial antigen", "SCMV", and "reverse vaccinology". English, Spanish, Portuguese, and French language papers were reviewed. The date limits of the searches were February, 2008, to November, 2009.

membrane vesicle vaccines, have a lower likelihood of escape variants. On the other hand, those that include multiple variants of the same antigen, such as the fHbp subfamily A and B, and nonavalent PorA outer membrane vesicle vaccines, reduce the problem of antigen diversity. A vaccine with 90% strain coverage that induced a response in 80% of recipients and had 90% uptake would have an effectiveness of 36%, which is similar to the contribution of MenC to the prevention of overall invasive meningococcal disease in the UK. Data on diversity and expression of all new vaccine antigens among circulating strains is therefore urgently needed to provide confidence that clinical trial data derived with a small number of target strains can be translated into broad protection. It would be useful to add antigens from any vaccine used in the future to routine typing, including assays of surface expression levels, to aid postlicensure monitoring.

Clinical trials are focusing on young children as the target population because they have the highest incidence of disease. Persistence of antibody after immunisation in infancy, however, is poor so one approach would be to give multiple doses throughout childhood to provide long-term protection. An alternative approach exists if there is a herd immunity effect, similar to that seen for MenC. Studies examining the effect of herd immunity should be included in the development plan for serogroup B vaccines given the potential for herd immunity to complement and enhance direct protection. If herd immunity was induced, fewer doses could be given in early childhood, and population protection might be achieved by reducing transmission via immunisation of teenagers and young adults, who have the highest rates of meningococcal carriage.

These vaccines need to be economically viable. Potential cost of the hexavalent PorA outer membrane vesicle vaccine in the Netherlands was estimated at €2145 per life-year saved and €1575 per quality adjusted life-year gained, compared with €6529 per life-year saved for MenC in the UK. The threshold for recommendation of new treatments by the National Institute for Clinical Excellence in the UK is usually £20000–100000 per quality adjusted life-year gained. Strain coverage, vaccine efficacy, cost per dose, and number of doses needed will be the key factors in determining cost-effectiveness.

Conclusion

Lack of immunogenicity of the serogroup B polysaccharide was shown in 1972 and since then, despite studies involving almost 6 million people, the search for a vaccine that is immunogenic in all age groups, and provides broad protection against serogroup B disease, continues (panel). During the past 40 years there has been some success, with outer membrane vesicle vaccines contributing to disease control in Cuba and New Zealand. However, these vaccines elicit only limited protection against PorA heterologous strains and are poorly immunogenic in young children; moreover, multiple doses are needed to provide long-term immunity. They are therefore useful for epidemics caused predominantly by a single strain, but not for endemic disease. Vaccine candidates in late phase development are based on subcapsular proteins and, if successfully implemented, could have an effect on other serogroups. Recent clinical trials have produced encouraging initial results, leading to media interest, and hope that substantial control of meningococcal disease is within reach. The major outstanding issue is that the persistence and breadth of protection that these vaccines induce remains unknown. Countries with a high incidence of invasive meningococcal disease, such as the UK, might be in a position to prevent more of the burden of meningococcal disease beyond serogroup C in the near future, but policy makers will have the challenge of deciding how much protection is enough to justify the use of such a vaccine.

Contributors

MS reviewed published work and drafted the paper. AJP assisted with selection and interpretation of included studies and with preparation of the paper. Both authors read and approved the final version.

Conflicts of interest

AJP acts as chief investigator for clinical trials done on behalf of Oxford University, sponsored by vaccine manufacturers Novartis Vaccines, GlaxoSmithKline, Sanofi-Aventis, Sanofi-Pasteur MSD, and Wyeth Vaccines. Industry sourced honoraria for lecturing or consultancy, travel expenses, and grants for education and attendance at scientific meetings are paid directly to an educational/administrative fund held by the Department of Paediatrics, University of Oxford. AJP does not receive any personal payments from vaccine manufacturer. MS has no conflicts of interest to declare.

Acknowledgments

This work was supported by the Oxford Partnership Comprehensive Biomedical Research Centre Programme with funding from the UK Department of Health’s NIHR Biomedical Research Centres funding scheme. The views expressed in this Review are those of the authors and not necessarily those of the Department of Health. AJP is a Jenner Institute Investigator. MS is supported through a Research Training Fellowship (RTF1036) awarded by Action Medical Research, UK.

References


Proceedings of the SAGE Working Group on Rubella

March 17, 2011
Preamble

Rubella is usually a mild viral rash illness in children and adults; however, infection early in a woman’s pregnancy, particularly during the first 16 weeks, can result in miscarriage, fetal death, or an infant born with birth defects (i.e., congenital rubella syndrome [CRS]). In 2000, the World Health Organization (WHO) published the first rubella vaccine position paper (PP) to guide introduction of rubella-containing vaccine (RCV) in national childhood immunization schedules.

Since the publication of the PP in 2000, several areas have changed including additional countries have introduced RCV, 2 regions (AMR, EUR) have established rubella elimination goals, and additional information on rubella vaccine safety when administered to unknowingly pregnant women.

As part of updating the PP, a working group (WG) was established and was asked to review and propose necessary updates to the WHO rubella vaccine PP of 2000. In addition, identify the information gaps, guide the work required to address information gaps, and prepare for a SAGE review of the updated vaccination strategies. Specifically the working group was asked to address the following questions:

1. What are the possible goals for rubella/CRS prevention and rubella/CRS elimination (country, regional or global)?
2. With the goals mentioned in question 1, what are the most appropriate vaccination strategies to achieve these goals?
3. What is the minimum required routine childhood immunization coverage that should be achieved and maintained to ensure that the introduction of rubella-containing vaccine does not increase the risk of CRS?

To address these requests, the WG has had 10 teleconferences in addition to a face-to-face meeting. To address the first two questions on the possible goals and appropriate strategies, WG members heard either through the conference calls or the face to face meeting, several presentations on various topics including update on the global vaccine use; regional goals and strategies and experiences; regional and country experiences with different vaccine strategies; strawman document on proposed goals and strategies; optimal age for administration of 1st dose of RCV; cost-effectiveness of rubella vaccination; update on the global and regional burden of rubella and CRS; and information on the safety, precautions/contraindications, duration of immunity and vaccine effectiveness of rubella vaccines.
To address the 3rd question on the minimum required routine childhood coverage, the WG heard presentations on modeling to assess the impact of different vaccination strategies on CRS and country experiences with different vaccine strategies. Additional presentations addressed surveillance needs and challenges.

**The 2000 Rubella Vaccine Position Paper**

The 2000 rubella vaccine PP was reviewed and its key contents are summarized in the subsequent five paragraphs. The primary objective of rubella vaccination is to prevent the occurrence of congenital rubella infection including congenital rubella syndrome (CRS) which is an important cause of deafness, blindness and mental retardation. It noted that while an estimated 100,000 cases of CRS occur annually in developing countries, the global burden of CRS in all regions had not been well described. Cost-benefit studies conducted in middle to high income countries have demonstrated that the benefits of rubella vaccination outweigh the costs.

In the 2000 rubella vaccine PP, WHO recommended the use of RCV in all countries with well-functioning childhood immunization programs where reduction or elimination of CRS is considered a public health priority and where resources are available. For all countries, they should assess their rubella situation and if appropriate, make plans for introduction of RCV.

When introducing rubella, two approaches are recommended: 1) prevention of CRS only and 2) elimination of rubella as well as CRS. For CRS prevention only, adolescent girls and/or women of childbearing age (WCBA) are targeted for vaccination. Vaccination strategies include delivery through mass campaigns or routine services. For elimination of rubella and CRS, RCV is introduced through the universal childhood immunization program while assuring immunity among WCBA. All countries undertaking rubella elimination should achieve and maintain an immunization coverage of >80%. In deciding which approach to use, several areas need to be considered including: burden of CRS, level of susceptibility in WCBA; strength of the immunization program; resources both financial and personnel; and other disease/public health priorities.

In considering the two approaches, vaccination of adults is essentially free of risks for altering the rubella transmission dynamics. However, if a childhood vaccination program doesn't achieve and/or maintain high coverage (>80%), the low vaccination coverage may decrease virus circulation sufficiently to shift both the average age of exposure to rubella and rubella susceptibility from children to older age groups including women of childbearing age, and therefore potentially increase the risk for CRS. Routine childhood immunization in the private sector should be monitored closely because it may also alter the rubella transmission dynamics.
Countries with measles elimination goals should consider taking the opportunity to eliminate rubella/CRS as well by using combined measles-rubella (MR) vaccine or measles-mumps-rubella (MMR) vaccine.

**Burden of CRS**

In 1996, it was estimated that approximately 110,000 infants with CRS were born in developing countries annually. Even with the introduction of RCV into additional countries, the burden of CRS remains significant especially in the African and South East Asian Regions. In 2009, the global estimates for CRS were revised yielding an estimated 120,000 infants born with CRS in 1996 and 112,000 CRS cases in 2008. The changes in the estimates were due to the availability of more seroprevalence data and success in the immunization programs in the Region of the Americas and Europe.

**Rubella Vaccines**

There are 5 different rubella virus vaccine strains that are currently being administered. The RA 27/3 virus strain is the most commonly used vaccine strain globally. Other vaccine strains include: Takahashi, Matsuura, and TO-336 strains used primarily in Japan whereas the BRD-2 strain is used in China.

The adverse events following vaccination with the RA 27/3 rubella vaccine are mild, particularly in children. Most of the available data on adverse events are for the MMR combination. Common adverse events include pain, redness and induration at the site of injection. Low grade fever and rash, lymphadenopathy, are commonly reported. Acute joint symptoms tend to be rare in children (0%-3%) and in men, but are common among vaccinated susceptible adolescent and adult females; they include arthralgias (25%) and arthritis (10%) that usually last from a few days to 2 weeks. These transient reactions seem to occur in non-immunes only, for whom the vaccine is important. For MR containing vaccine, thrombocytopenia is reported in 1/30,000 doses as compared to 1/3000 cases in wild rubella disease.

Rubella vaccine is contraindicated in pregnant women, people who are severely immunocompromised due to congenital disease; severe HIV infection; advanced leukaemia or lymphoma; serious malignant disease; treatment with high-dose steroids, alkylating agents or antimetabolites; or who receive immunosuppressive therapeutic radiation. However, asymptomatic HIV-positive persons can be immunized. Combining all available data, follow-up of more than 2,700 susceptible women, who were unknowingly pregnant and received a rubella vaccine in early pregnancy, found no infants with CRS.

The seroconversion rates are similar between the different formulations using RA 27/3 vaccine (i.e., monovalent rubella vaccine, MR, MMR, MMRV). Rubella-
containing vaccine is highly protective. Studies on the RA 27/3 virus vaccine documented a vaccine effectiveness $\geq 95\%$. In a review of several studies for duration of protection of one dose of RCV spanning 10-21 years documented seropositivity of $\geq 95\%$.

In the 2000 WHO PP, “rubella vaccine is usually administered at 12-15 months but can also be administered to children as young as 9 months of age”. The age of administration of RCV is based on the appropriate age for measles vaccination. In the published literature on safety and immunogenicity of RCV, the reactogenicity between various MMR formulations between infants and children was similar. The immunogenicity in infants and children $\geq 12$ months of age was similar with seroconversion rates of $\geq 94\%$ in infants ($<12$months). Unpublished data from Dr. Grangeot-Keros, documented that the cell-mediated immune response at 9 months of age was adequate. In conclusion, published studies and unpublished data support that infants given RCV at nine months have just as good an immunological response as older children. Even though RCV can be administered to infants at 9 months of age, some countries with longstanding programs administer RCV in children $\geq 12$ months and consider RCV doses received before $\geq 12$ months as not a valid dose.

**Economic Analyses on the use of Rubella-containing vaccine**

In a literature review of economic analyses of use of rubella vaccines published between 1980 and 2010, 26 studies on the economics of rubella and rubella vaccination were identified; 20 studies were conducted in high-income countries, 5 in upper middle-income countries and 1 in a lower middle-income country. No studies were conducted in low-income countries. Other gaps in the literature include studies on the efficiency of including rubella vaccination with measles immunization and studies that establish the most cost-efficient rubella vaccination schedule. Some methodological limitations were also noted in the studies.

The findings in high and middle-income countries indicate that CRS is costly. The costs of treating CRS are estimated to be between $1,994 and $13,482 per case annually in middle-income countries and $18,664 and $43,920 in two high-income countries. The findings indicated that rubella vaccination programs are economically justifiable and demonstrated favorable cost-effectiveness or cost-benefit ratios in high-income and middle-income countries.

**Vaccine Introduction, Goals and Experiences**

Since 1996, there has been a steady increase in the number of member countries introducing RCV. In 2009, 130 countries (66\%) of WHO member countries use
rubella vaccine in their routine program. There are regional differences in the use of RCV. All countries in AMR and EURO have introduced RCV into their routine childhood program. Since 1996, there is a steady increase of countries in EMRO and WPR that have introduced RCV. However, only 2 of 46 member countries in AFRO and in SEAR, 4 of 11 member countries use RCV.

Among the 130 countries with RCV in their national immunization schedules as of December 2009, the first dose is recommended to be administered at ages 12–24 months in 122 (94%) member countries. Although only one RCV dose is recommended routinely, 119 (92%) countries use a 2-dose schedule because rubella vaccine is combined with measles vaccine, which requires a 2-dose schedule. Measles-mumps-rubella (MMR) vaccine is used in 115 (88%) countries, measles-rubella (MR) vaccine is used in 12 (9%) countries, measles-mumps-rubella-varicella vaccine is used in two (2%) countries, and single-antigen rubella vaccine is used in one country. Regions with highest estimated CRS burden are also the regions with the lowest uptake of vaccine.

In 2009, median MCV1 coverage was 96% (inter-quartile range: 92%–99%) for the 130 countries using RCV, including nine countries (Azerbaijan, the Cook Islands, the Dominican Republic, Ecuador, Haiti, Iraq, Lebanon, Palau, and Samoa) with MCV1 coverage <80%. For countries not using RCV, the median MCV1 coverage was 76% (inter-quartile range: 74%–91%), including 22 countries with sustained MCV1 coverage >80% in 2009 that have met the vaccination coverage criteria for introduction of RCV (See WER 2010;85:413–418).

Two regions (PAHO, EURO) have established rubella elimination goals by 2010. One region (WPRO) has established an accelerated rubella and CRS prevention goal by 2015. One region (EMRO) has established a goal of CRS prevention without a target date for countries that have introduced rubella vaccine in their national immunization schedule. Two regions (SEARO, AFRO) have not established any elimination, control or prevention goal. Vaccination strategies are defined according to the goals and the target dates set.

Regional Experiences

Status of Rubella Elimination in the Region of the Americas

Prior to establishing initial regional initiatives, some of the challenges that PAHO faced included: rubella was considered a mild disease; lack of information on burden of CRS and need for surveillance infrastructure. Prior to setting the elimination goal, the burden of CRS was documented in several countries in the region of the Americas.
In 1997, the Technical Advisory Group (TAG) of the Americas recommended that all countries in the Region introduce RCV into their childhood vaccination programs and reduce the number of susceptible WCBA through targeted efforts (e.g., post-partum vaccination). In 1999, TAG recommended an accelerated rubella control and CRS prevention initiative. Countries wishing to eliminate rubella and CRS rapidly were advised to conduct a one-time mass campaign that targeted adolescent and adult females and males with measles-rubella (MR) vaccine. Countries wishing to prevent and control CRS were advised to conduct a one time mass campaign in females only 5-39 years with MR vaccine. In 2003, the Directing Council for the Member States for the Americas established a goal for the elimination of rubella and CRS by 2010. Rubella and CRS elimination is defined as the interruption of endemic rubella virus transmission in all the countries of the Americas for a period greater than or equal to 12 months without the occurrence of CRS cases associated with endemic transmission, in the presence of high-quality surveillance.

In 2003, the TAG recommended that mass campaigns be conducted in both males and females. The target age group was selected on the basis of year of vaccine introduction, campaigns conducted, epidemiology and fertility rates in the countries. In 2007-2009, the three countries (Chile, Argentina, Brazil) that initially conducted female only mass campaigns documented outbreaks in adult males. All three countries subsequently conducted additional mass campaigns, two in males only (Argentina, Chile) and one in both males and females (Brazil).

Lessons learned from conducting adolescent and adult mass campaigns include: targeting of non-traditional groups (e.g., adult males); understanding the importance of broad and timely social mobilization; developing and implementing detailed plans of action with adequate monitoring and conducting mass campaigns involving large proportion of the population in a very short time period(< 6 weeks). These campaigns also strengthened vaccine safety practices such as monitoring and responding to events allegedly attributable to vaccination or immunization, ensuring and monitoring safe injections, identifying, evaluating and following up unknowingly pregnant women that have been vaccinated and coordination with blood banks. In 1999, TAG recommended that rubella vaccination is contraindicated for pregnant women; however if a pregnant woman is vaccinated, the available data does not support that abortion should be recommended. After the 1999 TAG recommendation, all countries in the Americas that planned to conduct adult mass campaigns chose to systematically follow-up pregnant women who had received rubella vaccine using a standardized protocol. Based on serological evaluation, 2,894 (10%) women were classified as susceptible at the time of vaccination from 6 countries; of their pregnancies 1,980 resulted in a live birth and were followed up. None of the infants had features of CRS as a result of rubella vaccination. With the
success of the PAHO elimination strategy, as of October 2010, the last endemic rubella virus was isolated in Argentina in early 2009 indicating that rubella and CRS have been successfully eliminated from the Americas.

The rubella/CRS elimination goal has benefitted from the measles elimination goal and the measles elimination goal has benefitted from the rubella/CRS elimination goal. Several aspects of rubella and measles elimination goals are integrated including use of combined vaccines (MR, MMR) and integrated rubella-measles surveillance. The vaccination strategies recommended for rubella/CRS elimination have helped to sustain measles elimination.

With PAHO’s successes, there are challenges to maintaining elimination of measles, rubella and CRS. These include risk of importations, secondary spread due to importations, and the financial and human resources needed to prevent and respond to outbreaks.

Discussion focused on the successes of the PAHO strategies including the strategies used to successfully vaccinate adult males. Costa Rica was cited as an example of low immunization coverage (<70% for first 10 years of vaccination program) resulting in a shift in rubella susceptibility to adolescents and young adults and potential increase risk of CRS. As a result of the increased susceptibility among adolescents and adults, a vaccination campaign covering susceptible cohorts was conducted and high childhood immunization coverage was achieved and maintained through enhanced immunization efforts.

**Status of Rubella Elimination in European Region**

The current goal is the elimination of rubella and prevention of congenital rubella (CRS) by 2015. This goal is an extension of the goal endorsed in 2005; however, the goal was not met by the original deadline of 2010.

The strategies recommended to achieve both measles and rubella elimination goals include: 1) ensure high coverage (≥95%) with 2 doses of measles vaccine and 1 dose of RCV; 2) strengthen measles-rubella and CRS surveillance; 3) provide rubella vaccination opportunities to all susceptible children, adolescents and WCBA and 4) enhanced communication and education about the benefits and risks of immunization. For example, European Immunization Week (EIW) provides an opportunity for countries to target communication to boost awareness and increase the uptake of immunization services. Country participation in EIW has increased from 6 countries in 2005 to 47 countries in 2010.

By end of 2009 in the EUR, all 53 member states had introduced 2 doses of measles- and rubella-containing vaccine (MMR in 52 and MR in 1). Of the 53 member states, 32 have reported a coverage of >95% with first dose and 22
reported a coverage of >95% with second dose. Since 2000, 22 measles and rubella SIAs have been conducted with over 57 million persons vaccinated. The age groups targeted included: 11 countries conducted speed-up campaigns targeting adolescent and adult males and females; 4 countries conducted catch-up campaigns targeting children aged less than 15 years and 9 countries conducted campaigns targeting WCBA and adolescent females.

With the completion of these mass campaigns, the number of cases of rubella has decreased by 97% from 800,000 reported in 1999 to approximately 24,000 reported cases in 2008. Even with decline in cases, rubella outbreaks continue to occur. From 2007-2010, outbreaks were reported from Austria, Bosnia and Herzegovina, Italy, Kyrgyzstan, Malta, Russian Federation and Ukraine.

In 2008, a survey of rubella and CRS surveillance activities was conducted by EUVAC.NET and WHO. The results of this survey document that 80% of countries conduct national rubella surveillance activities. However, only 60% of countries conduct the recommended case based surveillance. In addition, 4 large, economically developed countries do not have a national rubella surveillance system. The majority of countries reported having a nationwide CRS surveillance system. However, 6 (13%) countries reported having no CRS surveillance system. To strengthen MR and CRS surveillance updated surveillance guidelines were published in 2009.

Lessons learned from implementing rubella elimination strategies include:
1) Integrating measles and rubella surveillance is the most efficient way to manage resources and build upon the laboratory network on the pre-existing polio network.
2) Conducting successful SIAs targeting wide age ranges rapidly decreases rubella incidence enabling achievement of the elimination goal.
3) Immunization Registries provide useful information on vaccination status of cases.
4) European Immunization Week strengthens the political commitment and mobilizes communities towards the goal.

The main challenges for EUR include: underreporting, lack of immunization of Health Care Workers, sustaining high level commitment, and adequate required resources in the face of health system reforms that have led to weakened public health systems. Strategies are needed to reach unimmunized population such as migrants, Roma, persons with religious or philosophical objections.

During the discussion, three main topics were highlighted. First, how elimination will be achieved with the occurrence of measles and rubella outbreaks among high
risk unimmunized populations (e.g., Roma, philosophical/religious objectors). Second, the weak state of the rubella and CRS surveillance in many countries and third the role of seroprevalence surveys in determining age-specific susceptibility and the need for standardized methods such as those used in the European Sero-Epidemiology Network. It was noted that seroprevalence studies are methodologically challenging (need a statistically valid sample and accurate reproducible laboratory methods) and should not replace necessary improvements in coverage and surveillance data.

**Status of Rubella Control in the Western Pacific Region**

In the Western Pacific Region (WPR), from 1993 to 2003, less than 8,000 rubella cases (range: 965 to 7,854 cases per annum) were reported annually in the WPR. Beginning in 2004, China initiated reporting of rubella cases, and from 2004 to 2009, the number of reported rubella cases in the WPR has increased from 27,124 to 73,655, with a peak of 127,305 in 2008. RCV is used in 30 (83%) of the 36 member states. Of these 30, 23 (77%) use MMR and the other 7 use MR. Rubella incidence in the WPR is highest in the countries that have not introduced RCV or just recently introduced RCV. In 2009, most of the countries (21) in the WPR have an incidence <1 rubella case per 1,000,000 population; however, 4 countries (China, Cambodia, Singapore, Macau (China)) had an incidence ≥ 20 per 1,000,000 population. From 2007-2009, of the 286,196 reported cases, 4,351 (1.5%) included age and sex data. Among the latter, 83% occurred among persons aged <20 years.

In 2003, the WHO Regional Committee of the Western Pacific Region passed a resolution on measles elimination and hepatitis B control that urged member states to “use measles elimination and hepatitis B control strategies to strengthen EPI and other public health programmes, such as prevention of congenital rubella syndrome.” In 2009, a regional goal to achieve and maintain control of rubella and prevention of CRS was established. Rubella control is defined operationally as rubella incidence < 10 per million population, excluding imported cases and CRS prevention is defined operationally as a CRS incidence < 10 per million live births, excluding imported cases.

The epidemiology of rubella varies according to the duration of rubella vaccine use, strategies employed, and coverage achieved in national immunization programmes. Depending on the history of their vaccination programs, countries in the WPR were divided into 3 groups: 21 countries with long standing programs resulting in protection of all age cohorts including females ≥ 20 years; 4 countries using RCV > 10 years, protecting female and males up to 15 years but < 20 years, and 11 countries who recently introduced, or have yet to introduce, RCV.
Strategies for rubella surveillance included: enhancing or integrating with measles surveillance and encouraging the use of measles surveillance indicators. For CRS surveillance, countries were encouraged to establish sentinel surveillance.

The measles elimination goal has provided opportunities for accelerating rubella control and CRS prevention through integrated approaches using combined vaccines/strategies and measles case-based surveillance systems. However, the challenges for rubella/CRS goal include lack of CRS burden information in the many of the developing countries in the region; lack of motivation to embrace another goal; insufficient domestic production capacity (China, Vietnam) and missed opportunities to incorporate RCV in SIAs.

Discussion focused on production of vaccines in both China and Vietnam. Currently both countries manufacture their own vaccine. In China, the BRD-II strain is used; whereas, globally the RA 27/3 strain is used. As of 2011, China will have enough rubella for the entire birth cohort. Vietnam produces only measles single antigen vaccine, but plans to produce rubella-containing vaccine in the future. After review of some country data, discussion focused on the need to correlate surveillance data with the history of the vaccination program and the coverage achieved.

**Status of Rubella control in the Eastern Mediterranean Region**

For EMR countries that have introduced, or are planning to introduce RCV, the goal is to reduce the incidence of CRS to <1 CRS case per 100,000 live births. The recommended strategies include: MCV1 coverage > 80% for 3 years before introduction of RCV; administration of RCV together with MCV1; and ensuring rubella immunity in WCBA.

In 1995, the Gulf countries agreed to implement a rubella vaccination strategy that included adopting standardized case definitions for measles, rubella and CRS; achieving and maintaining high routine coverage; vaccination of susceptible (unvaccinated) postpartum women and establishing a laboratory network.

As of 2010, 16 of the 23 EMR countries have introduced RCV into their routine childhood program with 14 countries providing 2 doses of MR/MMR. One country (Tunisia) provides a single dose to school girls. Between 1994 and 2009, 154 SIAs were conducted of which 57 (37%) in 16 countries used RCV. In 2009, 18 countries had MCV1 coverage >80%.

During 2008-2010, reported rubella cases decreased from 1,783 to 614, with a majority of cases coming from 2 countries with relatively strong surveillance systems (Tunisia, Qatar). All countries have an integrated measles rubella surveillance. For suspected measles or rubella cases, some countries test...
simultaneously for both measles and rubella. CRS surveillance is established in 9 countries; however, these countries do not report CRS cases to the Regional Office of WHO.

Several challenges in implementing regional rubella control goals include inaccessible populations in conflict-affected countries; polio in Afghanistan and Pakistan, and rubella occurring in non-residents in several countries. However, there are several opportunities including integration of measles and rubella surveillance, integration of the goals, use of combined vaccine during follow-up campaigns and strengthening the regional laboratory network.

Discussion focused on the region’s plan to move forward with rubella control goals including integrating the rubella goal with measles elimination. In EMR, there are 6 GAVI eligible countries. Should countries with a 2 dose schedule and MCV1 coverage less than 80% introduce RCV into their program? Also, discussed was the role of the private sector in providing RCV.

**Status of Rubella Control in the Southeast Asian Region**

Of the 11 countries in the Southeast Asia (SEAR) region, 4 (Bhutan, Maldives, Sri Lanka, Thailand) have introduced RCV into their routine EPI. At the 2008 SEAR Immunization TAG meeting, recommendations for countries that have not introduced RCV included: 1) strengthen/establish rubella and CRS surveillance, and 2) review burden of rubella and CRS, build political and financial commitment to introduce RCV using the WHO guidelines.

Of the 4 countries that have introduced RCV, the impetus for introducing RCV was an outbreak. Of the 4 countries that have introduced RCV, 2 (Bhutan, Maldives) conducted wide-age range mass campaigns targeting in both males and females with additional age groups for adult females. The other two countries (Sri Lanka, Thailand) initially targeted females followed by introduction in the routine childhood program and a catch-up campaign (in Sri Lanka). Three of the 4 countries that have introduced RCV do not have CRS surveillance established. Of the remaining 7 countries, Nepal has plans to introduce RCV and the Democratic Peoples Republic of Korea, Bangladesh, Myanmar, and Indonesia have MCV1 coverage over 80% but have not yet introduced RCV.

All countries have identified rubella through the measles case-based surveillance system. For the countries that have not introduced RCV, most of the cases occur among children less than 15 years of age. Since 2007, in Bangladesh with excellent measles control, almost all of the outbreaks are caused by rubella.

Discussion focused around the factors (e.g., susceptibility in WCBA, private sector use) that would influence a country to introduce RCV into the national routine
childhood program. Dr. Bose noted that in India that there is private sector use in many urban areas and this could shift rubella susceptibility to the older age groups as described in the paradoxical effect. As for susceptibility in WCBA, there is no absolute cut-off for susceptibility that would lead to the introduction of RCV; there are other factors including risk of exposure that need to be considered.

**Status of Rubella control in the African Region**

Currently, two countries (Seychelles, Mauritius) in the African Region use RCV in their routine program and Cape Verde is planning to introduce RCV by end 2010. There is no regional goal for rubella control or CRS elimination. The 2008 AFR TAG recommended that countries considering introduction of RCV should be committed to a goal of rubella control and CRS prevention; ensure high levels of coverage with RCV (MCV1>80%) through routine services and have sufficient resources to use combined MR vaccine in subsequent measles SIAs.

Since the 1980s, the number of measles cases has decreased and the regional MCV1 coverage has increased to 73% in 2009. In 2008, using WHO-UNICEF coverage estimates, 20 of the 46 MS had MCV1 coverage >80%. However, in 2008, it was estimated that 7.6 million infants missed their first dose of measles vaccine. In 2009, of the countries with MCV1 coverage >80% for three years, several had large measles outbreaks occurring in 2009-2010 raising questions about the MCV1 coverage.

Rubella cases are being effectively identified through the measles case-based surveillance system. Between 2005-2009, there has been an increase in the number of measles IgM negative cases that have been tested for rubella IgM antibodies. Approximately 95% of the rubella IgM+ cases occur among children aged <15 years of age.

There are both challenges and opportunities that rubella control and CRS prevention provide for the AFR. The challenges include: lack of information on the use of RCV in the private sector; incomplete information on the burden of disease; weak infrastructure to maintain MCV1 coverage >80% and simultaneous introduction of new vaccines (rotavirus, pneumococcal) in several countries. The opportunities include: identification of rubella cases through the existing measles case-based surveillance system, increasing routine immunization coverage in a number of countries and the experience of conducting wide age range measles SIAs.

To assist in the documentation of the burden of CRS and rubella seroprevalence, the Bill and Melinda Gates Foundation has provided support for several selected countries to establish CRS surveillance and conduct rubella seroprevalence studies.
Discussion focused on the other competing priorities such as AIDS, TB and malaria in addition to the introduction of new vaccines against pneumonia and diarrhea that have a higher burden of disease than rubella and CRS. Discussion also focused on what is the minimum amount of data required to influence policy. It was noted by participants that the data requirements may vary from country to country and by region.

**Strategies used by Countries and the impact on rubella and CRS**

Background information for strategies used and examples of country experiences that have used different vaccination strategies was discussed. The goal of any rubella vaccination program is the prevention of congenital rubella infection which includes CRS.

With the introduction of RCVs in 1969 in the United States and 1970s and 1980s in other developed countries, two basic approaches were implemented: CRS prevention only by vaccination of adolescent and adult susceptible females only and 2) rubella and CRS elimination by providing universal vaccination to both males and females through the routine childhood program. After several years of experience, it was decided that a combination of these two strategies works the best.

One of the major concerns about introduction of RCV into their routine childhood program is that if high vaccine coverage in the routine childhood program is not achieved and maintained, the risk of CRS may increase due to a shift in rubella susceptibility to the older age groups including WCBA. In the 2000 WHO rubella vaccine position paper, it is recommended that countries achieve an immunization coverage of >80% before introducing RCV into the routine childhood program. One cited country example for the paradoxical effect is Greece. In 1975, RCV was introduced in the private sector only which was responsible for vaccinating approximately 50% of the children. Not until 1989 was RCV introduced into the national routine childhood program. Between 1975 and 1989, the vaccination coverage was not monitored; however, the estimated coverage was <50%. Between 1971 and 1991, several seroprevalence studies among women of childbearing age were conducted. Prior to introduction of RCV in 1975, the seropositivity was 88%; however, in 1984-1989, the seropositivity dropped to 76% and then by 1990-1991, the seropositivity was 64%. In 1993, a rubella outbreak occurred with 64% of the cases reported among persons >15 years of age. Following the outbreak, 25 laboratory confirmed CRS cases were confirmed. Review of previous outbreaks in Greece noted that there was no increase in CRS cases.
Seven different countries/subregions examples were presented representing different vaccination strategies used for rubella control and CRS prevention goals. In England/Wales and Singapore that initially introduced RCV through vaccination of adolescent and susceptible adult females only, impact on CRS was not immediate and to eliminate rubella/CRS, introduction of RCV through the routine childhood program with and without SIAs was essential. Approximately 70% of the countries/territories in the Caribbean initially introduced RCV through a selective program offering vaccine to females only. The United States introduced RCV through the routine program; whereas, Albania and Brazil conducted catch-up SIAs in addition introduction into the routine childhood program. The table below summarizes the result of the vaccination strategies used and the time to impact on CRS and time to elimination of rubella and CRS.

### Strategies used by countries and time to impact on CRS and Elimination

<table>
<thead>
<tr>
<th>Country</th>
<th>Strategy</th>
<th>Time to Impact on CRS*</th>
<th>Time to Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Universal (2dose) + adul/adult</td>
<td>10-11 yrs</td>
<td>31 years</td>
</tr>
<tr>
<td>England/Wales</td>
<td>Selective +Univ (2dose) + SIA</td>
<td>15-16 yrs</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Selective, Univ (2 dose)</td>
<td>5 yrs (selective vax)</td>
<td>15 yrs after univ</td>
</tr>
<tr>
<td>Caribbean</td>
<td>Selective, Univ, SIAs</td>
<td>CRS surveillance</td>
<td>10 yrs after catch-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>established later</td>
<td>conducted</td>
</tr>
<tr>
<td>Albania</td>
<td>Univ, SIAs (catch-up, F/U), WCBR</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Brazil</td>
<td>Univ. catch-up, WCBA, m/f adult SIA</td>
<td>CRS surveillance</td>
<td>15-20 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>established later</td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td>Selective, Univ (2dose) + SIA</td>
<td>16 yrs (probably sooner)</td>
<td></td>
</tr>
</tbody>
</table>

*≥50% reduction from pre-vaccine era

---

1 Sweden had a similar experience requiring universal vaccination to achieve elimination.
Proposed Goals and Strategies

A “Strawman” Proposal for Updated Vaccination Strategies

Proposed vaccination goals and strategies were discussed. Experiences from regions and countries have capitalized on the use of combined measles-rubella-containing vaccine and incorporating RCV into the measles vaccination strategies. MCV delivery strategies vary depending on the strength of the infrastructure of the routine childhood program. Countries with stronger health care infrastructure have higher MCV1 coverage and usually both doses of MCV are given through the routine program. In countries using two doses routine only; all 40 countries have introduced RCV; among countries with a 2 dose routine program that have conducted one SIA, 33 of 35 (92%) have introduced RCV; among countries with a 2 dose routine program that conduct regular SIAs, 47 of 58 (82%) have introduced RCV; and among countries that have a 1 dose routine program and conduct regular SIAs, only 9 of 59 (15%) have introduced RCV.

Of the 4 regions with measles elimination goals, 2 (AMR, EUR) have rubella elimination goals and the other two (WPR and 16 countries in EMR) have accelerated rubella control and CRS prevention goals. For the two WHO regions with rubella elimination goals, each region started with rubella control or CRS prevention goal prior to establishing the rubella elimination goal. For AMR, in 1997, the TAG recommended to implement a rubella control and CRS prevention initiative, in 1999, an accelerated rubella control and CRS prevention goal was established, followed by in 2003, rubella and CRS elimination. In EUR, the initial goal established in 1998 was reduction of incidence of CRS by 2010 and in 2005, the goal was changed to rubella elimination and prevention of CRI by 2010.

The options for regional or country rubella and CRS control goals are

- CRS prevention without rubella control
- Rubella control and CRS prevention
- Accelerated rubella control and CRS prevention
- Rubella and CRS elimination

These proposed goals represent a continuum of different levels/phases of rubella control and CRS prevention. The figure below highlights the proposed goals with the vaccination strategies. With the rubella control goals, each vaccination strategy when implemented well will ultimately result in elimination of rubella and CRS, but over different time frames. Rubella and CRS will be eliminated in 20-30 years using
the rubella control and CRS prevention goal strategies; within 10-20 years using accelerated rubella control and CRS strategies and within 1-10 years using the rubella and CRS elimination strategies.

In determining the most appropriate goal/strategy for countries and regions, several issues should be assessed including: disease burden of rubella and CRS; cost-effectiveness of proposed strategies; establishing rubella/CRS prevention as a health priority and identifying sustainable financing. Each goal established should have a time frame in which this goal should be achieved. For countries planning to establish a rubella control or elimination goal, the preference is to administer RCV with the MCV1 dose in the routine childhood program instead of with the MCV2 dose due to the higher coverage that is usually achieved with the MCV1 dose. Based on country experience and the available information on the seroconversion, duration of immunity and vaccine effectiveness of 1 dose of RCV, only one dose of RCV is necessary. However, when combined with the measles vaccination strategy, it may be programmatically easier to provide a 2nd dose of RCV using the same combined measles-rubella vaccine for both doses. This strategy also provides an opportunity for those few vaccinees who were not protected following the first RCV dose to seroconvert.

As part of goal and vaccination strategy, countries and regions should establish or strengthen rubella and CRS surveillance system. In all stages of rubella control including countries that have not introduced RCV, rubella surveillance should be integrated with the measles case-based surveillance system and all febrile rashes in
pregnant women should be investigated. CRS surveillance should be established. As rubella control progresses towards elimination, the sensitivity and specificity of the surveillance systems should increase.

Discussion focused on the need to integrate the rubella and CRS prevention strategies with the measles goals and vaccination strategies. However, there may be additional strategies needed to ensure that the rubella/CRS goals are achieved. Questions were posed regarding the type of data necessary for monitoring impact and the costs of each of the goals/strategies. For the CRS prevention only goal, communication and establishing partnerships was an effective way to successfully target adolescent and adult females.

It was felt that countries should also be given the option not to introduce RCV, so it was recommended that the diagram be modified to include this phase of rubella control. In addition, a summary table should be prepared that includes immunization and surveillance strategies according to the programme goal (see below).

<table>
<thead>
<tr>
<th>Goal</th>
<th>Vaccination Strategy</th>
<th>Surveillance Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No introduction</td>
<td>Not applicable</td>
<td>• Detection of rubella cases through measles case-based surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• During outbreaks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Investigation of all rash illness (suspected rubella) in pregnant women including laboratory testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Conduct laboratory testing of at least first 5-10 rash illnesses per month to confirm rubella as cause of outbreaks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Investigate outbreaks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Conduct active CRS surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Collection of specimens for molecular epidemiology (may want to include earlier)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sentinel case-based CRS surveillance in infants 0-11 months</td>
</tr>
<tr>
<td>CRS prevention only</td>
<td>• Target adolescent girls and/or women of childbearing age for immunization either through routine services or mass campaigns</td>
<td>• Including strategies above and <em>Rubella vaccination coverage monitoring</em></td>
</tr>
</tbody>
</table>

*Rubella vaccination coverage monitoring*
<table>
<thead>
<tr>
<th>Rubella control and CRS Prevention</th>
<th>• Including strategy above and • <strong>Introduction of RCV into the routine childhood program</strong> – preferable to be introduced combined with both MCV1 and MCV2. • <strong>“Follow-up” MR or MMR campaigns targeting preschool-aged children (aged 1 to 4 years)</strong>†</th>
<th>• Including strategies above and • <strong>Detection of rubella cases through measles case-based surveillance</strong> – transition to integrated measles-rubella case-based surveillance • <strong>Enhance investigation of outbreaks with laboratory testing of suspected cases</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated Rubella Control and CRS Prevention</td>
<td>• Including strategies above and • <strong>“Catch-up” MR or MMR campaigns targeting children aged less than 15 years.</strong></td>
<td>• Including strategies above and • <strong>Enhancing integrated measles-rubella case-based surveillance</strong> – start to investigate every suspected case</td>
</tr>
<tr>
<td>Rubella/CRS Elimination</td>
<td>• Including strategies above and • <strong>“Speed-up” campaigns targeting adolescents and adults, men and women.</strong></td>
<td>• Including strategies above and • <strong>Strengthening integrated measles-rubella or febrile rash illness surveillance</strong> – testing and investigating all suspected cases • <strong>Seroprevalence studies in WCBA?, as appropriate</strong></td>
</tr>
</tbody>
</table>

*The red italicized text indicates new activities/strategies in comparison to the previous strategy

†Follow measles guidelines for continuing or discontinuing follow-up campaigns

**Levels of Coverage needed for rubella vaccination**

**Minimum levels of rubella vaccination coverage needed to ensure a reduction in CRS**

Preliminary results from a mathematical model to assess the minimum immunization coverage required to ensure that the introduction of rubella-containing vaccine does not increase the risk of CRS was presented. The current strategies used for measles mortality reduction and elimination provide a unique opportunity to introduce RCV into the routine childhood schedule and SIAs. Previously, different modelling approaches have theoretically shown that if high routine childhood vaccination coverage is not achieved and maintained, this could result in an increase in the average age of infection and potentially increase the
burden of CRS. In the 2000 WHO rubella vaccine PP, countries are recommended to achieve and maintain childhood vaccination coverage of >80% as a requirement for introduction of RCV.

Various combinations of rubella vaccination through routine services and SIAs proposed in the “Strawman” modelled using different routine coverage levels (50, 80, 90%) and different parameters such as birth and transmission rates to compare the short- and long-term effects of the different vaccination combinations were presented. Birth rates vary; however, most countries in the world have birth rates <40 births per 1,000 persons with exception of several countries mainly in AFR (14 of the 46 countries). Magnitude of transmission was captured via the basic reproduction number, R0, i.e. the number of secondary infectious cases that would be caused by a single infectious individual in a completely susceptible population. R0 for rubella varies by region and countries; however, previous published values for R0 include: 2.4-7.8 (Europe), Mexico (3.1-10.8) and Addis Ababa, Ethiopia (6.9-11.8). Based on these ranges, R0 values of 6, 8 and 12 were used.

Discussion focused on considering the birth rates as an important factor in determining when to introduce rubella vaccine and the minimum coverage required. With higher birth rates, rubella infection occurs in younger individuals resulting in relatively higher immunity among women of childbearing age; the reverse is true for low birth rates (for example in Europe and China) where introduction of rubella vaccination is imperative to reduce the risk of rubella infections during pregnancy. Declining birth rates may be a factor of relevance in considering introduction of rubella vaccine.

Even though R0 may be important in modeling risk of CRS, it is dependent on the population interaction (i.e., contact rates) and may vary within or between countries. Unlike birth rates, R0 is an estimated parameter that requires specific data that may be hard to obtain for specific countries and hence is less useful for determining immunization policy. New graphs (Annex 1) were generated that reflected routine coverage and birth rate on the axes. In each square is the number is the critical R0 above which a population with the given birth rate and coverage characteristics will experience an increase in the burden of CRS over 30 years. There are 4 graph: one graph with routine childhood vaccination only and 3 of the 4 graphs include the impact of follow-up campaigns (targeting preschool-aged children (aged 1 to 4 years)) at different coverage levels (60%, 80%, 90%). Colors range from green, indicating a high confidence of a reduction in CRS burdens (less than a 5% chance R0 is above the stated value), to red, indicating a high confidence of an increase in CRS cases (at least a 95% chance R0 is above the stated value). The graphs highlight the impact of SIAs even at 60%. Even at the
highest birth rate (50 per 1000 population), countries would be able to introduce RCV with a sustained routine immunization coverage of 80% (MCV1) or greater. Countries with routine coverage <80% may also safely introduce RV if they conduct regular SIAs achieving immunization coverage of 80% or greater. In making any recommendation for rubella control/elimination, RCV will be combined with the measles vaccine which requires a higher coverage than any of the estimates projected for rubella vaccine. Thus, aiming for the measles vaccine coverage requirement would provide a “safety” net for rubella vaccine.

Other variables that may affect the burden of CRS are social and spatial factors. Critical community size is the population size above which rubella will persist (in the absence of vaccination) because the number of new births is sufficient to sustain transmission in the community. The smaller the community the greater the likelihood that transmission will "fade out" periodically and persons will make it to adulthood still susceptible. If one country/community is vaccinating and the neighbouring country/community is not, depending on the vaccination coverage achieved and migration pattern, the country that is vaccinating may be at risk for increase burden of CRS. This situation is relevant to public versus private vaccination in countries, and highlights the importance of considering regional or social variability in vaccination coverage in assessing whether immunization systems are strong enough to support the introduction of the rubella vaccine: national levels of coverage attained should not be the only feature considered.

With the experiences of AMR and EUR, it was felt that the rubella strategy needs to be integrated with the measles strategy. With the measles goals, a higher coverage is necessary which exceeds the coverage required for rubella vaccination even at the highest R0 and birth rate. Again, given the potential for build-up of pockets of older susceptible individuals, regional or social variation in vaccine coverage should be especially considered for rubella.

Rubella vaccination coverage needed to interrupt transmission

Various rubella transmission models have been developed to assess the level of coverage needed to eliminate/eradicate rubella. For two of the models (Anderson/Grenfell for the UK- 1986, Gay-1998), a vaccine coverage of 80-84% and >85%, respectively are needed to eliminate rubella/CRS. Models based on the epidemiological profile of disease in the United States in the pre-vaccine era suggest that population immunity must be >87.5% to interrupt rubella virus transmission. In a national serosurvey conducted between 1999-2004, the overall seropositivity was 91.3%. In 2004, an independent panel of internationally recognized experts in public health, infectious diseases, and immunizations reviewed the available data and unanimously agreed that rubella is no longer endemic in the United States. Country experience and mathematical modeling
indicate that >75-88% population immunity is required to stop transmission of rubella virus thereby eliminating cases of CRS due to endemic virus transmission. Assuming rubella vaccine effectiveness of 95%, this translates to an immunization coverage of 80-93%.

**Rubella control and Elimination: Surveillance Needs and Challenges**

The primary purpose of a rubella surveillance system is to detect in a timely manner, all areas where the rubella virus is circulating, to implement outbreak control and CRS prevention measures. In the 2000 PP, several recommendations were made for rubella and CRS surveillance. Rubella surveillance should be integrated with measles and dengue surveillance. CRS surveillance should include hospital record review, deaf/blind surveys, clinician reporting, and active searches for CRS cases after outbreaks of acquired rubella. Surveillance of therapeutic abortion registries should be examined. If possible, longitudinal sero-surveys in antenatal clinics should be conducted.

For all surveillance systems, there are general requirements such as standardized case definitions; guidelines; trained personnel; collaboration between epidemiologists, laboratory workers and health care workers; availability of an accredited laboratory; standardized case investigation forms and standardized reporting system. In addition to these requirements, rubella and CRS surveillance have additional requirements. Rubella surveillance should be integrated with measles case-based surveillance system. For rubella surveillance, all febrile rashes in pregnant women need to be investigated. As a part of the rubella and CRS surveillance, specimens for virus detection, isolation and genotyping should be collected and analyzed. CRS surveillance system requires the collaboration of multiple sites and medical specialties (e.g., cardiology, ENT, ophthalmology). Programmatic and performance indicators should be developed and monitored for both surveillance systems.

Some of the challenges for the surveillance systems include: obtaining adequate and timely clinical specimens for testing, availability of an accredited laboratory, reporting from the private sector, and follow-up of infected pregnant women.

Because of the different goals, the surveillance systems should match the country goal and strategies. There are surveillance requirements for all levels of rubella control. These include: case-based CRS surveillance, outbreak investigations, investigation of all febrile rash illnesses in pregnant women and coordination between field surveillance and the laboratory. As rubella control progresses, additional requirements include integration of rubella surveillance into the measles case-based surveillance system.
First meeting of the GPEI Independent Monitoring Board

The new Independent Monitoring Board (IMB) convened its inaugural orientation meeting on 21–22 December 2010 in Geneva, Switzerland. The IMB was established at the request of the Executive Board of WHO and the World Health Assembly in 2010, to monitor the implementation and impact of the new Global Polio Eradication Initiative (GPEI) Strategic Plan 2010–2012, against the major milestones and process indicators established for that purpose, and advise countries and partner agencies on corrective actions as appropriate.

The focus of the IMB's deliberations at this first orientation meeting was threefold: (i) establishing the IMB's method of work; (ii) assessing the status (as at December 2010) of the GPEI Strategic Plan 2010–2012 milestones and process indicators; (iii) discussing the emergency action plans of Pakistan, Angola and the Democratic Republic of the Congo with the Minister of Health and senior health authorities from each country. This report summarizes the work of the IMB in each of these areas.

1. IMB working methods:

The IMB decided that it will meet on a quarterly basis, usually at WHO headquarters in Geneva, with a minimum of 6 of the group's 9 members constituting a quorum. Meetings will follow a flexible format, depending on programme priorities, the evolving epidemiology of poliovirus, and issues of concern to the IMB. Recognizing the need to share rapidly its findings with key stakeholders, the IMB will endeavor to summarize its initial perspectives with interested parties through a telephone-conference at the end of each meeting. Final meeting reports will be presented within 14 days of each meeting to the heads of agencies of the GPEI spearheading partner agencies, WHO, Rotary International, the US Centers for Disease Control and Prevention and UNICEF, and to the Bill & Melinda Gates Foundation. The reports will also be provided to Ministers of Health of affected countries, funding agencies and other interested parties, made available at http://www.polioeradication.org, and published in the Weekly Epidemiological Record. The final method of work of the IMB will be published at http://www.polioeradication.org.

2. Status of GPEI Strategic Plan 2010–2012 milestones and process indicators:

Progress against each of the major milestones of the GPEI Strategic Plan 2010–2012 at 21 December 2010 was as follows:

i. Countries with polio outbreaks due to an imported poliovirus: of the 15 countries which experienced an outbreak due to a new importation in 2009, none had detected polio cases due to that importation since mid-2010. In the 11 countries in which there had been new outbreaks in 2010, no outbreak had persisted for longer than 6 months; however, efforts were still ongoing to address the recent-onset outbreaks in the Republic of Congo, on the Uganda/Kenya border, in the Russian Federation, and in Chad, which was affected by a new importation of wild poliovirus type 1 in September 2010.
ii. Countries with re-established poliovirus transmission: the re-established wild poliovirus type 1 in southern Sudan had not been detected since 27 June 2009 and the re-established wild poliovirus type 3 in Chad had not been detected since 10 May 2010.\footnote{Since the December 2010 meeting of the IMB, a new case due to a wild poliovirus type 3 has been detected in Chad (with onset of paralysis on 23 December 2010), and is under investigation. If genetic sequencing of this virus demonstrates it is due to ongoing transmission of the re-established virus, the IMB may determine that the country be considered ‘off track’ for achieving its end-2010 milestone.} Angola and the Democratic Republic of the Congo were at risk of becoming “off track” due to ongoing transmission of the re-establishment of wild poliovirus during the 4th quarter of 2010.

iii. Countries with indigenous polioviruses: overall, in the 4 remaining endemic countries, cases had declined by 82% in 2010 compared to the same period in 2009 (as of February 2011). In Nigeria, cases had declined by 95%, in India by 95% and in Afghanistan by 35%. Pakistan was at risk of becoming “off track” because of a 61% increase in the number of polio cases.

The IMB will next review progress against each of the milestones at its next meeting on 31 March 2011.

3. Angola, the Democratic Republic of the Congo, and Pakistan:

Recognizing the risks to the relevant Strategic Plan milestones in Angola, the Democratic Republic of the Congo and Pakistan, the IMB invited the Ministers of Health of these countries to participate in this first orientation meeting of the IMB. In keeping with the goals of the GPEI Strategic Plan 2010–2012, all 3 countries had initiated the establishment of a new or updated emergency plan to address urgently the gaps in programme implementation. The IMB was presented with the main elements of these plans by the Ministers of Health of Angola and the Democratic Republic of the Congo, and the Director-General for Health of Pakistan. The IMB encouraged the rapid finalization and introduction of the emergency plan in each country and welcomed their close oversight by the respective Head of State to facilitate successful implementation.

The IMB requested a summary report on progress against each of these plans at its March 2011 meeting and at subsequent meetings until such time as these countries' polio eradication efforts are deemed to be back on track.
Progress reports

Report by the Secretariat

CONTENTS

C. Eradication of poliomyelitis (resolution WHA61.1) ................................................................. 2

D. Prevention and control of influenza pandemics and annual epidemics (resolution WHA56.19) ........................................................................................................ 3

E. Onchocerciasis control through ivermectin distribution (resolution WHA47.32) ............... 5

F. Climate change and health (resolutions WHA61.19 and EB124.R5) .................................... 7

G. Improvement of health through sound management of obsolete pesticides and other obsolete chemicals (resolution WHA63.26) ......................................................... 9

H. Improvement of health through safe and environmentally sound waste management (resolution WHA63.25) ........................................................................ 10

I. Working towards universal coverage of maternal, newborn and child health interventions (resolution WHA58.31) ................................................................. 12

J. Female genital mutilation (resolution WHA61.16) ............................................................... 14

K. Strategy for integrating gender analysis and actions into the work of WHO (resolution WHA60.25) ............................................................................................. 15

L. Progress in the rational use of medicines (resolution WHA60.16) ...................................... 17

M. Implementation by WHO of the recommendations of the Global Task Team on improving AIDS coordination among multilateral institutions and international donors (resolution WHA59.12) ................................................................. 19

1 See documents EB128/35 for reports A and B, and EB128/2011/REC/2, summary record of the eleventh meeting.
C. \textbf{ERADICATION OF POLIOMYELITIS (resolution WHA61.1)}

1. In 2008, the World Health Assembly in resolution WHA61.1 requested the Director-General to develop a new strategy to renew the fight to eradicate poliomyelitis from the remaining affected countries. In order to lay the basis for the new strategy, a special, one-year Programme of Work 2009 of the Global Polio Eradication Initiative was undertaken. It included evaluating tactical innovations, conducting clinical trials of new vaccine formulations (e.g. bivalent oral poliovirus vaccine) and facilitating an independent examination of the major barriers to interrupting poliovirus transmission. The Sixty-third World Health Assembly noted the progress made and concurred with the framework for a new strategic plan for 2010–2012, which was subsequently finalized and launched in June 2010.

2. The Executive Board, at its 128th session, considering a previous version of this report, noted the impact of the new Strategic Plan 2010-2012, in particular the strong progress achieved in India and Nigeria, and expressed concern at the ongoing transmission of some re-established polioviruses, the continued international spread of wild poliovirus, and, in particular, the Global Polio Eradication Initiative's gap in financing which threatened to undermine recent progress. In addition, the Board welcomed the establishment of the Independent Monitoring Board, which held its inaugural meeting on 21-22 December 2010 and will meet quarterly to monitor the implementation and impact of the new Strategic Plan 2010-2012 against the major milestones and process indicators established for that purpose, and advise countries and partner agencies on corrective actions as appropriate. The Board noted that the Independent Monitoring Board created a new dynamic for poliomyelitis eradication and called on Member States to commit additional resources to ensure the full implementation of the Strategic Plan 2010-2012.

3. As at 1 March 2011, status of the three major milestones of the Strategic Plan 2010-2012 was as follows:

   i. Countries with new outbreaks of poliomyelitis due to an imported poliovirus: since mid-2010, no cases of poliomyelitis had been detected due to the original importation in any of the 15 countries that had reported new outbreaks in 2009. In the 11 countries in which there had been new outbreaks in 2010, no outbreak had persisted for longer than six months.

   ii. Countries with “re-established poliovirus transmission”: the re-established wild poliovirus type 1 in southern Sudan had not been detected since 27 June 2009. Countries which were considered to have ongoing transmission of their re-established poliovirus were: Chad (most recent case: 23 December 2010); the Democratic Republic of the Congo (27 December 2010); and, Angola (7 January 2011).

   iii. Countries with endemic transmission of poliovirus: overall, in the four remaining countries with endemic poliovirus transmission, cases of poliomyelitis had declined by 82% in 2010 compared to the same period in 2009 (232 cases in 2010 compared with 1256 cases in 2009, with endemic poliovirus transmission).
as at 1 March 2011). In Nigeria, cases had declined by 95% (21 cases compared with 388 cases), in India by 95% (42 cases compared with 740 cases) and in Afghanistan by 35% (25 cases compared with 38 cases). In Pakistan, cases had increased by 61% (144 cases in 2010 compared with 89 cases in 2009).

4. Although progress towards the first and third milestones of the Strategic Plan was broadly on track, serious obstacles remain. In particular, attainment of the second, end-2010 milestone of stopping all “re-established poliovirus transmission” was missed in Angola and at high risk of being missed in Chad and the Democratic Republic of the Congo. In Angola, more than 25% of children had been missed during supplementary immunization activities in some areas of the country, contributing to the persistence of transmission of the re-established virus, the outbreak in 2010 and the cross-border spread into the Republic of Congo and the Democratic Republic of the Congo. In addition, in the Democratic Republic of the Congo, a virus strain that had not been detected since 2008 was isolated in the eastern province of Katanga in June 2010 through at least December, illustrating failures in the implementation of both surveillance and supplementary immunization activities in the area. Achievement of the third, end-2011 milestone of stopping poliovirus transmission in countries where the virus is endemic is at risk in Pakistan because of continued operational difficulties in optimizing the quality of supplementary immunization activities in the persistent reservoir areas of poliovirus in the country. These problems were further complicated by insecurity and conflict in the Federally Administered Tribal Areas and the severe floods affecting the country in mid-2010. Recognizing these risks, and in keeping with the provisions of the Strategic Plan 2010-2012, Angola, the Democratic Republic of the Congo and Pakistan established or updated their emergency plans to intensify eradication activities, under the authority of their respective heads of state. These plans were presented to the Independent Monitoring Board on 21-22 December 2010, with implementation beginning in January 2011. Chad was invited to present its emergency plan to the Independent Monitoring Board at its end-March 2011 meeting.

5. International spread of wild polioviruses continues to pose a substantial risk to achieving a polio-free world. All of the 11 new outbreaks in 2010 have been stopped within six months, or are on track to be stopped in such a time frame. However, the explosive nature of the outbreaks in the Congo and Tajikistan, both of which are associated with further international spread of wild poliovirus, clearly demonstrates this ongoing risk. As at March 2011, the highest priorities for stopping outbreaks associated with new, recent importations were: the Republic of Congo; Gabon; the border area between Uganda and Kenya; the Russian Federation; and, especially, Chad which was re-infected with a new importation of wild poliovirus type 1 in September 2010.

6. With the declining incidence of wild poliovirus globally, Member States are taking additional measures to reduce the risk of new outbreaks caused by the international spread of wild polioviruses or the emergence of circulating vaccine-derived polioviruses. These measures include supplementary and routine immunization activities to close gaps in population immunity and vaccination of travellers to and from poliomyelitis-affected areas. Similarly, ensuring timely vaccination responses to circulating vaccine-derived polioviruses has become increasingly important as progress is made towards eradication of wild poliovirus. In 2010, outbreaks due to circulating vaccine-derived polioviruses have occurred in Afghanistan, the Democratic Republic of the Congo, Ethiopia, India and Nigeria.

7. At the launch of the Strategic Plan 2010–2012, the results of a new study on the economics of the Global Polio Eradication Initiative were released. These indicated that the incremental net benefits

---

1 Data available at http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
of completing poliomyelitis eradication, aggregated over the period 1988–2035, would be at least US$ 42 000 million.\textsuperscript{1} However, shortfalls in the financing of the Global Polio Eradication Initiative continue to result in a scaling back of supplementary immunization and surveillance activities in some areas, delays in implementing outbreak response activities in others, and reductions in the long-term technical assistance provided by the Secretariat to some Member States. As at March 2011, 38% of the 2011–2012 budget of US$ 1860 million remained unfunded.

FACTS & FIGURES

• There have been 34 cases globally* in 2011 (all wild poliovirus type 1 – WPV1), compared with 34 cases at the same time in 2010 (7 type 1 and 27 type 3).

• To date there have been 975 cases reported globally* for 2010 (888 type 1 and 87 type 3), compared with 1606 cases at the end of 2009 (479 type 1 and 1,124 type 3, and 3 mixtures).

• The endemic states of Uttar Pradesh and Bihar in India have not reported cases in more than six months. The most recent case had onset of paralysis on 01 September.

HEADLINES

Gabon reports first case in 10 years: Gabon has reported its first case of polio in more than ten years, a WPV1 with date of onset 15 January 2011. This serves as a reminder that even polio-free countries are not safe from the virus until the disease is completely eradicated. Genetic sequencing is under way to determine the origin of the virus.

President of DRC expresses commitment to eradicating polio: At the invitation of President Laurent Kabila Kabange, the Director-General of the World Health Organization (WHO), Dr Margaret Chan, and the WHO Regional Director for Africa, Dr Luís Gomes Sambo, visited the Democratic Republic of the Congo in February. Dr Chan and Dr Sambo met President Kabila, who expressed his government’s firm commitment to ending the current polio outbreak; they also met with donors, partners and government officials to discuss emergency response plans.

Rotary celebrates 106th anniversary: On 23 February, Rotary International celebrated its 106th Anniversary. In celebration, the organization lit up around 20 of the world’s most recognizable landmarks with the slogan ‘End Polio Now’. The illuminated landmarks included the Trevi Fountain in Italy, the parliament building in the Hague, Netherlands and Charminar in India. More

Polio eradication mourns loss of Bill Sergeant: Former Vice-President of Rotary International, William ‘Bill’ Sergeant, passed away on 13 February. Mr Sergeant was chairman of Rotary’s International Polio Plus Committee of the Rotary Foundation from its inception in 1994 until 2006. The polio eradication champion’s dedication was honoured by the World Health Assembly in 2006. More

ENDEMIC COUNTRIES

AFGHANISTAN

• Afghanistan has reported one case in 2011, WPV1 in Kandahar with onset of paralysis 11 January.

• Activity plans for the next 12 months were finalized during the national planning meeting that was held on 13-14 February. Plans include a more systematic application of the Short Interval Additional Dose (SIAD) strategy and the monthly updating of district-level planning.

INDIA

• No new cases were reported in February. Therefore, the total number of cases for 2011 remains 1 (wild poliovirus type 1 (WPV1), Howra, West Bengal). However this one case continues to raise concerns, given that it is in a district next to the densely populated city of Kolkata, within a highly mobile population. A mop-up round was held on 05 February in the highest risk areas surrounding the case, vaccinating 1.8 million children under 5 years of age. While the mop-up was regarded as generally successful, a number of operational improvements need to be implemented including strengthening microplans; sensitizing independent monitoring; ramping up transit strategy; and, increasing social mobilization to further engage communities.

• Efforts have focused on increasing access to the 13 high-risk districts of the Southern Region - the only districts in the country which remain affected by indigenous transmission of the virus.

• National Immunization Days (NIDs) are planned for 13-15 March.

• The endemic states of Uttar Pradesh and Bihar have not reported a case in over six months. The most recent case was a wild poliovirus type 1 (WPV1) case with onset of paralysis on 01 September 2010 in Champaran East district, Bihar.

• A joint UNICEF/National Polio Surveillance Project (NPSP) assessment was undertaken in mid-February, examining public perceptions of polio immunization in order to better tailor social mobilization campaigns.

• NIDs took place from 27 February, using a combination of bivalent Oral Polio Vaccine (bOPV) and trivalent Oral Polio Vaccine (tOPV). Sub-national Immunization Days (SNIDs) are planned for March.

*The Government of Congo has nearly completed the process of classifying status of 523 AFP cases lacking adequate specimens, of which approximately 300 are expected to be confirmed as polio.
NIGERIA

- No cases have been reported so far for 2011. This significant progress, however, is undercut by the findings of independent monitoring in the highest risk districts which shows that the quality of Supplementary Immunization Activities (SIAs) (especially mop-ups) needs to be improved.
- Nationwide Immunization Plus Days were held on 23-26 February using tOPV and measles vaccine. Borno state, which had not been part of the Immunization Plus Days which took place in January due to health worker strikes, carried out immunization activities from 02 February. This was the first SIA to take place in Borno since strikes began in October 2010. Staggered SNIDs were also held in Gombe and Akwa Ibom from 12-15 February using a combination of tOPV and bOPV.
- The next Expert Review Committee on Polio Eradication and Routine Immunization (ERC) is scheduled for 7-8 March. The ERC will review the latest epidemiology, and recommend an appropriate SIA strategy, including approaches to address the ongoing high-risk areas.

PAKISTAN

- Pakistan has not been able to rein in transmission of polio, reporting a total of 11 cases for 2011 (all WPV1). The country continues to be affected by geographically wide-spread transmission of polio, as underscored by the isolation of polioviruses in environmental samples from sampling sites across the country.
- Reports from the SNIDs that took place from 31 January - 02 February indicate that serious operational gaps remain despite President Asif Ali Zardari’s release of the polio emergency action plan last month. While the plan has re-invigorated efforts at the federal level, sufficient accountability and ownership at the provincial and district-levels is crucial.
- NIDs using tOPV will be held on 7-9 March, followed by SNIDS in April.

RE-ESTABLISHED TRANSMISSION COUNTRIES

ANGOLA

- Angola reported one case in February, the first for the year. If genetic sequencing confirms that the case is related to virus circulating in Angola in 2010, the country will be considered to have missed the milestone of interrupting re-established polio transmission by end-2010.
- This most recent case is in the south-east of the country, close to the borders with Namibia and Zambia. It is from this area that polio spread into Namibia in 2006, causing a deadly outbreak affecting primarily adults. Authorities in both Namibia and Zambia have been alerted as to the proximity of this latest case close to their borders, and efforts are ongoing in both countries to further sensitize disease surveillance and assess population immunity levels. A Technical Advisory Group meeting for Angola, the Democratic Republic of the Congo, Namibia and Zambia is scheduled to meet on 14-15 March.
- Mop-ups using monovalent Oral Polio Vaccine type 1 (mOPV1) were held on 18-20 February in Luanda, Benguela, Bengo and Kuanza Norte - the first campaigns to be conducted in response to the latest cases in Luanda and Benguela in November. Further mop-ups were conducted on 25-27 February, in Kuando Kubango, and other infected and high-risk areas, including Luanda and Benguela. The next scheduled SIAs will be nationwide campaigns to take place in March and April. These activities are considered particularly crucial to minimizing the risk of further international spread.
- Given the appearance of adult cases in Kikwit, Bandundu, it was decided that SIAs conducted in the region should be expanded to cover the whole population (instead of vaccinating only children under five years of age). The entire population of sixteen districts of Bandundu were vaccinated using mOPV1 during SNIDs on 20 January and 24 February, and discussions are under way to expand the age-group of upcoming campaigns in Kinshasa.
- In Katanga, a logistically difficult area to operate in, strategies are being tailored to increase outreach to hard-to-reach areas.

CHAD

- Genetic sequencing is under way to determine whether a case of WPV3 reported with date of onset 23 December 2010 in Dar Sila in the east of the country is related to virus last seen in southern Chad on 10 May 2010. Due to sub-national surveillance gaps, ongoing undetected transmission cannot be ruled out.
- Chad is also affected by a WPV1 outbreak, due to a new importation from September 2010. Chad has seen 5 cases of WPV1 for the year so far. An outbreak response plan is currently under development.
- NIDs using bOPV took place on 10-12 February. Independent monitoring was implemented in highest-risk areas, including in the greater N'Djamena area.

DEMOCRATIC REPUBLIC OF THE CONGO (DR CONGO)

- DR Congo has already reported 13 cases for 2011. None of these cases are from Katanga province, the locus of the re-established polio transmission in the country. While genetic sequencing is awaited, it is likely these cases represent continuation of the new Bandundu-centred outbreak.
- Given the appearance of adult cases in Kikwit, Bandundu, it was decided that SIAs conducted in the region should be expanded to cover the whole population (instead of vaccinating only children under
REPUBLIC OF CONGO

• One case has been reported for 2011, a WPV1 with onset of paralysis on 22 January. The final classification of 523 AFP reported during the 2010 outbreak for which no adequate specimens were collected is almost complete. The Government of Congo has indicated that the classification process should be completed in the first half of the month. It is expected that approximately 300 of these cases will be confirmed as polio. Presently, the total for 2010 stands at 86.
• The most recent NIDs were held from 22 February using bOPV.

HORN OF AFRICA

• An international risk assessment for polio eradication in the Horn of Africa has been finalized. In addition to ongoing risks in the Uganda/Kenya border area (with confirmed ongoing transmission of WPV1), other areas of the Horn of Africa were assessed to be at very high risk for re-infection. In particular, parts of Somalia have been inaccessible during SIAs over the past two years due to insecurity, and a large susceptible population now exists, particularly in the southern part of the country and in/around Mogadishu. Upwards of 800,000 children have not been accessible for over a year. Parts of Ethiopia are also deemed to be at risk, particularly in the southern part of the country.
• Following a successful January referendum for independence that was associated with huge (and on-going) migrations into Southern Sudan from the north and neighboring countries, the first round of polio NIDs using tOPV was conducted from 22-25 February, while the second round is planned for 29 March - 01 April. Southern Sudan has not recorded any WPV cases for over 20 months now but with the ongoing situation across the borders in Uganda, Congo and DRC, keeping this status requires the maintenance of high quality polio campaigns and AFP surveillance. Communication support for polio eradication activities has been boosted with the recruitment of 10 polio communication officers to support data-driven planning and implementation of advocacy and social mobilization activities with special focus at community levels in all the States.
• In Ethiopia, a vaccine-derived poliovirus (VDPV) type 3 (with onset of paralysis on 4 November) was found to be unrelated to a circulating VDPV type 3 from the early part of 2010. It is important to note that no secondary cases have been reported.
• In Kenya, an international mission of technical experts met early in the month, finalizing SIA plans and reviewing operational plans to strengthen disease surveillance.
• Ethiopia completed the second phase of Child Health Days including tOPV (the first was held in October). In Somalia, preparations are also underway for NIDs in late March and late April. Both countries continue to be at risk of polio, given ongoing WPV transmission in the Uganda/Kenya border area, and evidence of a cVDPV in Ethiopia in early 2010. Sudan is currently carrying out NIDs using tOPV.

CENTRAL ASIA AND RUSSIA

• Central Asia and Russia have not seen any cases in more than four months; however constant vigilance is crucial to ensure that no more children from this region will suffer from polio.
• Tajikistan, Turkmenistan and Kazakhstan are all conducting nationwide immunization activities in April, and Russia is planning SNIDs in the Caucasus. Kazakhstan held SNIDs last week.

NEPAL

• No cases have been reported for 2011, and the last case had date of onset 30 August 2010.
• NIDs were held from 12-13 February and will be followed by further NIDs from 12-13 March.

WEST AFRICA

• Burkina Faso held NIDs on 04 February. Further rounds are planned for 25 March and 22 April for Mali, Liberia, Senegal, Mauritania, Sierra Leone, Guinea, Côte d'Ivoire, Togo and Ghana using a combination of bOPV, tOPV and mOPV 1, depending on recent epidemiology and priority.
• The key now is to further raise population immunity levels to both type 1 and type 3 poliovirus, to minimize the consequences of any further international spread of virus into west Africa.

GABON

• Gabon has reported its first case in more than ten years, a WPV1 from Ogooue-lolo province with onset of paralysis on 15 January.
• Outbreak response immunization activities have already begun, with NIDs using bOPV held from 22 February, and further SIAs planned for March.

MYANMAR

• Myanmar is carrying out a response to the single vaccine-derived poliovirus (VDPV) case detected in Yamethin Township in Mandalay Division in December 2010. Two rounds of SIAs are planned, to vaccinate 3.4 million children under the age of 5 years with oral polio vaccine (tOPV) in 115 Townships in Myanmar. No secondary spread has been found and there is active surveillance going on to verify this.
DRAFT GUIDELINES FOR WHO AND SAGE DEVELOPMENT OF EVIDENCE-BASED VACCINE RELATED RECOMMENDATIONS

Table of Contents

1. Introduction .................................................................................................................. 2
   1.1 Background ............................................................................................................. 2
   1.2 Past Use of GRADE in Vaccine Position Papers ................................................. 4

2. SAGE Process for Reviewing the Evidence ................................................................ 4
   2.1 Definition of questions to inform recommendations ......................................... 5
   2.2 Identification of critical questions for which the GRADE approach should be
       applied .................................................................................................................... 7
   2.3 Systematic review of the literature and of unpublished data ............................. 7
   2.4 Identifying study limitations through risk of bias .............................................. 8
       2.4.1 Risk of bias in RCTs ..................................................................................... 8
       2.4.2 Risk of bias in observational studies ............................................................ 9
       2.4.3 Impact of bias .............................................................................................. 9
       2.4.4 Quality of systematic reviews and meta-analyses ....................................... 10
   2.5 Scoring of the Quality of Evidence ...................................................................... 10
   2.6 Discussion and deliberation leading to the development of proposed
       recommendations ................................................................................................. 10
   2.7 Presentation of proposed recommendations to SAGE along with the supporting
       evidence .................................................................................................................. 10
   2.8 SAGE discussion, deliberation, and ultimate decision regarding the proposed
       recommendations to WHO .................................................................................... 11

3. Scoring of the Quality of Evidence ........................................................................... 11
   3.1 Categorization of studies .................................................................................. 12
   3.2 GRADE quality assessment criteria .................................................................. 12
   3.3 Quality of evidence rating ................................................................................ 14
   3.4 Application of GRADE to Recommendations ................................................. 14
   3.5 Presentation of GRADE Tables .......................................................................... 15

4. Vaccine Recommendation Development - Beyond Scoring the Evidence ............. 15
   4.1 Other considerations when making recommendations ...................................... 15
   4.2 Updating Recommendations ............................................................................. 16
   4.3 Emergency situations ...................................................................................... 16

5. Conclusions ............................................................................................................... 17

Appendix 1. Draft Data Extraction tool .......................................................................... 18
Appendix 2. Checklists for Reviewing Study Quality .................................................... 20
   Appendix 2a. Checklist for RCTs ........................................................................... 20
   Appendix 2b. Checklist for Case-Control Studies .................................................. 20
   Appendix 2c. Checklist for Cohort Studies ............................................................... 20
   Appendix 2d. Checklist for Systematic Reviews .................................................... 20

Appendix 3. Draft Summary Table for Evidence Review .............................................. 21
Appendix 4. Rating the Quality of the Evidence ........................................................... 22
Appendix 5. Template of a GRADE table used to score the quality of evidence........... 23
DRAFT GUIDELINES FOR WHO AND SAGE DEVELOPMENT OF EVIDENCE-BASED VACCINE RELATED RECOMMENDATIONS

1. Introduction

Vaccines are one of the most successful public health interventions of all time. Millions of lives have been saved and disability averted due to the advent of critical vaccines. Much work is devoted to the development and testing of vaccines, ultimately leading to their licensure and use in a population. However, availability of the products does not ensure their appropriate use. The World Health Organization (WHO) is tasked to provide leadership in global health, shape research agendas, provide guidance and standards for public health practice, and provide support to country programmes. To fulfil its mission for vaccines, since 1998 the WHO has published vaccine position papers with global recommendations for vaccine use. Each position paper is specific to a vaccine preventable disease and includes four sections: an introduction, a section providing information on the respective disease (disease epidemiology, the pathogen, the disease), a section providing information on the available vaccines (composition, safety, immune response, efficacy and effectiveness, cost effectiveness and any other relevant issue), and the WHO position on the optimal vaccine use.

The Strategic Group of Advisory Experts on immunization (SAGE) is an independent advisory committee tasked to advise the WHO on the development of policy related to vaccines and immunization. SAGE makes recommendations to the WHO on vaccine-relevant topics identified as priorities of public health importance. These recommendations are captured in the SAGE meeting reports and published in the Weekly Epidemiological Record following each meeting. All reports, meeting presentations, and background documents are available online.

Since 2006, SAGE has been charged with reviewing WHO vaccine position papers. Working Groups of SAGE review the evidence relating to issues addressed in the vaccine position papers and propose recommendations for SAGE to consider. After discussion and deliberation by SAGE, SAGE makes recommendations on the use of vaccines that are incorporated by WHO into the vaccine position papers.

1.1 Background

A careful review and consideration of the scientific evidence is a necessary step in recommendation and guideline development. The results of the full range of studies on a given topic should be carefully considered to identify trends in magnitude, geographic variability, and other factors that are important for impact and generalizability. For developing the most appropriate recommendations, committees should weigh the desirable and undesirable consequences based on the best available evidence and take into account societal values and preferences. While the evidence reviewed is the result of scientific

3. SAGE Terms of Reference: http://www.who.int/immunization/sage/SAGE_TOR_1_September_2010.pdf
endeavours, evaluating the quality of the evidence and making recommendations are activities that require expert interpretation and judgement in addition to rigorous scientific review.

Factors that are taken into consideration include disease epidemiology and clinical characteristics, vaccine and immunization characteristics, economic considerations, health system opportunities, and interaction with other existing intervention and control strategies. In addition to the results of studies themselves, consideration is given to the methodology and study design used to conduct such studies. It is generally accepted that randomized controlled trials (RCTs) are the gold standard to minimize various forms of bias when looking for associations between interventions and health outcomes, but there are many characteristics of RCTs or observational studies that determine their quality and relevance. In some cases, faulty randomization or blinding may reduce the quality of an RCT below that of a well-designed observational study. Therefore, a review of the potential risks for bias and other aspects of study design quality is crucial when drawing conclusions from a study of any type. The quality of evidence reflects the extent to which confidence in the estimation of effect is adequate to support a particular decision or recommendation.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is one of many frameworks developed over the years to assess the quality of evidence and it has been adopted by the WHO. The use of the GRADE methodology to score the quality of evidence in support of key recommendations included in the WHO vaccine position papers was introduced in April 2007. In addition to recommendations for vaccine usage SAGE also makes strategic recommendations regarding public health programmes and research priorities, which do not undergo formal GRADE scoring. However SAGE recommendations are evidence-based and follow the overall framework of GRADE. Available data to support many critical policy decisions are assessed using the other steps of GRADE without formal scoring. All critical recommendations for interventions are scored using the GRADE framework to assess the quality of related evidence.

The formal GRADE process has been described elsewhere. In short, questions of importance related to a recommendation are identified, a systematic literature review is conducted to identify what is known to answer the question(s), and the quality of relevant evidence is reviewed and scored. Five criteria (limitations in study design commensurate with the type of study, inconsistency, indirectness, imprecision, and publication bias) are used to downgrade the quality of evidence when studies do not meet the published standards, and three criteria (magnitude of the effect, dose-response gradient, and ability of the study to limit biases and control for confounding) are used to upgrade the quality of evidence when study results increase one's confidence in their validity. Based on this score, as well as other factors (balance between benefits and risks, societal values and preferences, and cost and resources), recommendations are made and scored as strong or weak.

The GRADE framework is an attempt to provide structure and guidance for objectively reviewing the quality of evidence and risk of bias. Nevertheless, some decisions to up- and downgrade the evidence may be a matter of individual judgement. A hallmark of GRADE
its aim to improve transparency in decision making. Although GRADE remains subject to some individual interpretation, interested parties are able to follow the logic and processes that led to a given conclusion, recommendation, and/or guideline. Such a process also promotes useful dialogue and opportunities to reassess the evidence as needed. The GRADE framework and particularly the scoring process has undergone and will continue to undergo improvements over time, based on the collaborative work of the open ended GRADE working group.

1.2 Past Use of GRADE in WHO Vaccine Position Papers

Since 2007, GRADE tables have accompanied WHO vaccine position papers and were made available as attachments online. GRADE tables for vaccine position papers attempted to apply the GRADE framework strictly, although some GRADE evidence profiles and summary of findings tables were adjusted to the specific needs of vaccines and provided additional information in footnotes and narrative text as thought necessary.

GRADE tables are only applied to issues regarding the effectiveness and safety of vaccines and are created for overall vaccine efficacy/effectiveness and safety, and occasionally other more specific considerations of the effectiveness/safety of the intervention (such as the duration of protection, schedule considerations, and use in subpopulations, such as specific age or risk groups or HIV-infected populations). Over the past few years, SAGE members expressed concern about the use of the GRADE scoring methodology and specifically how it was applied to vaccines, as relevant and important data were sometimes excluded or given a low quality score despite providing convincing relevant evidence. When strictly applied, the GRADE scoring at times ranked the quality of evidence as low or moderate, which SAGE did not feel appropriately reflected the quality of the evidence base. This was particularly true for traditional vaccines for which, despite many years of successful field use and impact demonstrated through many observational studies or population impact demonstrated by rigorous surveillance, the evidence quality level could not be upgraded. At the end, the score was still that of low quality evidence. Not only did these rankings present a problem for communicating the basis for a recommendation to use a vaccine, but there was concern that these low rankings could be misunderstood by the general public or misused by those promoting an anti-vaccine agenda. Thus, instructions on how to apply the GRADE framework, including minor adjustments, were proposed based on SAGE members’ review of the GRADE methodology and many years of experience working with vaccines and assessing the quality of data to inform public health policy. In addition discussions were held and following discussions with other national technical advisory groups and a review of specific examples was conducted with the GRADE working group, which resulted in some adjustments to the GRADE scoring scheme itself.

The following provides a framework that better fits the needs of vaccine evidence and integrates the GRADE approach with SAGE and WHO recommendation development processes.

2. SAGE Process for Reviewing the Evidence

---

Complex issues are routinely examined in careful detail by SAGE Working Groups. Working Groups (WGs) review the evidence pertaining to a given topic and present proposals for recommendations to SAGE, which then discusses, deliberates, and ultimately provides its recommendations to WHO. Thus, the initial review of the evidence occurs in WGs. The key activities involved in creating evidence-based SAGE recommendations are as follows:

1. Definition of the questions to inform recommendations
2. Identification of the critical questions for which an in-depth review is needed
3. Systematic review of the literature with or without meta-analysis and, where necessary, implementation of research to address gaps in the evidence
4. Review the quality of the evidence in particular through assessment of the risk of bias and confounding
5. Scoring of the quality of the evidence (using the GRADE approach for data on safety and effectiveness)
6. Discussion and deliberation, leading to the development of proposed recommendations
7. Presentation of proposed recommendations to SAGE, along with the evidence used to support the recommendations
8. SAGE discussion, deliberation, and decision regarding the proposed recommendations to WHO

Each of these steps is discussed in the sections that follow. The guiding principles are that careful review and consideration of the evidence should precede development of recommendations and the entire process should be transparent.

2.1 Definition of questions to inform recommendations

An essential part of the recommendation development process is defining the information that will influence the making of a recommendation. There are many important factors to consider; in the case of vaccines, these may include the burden of the disease, the effectiveness and safety of a vaccine, and the optimal schedule for protection given programmatic realities. All of these may need to be considered in the general population, in different geographic regions, and in various subpopulations. A well-accepted methodology associated with framing of questions addressing alternative management strategies in systematic reviews mandates carefully specifying the patient population, the intervention of interest, the comparator, and the outcomes of interest. The value of the methodology popularly known as PICO (patient/intervention/comparator/outcome) in helping achieve focused recommendations is increasingly recognized and proposed by GRADE11. Outcomes of interest should be those important to patients: if patient-important outcomes are represented by a surrogate, they will frequently require down-rating of the quality of evidence for indirectness. For a guideline, an initial rating of the importance of outcomes should precede the review of the evidence. One should specify all potential patient-important outcomes and make a preliminary classification of outcomes into those that are critical, those that are important but not critical, and those of limited importance. The first two classes of evidence will have bearing on guideline recommendations; the third may or may not. Since

10 http://www.who.int/immunization/sage/working_groups/en/index.html
11 Guyatt GH, Oxman AD, Kunz R. et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. Journal of Clinical Epidemiology 64 (2011) 395-400
GRADE decisions regarding the overall quality of evidence supporting a recommendation may depend on which outcomes are designated as critical for making the decision and which are not, it is important to define those critical outcomes. For pragmatic reason, scoring proposed in step (5) above will only be applied to those critical outcomes.

At the beginning of its work, a WG should come to consensus on the key questions for consideration, so that a detailed literature review may be conducted. The questions of efficacy/effectiveness, safety, and burden of disease are generally key questions for the WG to factor into the development of proposed recommendations/options for vaccine use.

Issues for the SAGE WG to consider when developing proposed recommendations and for SAGE when making recommendations, include the following:

- **Epidemiologic features of the disease**
  - Disease burden, including age specific mortality, morbidity, and societal impact
  - Specific risk groups
  - Epidemic potential
  - Disease occurrence over time (i.e. secular trends)
  - Serogroup or serotype distribution for serogroup or serotype specific vaccines
  - Changes in epidemiology over time

- **Clinical characteristics**
  - Clinical management of disease
  - Disease severity and fatality
  - Primary/secondary/tertiary care implications
  - Long term complications of disease and medical requirements

- **Vaccine and immunization characteristics**
  - Efficacy
  - Effectiveness and population impact of the vaccine (including herd immunity)
  - Safety
  - Indirect effects (potential impact on strain selection, herd immunity, potential safety concerns of live attenuated vaccines in contact of vaccines)
  - Cold chain and logistical concerns
  - Vaccine availability
  - Vaccine schedules
  - Schedules’ social and programmatic acceptability
  - Ability to reach the target populations
  - Ability to monitor program impact

- **Economic considerations**
  - Cost of illness
  - Vaccine and vaccine delivery costs
  - Potential for vaccine price reductions
  - Vaccine cost and cost-effectiveness of immunization programmes
  - Affordability of immunization

- **Health system opportunities and existence of and interaction with other existing intervention and control strategies**
- **Social impacts**
- **Legal considerations**
- **Ethical considerations**
2.2 Identification of critical questions to which the GRADE approach should be applied

Because many factors are considered in making recommendations, WGs will often identify many questions in the categories in section 2.1 for which answers will be sought. However, it is clearly impossible to dissect all issues to a granular level, and questions must be prioritized by the WG. Questions or outcomes that are particularly contentious and critical for decisions to implement an intervention are prioritized for GRADing of the quality of evidence. The GRADE scoring needs to be applied only to the critical questions, preferably no more than five questions unless there are unusual circumstances. The formal scoring is appropriate only for questions regarding an intervention (e.g. vaccine use), not for disease burden, economic considerations or strategic recommendations (e.g. research gaps, decision to pursue an eradication goal, etc.). However, an in-depth look at the evidence will be conducted even for those questions that are not formally GRADEd and a systematic literature search needs to be performed. For assessing the quality of economic and cost-effectiveness evaluations, other guidelines (e.g. WHO guide for standardization of economic evaluations of immunization programmes http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.14_eng.pdf) can be used. In evidence-based recommendations, the steps listed above (steps 1-8) will always be conducted, with the exception of the formal scoring (5). It is the role of the WG to help identify the critical questions to be scored using GRADE.

2.3 Systematic review of the literature and of unpublished data

An essential step in the process is to conduct a careful literature review for data relevant to the questions at hand. The review of the literature should be presented to the WG for consideration and to ensure its completeness. Efforts should also be made to identify any unpublished but relevant data that would inform WG and SAGE deliberations.

Literature searches should be carefully documented, transparent, and reproducible. Some of the literature reviews may be done in advance of a WG defining the questions, (e.g. for safety and efficacy, which will likely always be considered critical). A list of relevant papers should be provided to the WG. The data should be extracted using a data extraction tool (e.g. Appendix 1) and consolidated to facilitate review by the WG. Data may be combined into a meta-analysis.

Literature searches are also important for identifying knowledge gaps and helping prioritize future research agendas. Those important areas where data are lacking should be highlighted by the WG and SAGE to encourage additional studies. In some instances a final decision regarding a recommendation to use a vaccine will not be taken until the critical missing data are made available.

In rare instances, recommendations may be needed for interventions for which there is very limited evidence base. For example, although a few case studies have reported infection with yellow fever vaccine virus in infants born to vaccinated mothers, data needed to evaluate this risk or association are not available. In these circumstances, what little evidence is available and results from related but indirect studies (e.g. studies evaluating other live vaccines given to pregnant women) carefully considered by the key experts may be the foundation for a
recommendation. When only very low or low quality of evidence is available but a recommendation must be formulated, a clear explanation should be provided.\textsuperscript{12}

Data considered by SAGE and WHO may be published or unpublished. While RCTs are considered the gold standard for assessing the effect of an intervention, for vaccine effectiveness and safety important sources of data and constitute a significant component of the body of evidence use for making recommendations. Types of available studies include randomized-controlled trials, observational studies, outbreak investigations, country surveillance, program evaluations, cost-effective analyses, forecasting, and landscape analyses.

2.4 Identifying study limitations related to bias

As important studies are identified they should be documented in a summary table (e.g. Appendix 3). This will allow for easier comparison and evaluation of studies for scoring.

There are a number of characteristics that may put studies at risk of bias (that is, systematic errors or differences from the true results) that could affect internal validity that need to be considered when reviewing the quality of the evidence. These specific characteristics depend on the type of study and the outcomes evaluated. Both the Cochrane Collaboration and the Critical Appraisals Skills Programme have developed useful tools for evaluating study quality. Standardized approaches to evaluating the quality of non-randomized trials are less well developed, although some guidance is available as follows. The tools listed below are adapted from the Cochrane Handbook\textsuperscript{13} and Critical Appraisals Skills Programme.\textsuperscript{14} As noted in the Cochrane handbook, there are other important aspects of study quality (e.g. reporting quality and ethical approval) which are not addressed in this section. Rather, the primary focus is on the risk of bias that could affect the interpretation of the results.

For reviewers of studies of vaccines, the draft data extraction tool (Appendix 1) permits consideration of these factors and may be used to evaluate the limitations of individual study. Appendix 2 provides four checklists developed by the Critical Appraisals Skills Programme that may be used and adapted to assess study methods and potential limitations of vaccine studies.

2.4.1 Risk of bias in RCTs

When properly conducted and of adequate size, RCTs have the lowest risk for bias. The Cochrane Collaboration highlights six characteristics to consider concerning the risk of bias in RCTs especially confounding these:

- Sequence generation refers to the method of randomly allocating an intervention to study participants

\textsuperscript{12} For example, in the 2007 Vaccine Position Paper on Rotavirus vaccine, WHO states "...until the full potential of the current rotavirus vaccines has been confirmed in all regions of the world, in particular in Asia and Africa, WHO is not prepared to recommend global inclusion of rotavirus vaccines into national immunization programmes." WHO later amended the recommendation once data were available supporting widespread use. This recommendation was also influenced by consideration of factors other than the quality of the evidence (see section 4.1)

\textsuperscript{13} Available at \url{http://www.cochrane-handbook.org/}. In particular, see chapters 8 and 13.

\textsuperscript{14} \url{http://www.sph.nhs.uk/what-we-do/public-health-workforce/resources/critical-appraisals-skills-programme}
Allocation sequence concealment refers to the prevention of knowledge (or prediction) of intervention assignment by study participants and investigators.

Blinding refers to the masking of to the intervention assigned study participants and investigators.

Incomplete outcome data may be the result of participant drop out (missing data) or exclusion of data from the study results.

Selective reporting (i.e., reporting bias) is the incomplete publication of results based on their results.

Other sources of the reporting bias may include design-specific risks of bias, early stopping, baseline imbalance, blocking of experimental units in unblinded studies, differential diagnostic activity, always others issues.

For more detail on each of these, see the Cochrane Handbook (Section 8). Each feature should be evaluated to determine the risk of bias in each study (using the data extraction tool and checklist) and then should be documented in the Summary Table for Evidence Review (Appendix 1).

2.4.2 Risk of bias in observational studies

Observational studies are particularly susceptible to selection bias and confounding, because different types of observational studies carry different risks of bias, it is more challenging to standardize the evaluation of bias across study types. Two checklists have been included in Appendix 2 for reviewing the quality and risks of bias in case control and cohort studies. They can be modified for other study designs. For interventions at the individual level, the Cochrane Collaboration suggests consideration be given to differences in the comparison groups or within participants over time; allocation to comparison groups and potential temporal, geographic, treatment, or other differences that could bias the results; and prospective and retrospective aspects of the studies. A clear description of potential confounders the direction, in which direction they would likely bias the results, and what the authors did to address confounding (e.g., matching, stratification, modeling, etc.) should also be clearly outlined.

All of these features are included in the data extraction tool and checklists to aid reviewers’ consideration of the risks of bias. The collective results should then be reflected in the GRADE scoring under the “Limitations” criterion (see section 3).

2.4.3 Impact of bias

After carefully reviewing each study for potential biases, an overall assessment of the evidence for bias as well as the likely direction(s) and magnitude of the bias(es) should all be taken into account. If many of the studies that constitute the evidence base have a high risk of bias, any conclusions from the body of evidence must be drawn carefully. Studies at high risk for bias may be excluded if the results are deemed too unreliable to consider.

---


2.4.4 Quality of systematic reviews and meta-analyses

Systematic reviews and meta-analyses can be useful tools for evaluating effects across studies. Their validity will depend on the completeness of their study search, their assessment of the quality of studies, the appropriateness of combining data across studies, and the relevance of the outcomes considered. In reviewing the quality of an existing systematic review, careful attention should be paid to the following: search methodology, heterogeneity, and inclusion/exclusion criteria (particularly for observational studies), in addition to the attributes discussed above for individual studies. If any of these are in question, the results of the systematic review should be viewed cautiously. Some reviews do not consider all of the data that may be relevant to an assessment of vaccine efficacy and safety (e.g. observational studies, outbreak investigations, surveillance reports, etc.). Appendix 2 provides a checklist to use when reviewing the quality of systematic reviews.

In some cases, a systematic literature review may already have been done by WHO or another group (e.g. Cochrane Collaboration), independent of or on behalf of WHO. Previous reviews may serve as the basis for analyzing the evidence base, although a search should be conducted to ensure studies published since the previous review was published are not missed.

2.5 Scoring of the Quality of Evidence

Please see Section 3.

2.6 Discussion and deliberation leading to the development of proposed recommendations

WG meetings meet on a regular basis until they have completed all objectives in their Terms of Reference, which may take 6 to 12 months. WGs often meet 1-3 times in person and participate in frequent (often monthly) conference calls. During these meetings, WG members review the evidence (provided in the form of presentations from WHO, outside consultants, and/or WG members), highlight issues, and make proposals for recommendations. Draft documents (such as background papers, summaries of the evidence, etc.) and presentations to SAGE are discussed and vetted by the WG, and proposed recommendations are agreed upon by consensus. For additional information on WGs, please see Annex 3 of the SAGE Terms of Reference.17

2.7 Presentation of proposed recommendations to SAGE along with the supporting evidence

WG chairs (who are also SAGE members) present their proposed recommendations to SAGE. SAGE receives updates throughout the WG progress. For each recommendation proposed by the WG, a written rationale with supporting evidence should be provided (for an example, see background material for pertussis vaccines18) along with the important considerations underlying each recommendation. The recommendation and rationale are provided in advance of the SAGE meeting. These elements are also summarized in a presentation given by the WG chair to SAGE.

17 http://www.who.int/immunization/sage/SAGE_TOR_1_September_2010.pdf
The format for how data and their synthesis are provided and presented to the WG will depend upon the terms of reference for the WG. In addition to the point-by-point recommendations and justifications, additional background materials will often be appropriate. In general, when providing evidence in support of recommendations for a new vaccine, an in-depth background paper should be provided to SAGE. For many recommendations, an appropriate format for displaying the evidence may be using the major categories of disease epidemiology, clinical characteristics, vaccine and immunization characteristics, economic considerations, health system opportunities, and existence of and interaction with other existing intervention and control strategies (section 2.1). The amount of information presented and level of detail will depend on the topic at hand.

2.8 SAGE discussion, deliberation, and ultimate decision regarding the proposed recommendation to WHO

Prior to the SAGE meeting, SAGE members will have received previous updates from the WG, meeting minutes from all teleconferences and in person meetings, and background materials important to the WG's deliberations. During the SAGE session on the topic at hand, SAGE members will discuss and deliberate upon the WG’s proposed recommendations in the open forum of a SAGE meeting. SAGE members may adopt the WG's proposed recommendations or make necessary adjustments.

SAGE adopts recommendations by consensus; the recommendations are then transmitted to WHO to incorporate into a WHO vaccine position paper. More information on SAGE and its role in policy development is available in Duclos et al.

3. Scoring of the Quality of Evidence

The GRADE approach and its application to SAGE vaccine recommendations are described below. SAGE has fully embraced the GRADE methodology with only minor adaptation to strengthen its relevance to immunization. Many of the adjustments to the more traditional presentation of the GRADE tables are an attempt to clarify its application to vaccines/vaccination recommendations without changing the intent. The adjustments ensure that the many types of data available for immunizations are reflected in the decision making process.

Vaccine development and testing has occurred over many decades and many old vaccines are still used today. Therefore, the evidence base that is used to formulate recommendations often includes studies spanning a long time horizon, and as randomized controlled trials are unethical once the impact of protection is evident, many data stem from observational studies. When robust RCTs exist, the scoring of the evidence concerning efficacy need only include those RCTs. However, when observational studies are important in the body of evidence used to formulate recommendations in addition to RCTs, multiple tables must be constructed for each category of study and reviewed in totality.

Throughout the evidence review process (steps 1-8), expert opinion is critical in the assessment of these factors and their importance to the question under consideration. The

---

application of the GRADE criteria and the inferences that may be drawn from the studies relating to the question under consideration are inherently subjective and rely on the judgement of skilled and experienced public health professionals.

Active participation of the WGs is essential to ensure that the most appropriate studies are utilized and the results are carefully considered. In addition to formulating the questions for GRADE, the WGs will review the evidence and the resulting GRADE tables.

3.1 Categorization of studies

Studies enter into the GRADE system at a particular level based initially on their study design. Because not all studies of a particular design are equal, the GRADE approach provides a framework to up- or down-grade the score of the evidence, based on methodological and quantitative assessment. To begin, however, all RCTs enter at level 4 ( ★ ★ ★ ★ ) and observational studies and surveillance data enter at level 2 ( ★ ★ ).

The GRADE criteria should then be applied to the studies, although studies should not be repeatedly penalized for limitations already factored into their starting score. As an example, a controlled observational study that enters into the scoring system at a level 2 ( ★ ★ ) should not be further downgraded because it was not randomized. Passive surveillance data of uncertain quality should, however, likely be downgraded through application of some of the limiting factors.

Only primary data sources should be entered into the table. Mathematical models do not represent primary data but build on other sources of information and therefore should not be reflected in the GRADE tables.

3.2 GRADE quality assessment criteria

Each study should be reviewed using the following criteria, while recognizing that application of the criteria is a subjective process and open to individual interpretation. For example, how similar studies are to each other in their estimate of effect and whether any differences warrant a point reduction for inconsistency is likely subjective, although it is guided by review of point-estimates, confidence intervals, and values of $i^2$ statistic of heterogeneity. Furthermore, it may be very difficult to assess conclusively whether publication bias is occurring. This may require detailed information held by the specific study team or close attention to missing data that should have been collected during the study. WGs are particularly well-positioned to comment on this parameter through their expertise in the field. Documenting the process in an open and transparent manner will allow others to review the process and propose alternative interpretations for consideration.

The following boxes outlines the criteria for down- and upgrading the strength of evidence (also see Appendix 4). The descriptions below are general and brief and provide specific instructions on how to apply GRADE in the area of vaccines and vaccination, and more detailed information may be found in GRADE documents.

---

Box 1. Criteria used to downgrade studies

Limitations: Studies may be downgraded by 1 or 2 points for serious or very serious methodological limitations. Examples of these limitations include inappropriate randomization; lack of concealment; violation of the intention to treat principle; inadequate blinding; substantial loss to follow-up; and early stopping for benefit. (See section 2.4 for how to evaluate risks of bias due to methodological limitations)

Inconsistency: Studies may be downgraded by 1 or 2 points if the effect is not similar across studies and if inconsistencies are serious or very serious

Indirectness: Studies may be downgraded by 1 or 2 points if there are serious or very serious issues with indirectness. Examples of indirectness may include using surrogate end points, indirect comparisons between two treatments, problems with generalizability to the population of interest, and test inaccuracies. It is suggested that when assessing clinical protection, there is no downgrading for immunogenicity studies when there are well established standard correlates of protection

Imprecision: Studies may be downgraded by 1 or 2 points if there is serious or very serious imprecision i.e. confidence intervals are wide or very wide

Reporting Bias: Studies may be downgraded by 1 or 2 points if publication bias is likely or very likely

Box 2. Criteria used to upgrade studies

Large effect/strength of association: Studies may be upgraded by 1 point if there is evidence from RCTs or observational (including surveillance) studies of vaccine effectiveness of 50% or higher ((OR/RR >=2 or < .5), based on consistent evidence from two or more studies with no major confounders. Studies may be upgraded by 2 points if there is strong evidence from RCTs or observational studies of a vaccine effectiveness of 80% or higher (or depending on the outcome a (OR/RR >=5 or < .2) based on consistent evidence from two or more studies with no major confounders

Dose-Response Gradient: Studies may be upgraded if there is evidence of a dose response gradient at the population level i.e.

Increase by 1 point if there is evidence of risk reduction in disease incidence with increasing population vaccine coverage. Evidence of decreased risk with increased vaccine coverage includes evidence of reversal at population level (disease returns when vaccine coverage decreases) and evidence of risk reduction in older or younger age-groups not targeted for the intervention but who benefit from herd immunity

Increase by 2 points if there is very strong evidence of risk reduction with increasing population vaccine coverage

Antagonistic bias and confounding

Major Confounders: Studies may be upgraded by 1 point if all major confounders would have reduced the effect.

Good quality study design: Increase by 1 point if there was good quality of study design to control for confounding and differential biases among cases and controls e.g. with population based record linkage, self controlled case series or other appropriate designs.

The score may be further upgraded by 1 point if there is consistency between studies across different settings, different investigators and different designs

---

21 Changed from "plausible" confounders in the formal GRADE framework.
22 This criterion has been slightly modified from the GRADE criteria, which specify that all "plausible" confounders would have reduced the effect.
23 This criterion is not included in the formal GRADE framework. It is only applicable to observational studies.
In the GRADE table, ratings are clearly indicated. For reductions in score, possible ratings include "none serious" (no downgrade), "serious" (downgrade by 1 point), or "very serious" (downgrade by 2 points). For upgrading the score, possible ratings include "not applicable" (no upgrade), "strong evidence" (upgrade by 1 point), or "very strong evidence" (upgrade by 2 points). Finals scores cannot exceed 4 points or drop below 1.

Whenever a downgrade or upgrade is applied, a footnote is needed to explain to others the rationale for the change in score. For example, current studies evaluating HPV vaccine efficacy may be downgraded under the criterion of "indirectness" at this time due to the use of surrogate endpoints in measuring vaccine efficacy. A footnote would be required explaining this in the table. In some cases, studies may not be downgraded, but footnotes should still be used to highlight any potential issues. This promotes transparency and shows readers that the full range of issues has been considered.

The decision to downgrade or upgrade a body of evidence is often subjective and depends on individual judgement. While two individuals may agree on the study limitations during a review of the evidence, whether or not such limitations warrant a change in score may not be clear. Similarly the amount of variation in results from multiple studies allowed before they are deemed inconsistent may be contentious. These examples illustrate the subjective nature of the exercise, the importance of expert opinion in interpretation and assessment of the criteria, and the need to explain one's thought process throughout the evaluation so that areas of agreement and disagreement are evident.

### 3.3 Quality of evidence rating

Using the criteria described above, individual studies and the collective body of evidence should be evaluated. The collection of studies will receive a score based upon analysis of the component studies. One should score the quality of scientific evidence using the GRADE scale:

- We are very confident that the true effect lies close to that of the estimate of effect on health outcome (score of 4, or ☐ ☐ ☐ ☐)
- We are moderately confident in the estimate of effect on health outcome: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (score of 3, or ☐ ☐ ☐)
- Our confidence in the estimate of the effect on the health outcome is limited: The true effect maybe substantially different from the estimate of the effect (score of 2, or ☐ ☐)
- We have very little confidence in the estimate of the effect on the health outcome. The true effect is likely to be substantially different from the estimate of effect (score of 1, or ☐)

The GRADE tables explicitly provide the score of the outcomes critical to the recommendation. These factors help inform whether or not a recommendation should be made.

### 3.4 Application of GRADE to Recommendations
Using the formal GRADE approach developed by the GRADE Working Group, scoring is also applied to the recommendations (i.e. strong versus weak or conditional recommendations). WHO and SAGE have made the decision not to GRADE vaccine recommendations as weak recommendations are of little value to country immunization programs. It is the goal of WHO and SAGE to provide only strong recommendations, which may be either for or against an activity, or may be condition-dependent.24

An informal review of WHO vaccine recommendations was undertaken in the summer of 2010. WHO and SAGE will now review all recommendations for their strength and refrain from making ambiguous or weak recommendations.

3.5 Presentation of GRADE Tables

GRADE tables are available on the IVB website together with the published vaccine position papers. In the body of the text of position papers, GRADE tables are cited as footnotes. They may be updated when new evidence becomes available. If additional evidence provides further scientific support for the recommendations, the GRADE tables may be updated by WHO without updating the position paper. If new evidence arises that necessitates a re-evaluation of the vaccine position paper recommendations, a more formal updating process will be initiated.

To construct GRADE tables, data extraction and quality review at the level of individual studies will be undertaken. Documentation of this process should be available upon request, but will not be published on the IVB website as part of the GRADE tables. A review of the totality of evidence will be done for each question, with multiple tables if necessary data come from a variety of design approaches. GRADE tables will be presented in the context of the question of interest, the setting, and the final recommendation that arises from the full review. See Appendix 5 for an example of a GRADE table.

4. Vaccine Recommendation Development - Beyond Scoring the Evidence

4.1 Other considerations when making recommendations

Much work goes into information gathering and synthesis that forms the basis of vaccine recommendations and guidance. Even recommendations that do not utilize a formal GRADE evaluation are the product of data review, discussion, and deliberation. In addition to the scientific evidence base, other factors are important to the final recommendation. GRADE has outlined the following five parameters to be considered.

---

24 In the formal GRADE framework, a conditional recommendation is synonymous with a weak recommendation. For WHO and SAGE, a conditional recommendation is a strong recommendation constrained to a particular subpopulation or country after having met given criteria. For example, a second dose of measles vaccine in national schedules is not recommended until a country has achieved 80% coverage of the first dose of measles vaccine for the last 3 years.
Box 3. Considerations in recommendation development

1. Effectiveness and safety of the intervention, with evidence quality scored by e.g. GRADE or SCOPE
2. Disease epidemiology, clinical characteristics, and economic considerations, with evidence assessed by systematic literature review and critical appraisal
3. Balance between benefits and risks
4. Opportunities for capitalizing on prevailing societal values and preferences
5. Immunization program concerns (e.g. cold chain, logistics, vaccine availability, fit with the other vaccine schedules, ability to deliver, resources needed, impact on budget)
6. Social, cultural, ethical and legal issues

All of these factors are taken into consideration when recommendations are proposed. The question of costs and resource at the global level is particularly challenging, again highlighting the need for transparent review of the data and key issues so that countries may make their own decisions and prioritize health interventions. SAGE should consider the societal perspective when evaluating cost and resource implications. The decision to implement a program will always have trade-offs which must be carefully reviewed at the national level prior to adoption of recommendations. Societal values are critical factors that have a strong impact on the vaccine policy decisions, such as timing of vaccination, whether it is mandated, number of doses for optimal protection, and goals of a program. It is only after careful review of the evidence, risk-benefit ratio, values, and feasibility that recommendations are made.

4.2 Updating Recommendations

As the evidence and/or other factors change, recommendations will be updated to reflect the best data available. Position papers are reviewed periodically by WHO staff to determine when a full update of a position paper is warranted. In some cases, a brief update may be sufficient. For example, in 2007 WHO recommended adoption of rotavirus vaccine only in countries where effectiveness data were available. After such trials were conducted in Africa and Asia, WHO published a brief update in 2009 in which WHO recommended inclusion or rotavirus vaccine in all national schedules. When a full update is needed, SAGE comprehensively reviews the evidence to update recommendations.

4.3 Emergency situations

When outbreaks, natural disasters, or humanitarian emergencies occur, lack of time and context-specific data may necessitate a modified process for development of recommendations. Quick decisions may be needed that rely on indirect data interpreted using expert judgement. In such a situation, recommendations may be issued quickly and revised as the context changes and/or additional data are available.

25 For example: http://www.who.int/entity/wer/2009/wer8451_52.pdf
5. Conclusions

Evidence-based vaccine policy is critical for the development of global recommendations. Creating guidance for vaccine use with various products in different geographic and cultural contexts is a challenging endeavour that must have a foundation in the best scientific evidence available. The approach described above represents thinking from a range of immunization experts on how best to apply a rigorous approach to evaluating the quality of scientific evidence. Judgements will always be necessary in policy development, requiring transparency throughout the process. These guidelines are intended to increase transparency and standardization of the development of WHO vaccine recommendations development.
Appendix 1. Data Items to Consider for Extraction from Included Studies
Data extraction forms should be tailored for each systematic review. The data items below represent key fields to consider including in the data extraction form when appropriate

1. Study Author, Year
2. Name of reviewer
3. Date of review

4. Methods
   4.1. Study design
   4.2. Source of sample(s)
   4.3. Sampling method
   4.4. Sample size
   4.5. Entry criteria/exclusions
   4.6. Non-respondents/Loss to follow up
   4.7. Which parts of the study were prospective

5. Participants
   5.1. Setting
   5.2. Country
   5.3. Age (range and mean/median)
   5.4. Gender (% male/female)
   5.5. Ethnicity
   5.6. Control group
   5.7. Definition of controls
   5.8. Source of controls
   5.9. Comparability
      5.9.1. Potential confounders identified
      5.9.2. Baseline assessment of outcome variables

6. Group Allocation
   6.1. Randomization
      6.1.1. Sequence generation
      6.1.2. Allocation sequence concealment
      6.1.3. Blinding
   6.2. Allocation by
      6.2.1. Quasi-randomization
      6.2.2. Time differences
      6.2.3. Location differences
      6.2.4. Treatment decisions
      6.2.5. Participants' preferences
      6.2.6. On the basis of outcome
      6.2.7. Other important processes

7. Intervention
   7.1. Vaccine (formulation, dose, etc)
   7.2. Length of follow up

8. Outcomes
   8.1. How defined
8.2. Intervals at which outcomes were assessed
8.3. Validity
8.4. Reproducibility
8.5. Quality control
8.6. Missing/incomplete data
8.7. Selective reporting

9. **Summary of Results**

10. **Summary of Possible Risks of Bias**
    10.1. Selection Bias
    10.2. Information Bias
    10.3. Confounding
Appendix 2. Checklists for Reviewing Study Quality (Appendix 2 in full with all 4 tools inserted in the text is available in the version posted on the SAGE website)

Courtesy of the Critical Appraisal Skills Programme

Appendix 2a. Checklist for RCTs

RCT Appraisal Tool.pdf

Appendix 2b. Checklist for Case-Control Studies

Case Control 11 Questions.pdf

Appendix 2c. Checklist for Cohort Studies

Cohort 12 Questions.pdf

Appendix 2d. Checklist for Systematic Reviews

S.Reviews Appraisal Tool.pdf
### Appendix 3. Draft Summary Table for Evidence Review

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Location</th>
<th>Study Population</th>
<th>Vaccination/Intervention</th>
<th>Methods</th>
<th>Limitations/Potential Sources of Bias</th>
<th>Relevant Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 4. Rating the Quality of the Evidence

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Quality starting factor is first assigned base on Study Design</th>
<th>Quality score is lowered(^1) if</th>
<th>Quality score is raised(^1) if</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are very confident that the true effect lies close to that of the estimate of effect on health outcome (4)</td>
<td>Randomised trials</td>
<td>1) Limitation of design:(^2)</td>
<td>1) Strength of association:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 RR or OR &gt;2 (or &lt;0.5) in 2+ studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+2 RR or OR &gt;5 (or &lt;0.2) in 2+ studies</td>
</tr>
<tr>
<td>We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (3)</td>
<td>Observational studies, disease surveillance and post market safety surveillance data</td>
<td>2) Inconsistency:</td>
<td>2) Dose response (population based):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Evidence of decreased risk with increased vaccine coverage including evidence of reversal at population level (disease returns when vaccine coverage is decreased) population based dose response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+2 Very strong evidence of decreased risk with increased coverage</td>
</tr>
<tr>
<td>Our confidence in the estimate of the effect on the health outcome is limited. The true effect may be substantially different from the estimate of the effect (2)</td>
<td></td>
<td>3) Indirectness:(^2)</td>
<td>3) Antagonistic bias and confounding:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 All major confounders would have reduced the effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+1 Ability of design to control for confounding and avoid biases</td>
</tr>
<tr>
<td>We have very little confidence in the estimate of the effect on the health outcome. The true effect is likely to be substantially different from the estimate of effect (1)</td>
<td></td>
<td>4) Imprecision:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>Ability of design to control for confounding and avoid biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+2 If in addition to design, consistency across different settings, different investigators, and possibly different designs</td>
</tr>
</tbody>
</table>

\(^1\) = move up or down one grade (for example from high (4) to intermediate (3)), \(^2\) = move up or down two grades (for example from low(2) to high(4))

\(^2\) Should be commensurate with study design.
**Appendix 5. Template of a GRADE table used to score the quality of evidence.** Different study designs may be graded separately in different tables (e.g. RCT and observational studies) or only the highest quality design used while including consideration of other sources of evidence through footnotes and adjusting the score as appropriate.

<table>
<thead>
<tr>
<th>Question necessary for recommendation development: s</th>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Studies/Starting Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitation in study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconsistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirectioness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imprecision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength of association</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose-Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antagonistic bias and confounding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors decreasing confidence</td>
</tr>
<tr>
<td>Factors increasing confidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of Findings</th>
<th>Final Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>Conclusion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Final Score for Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td></td>
</tr>
<tr>
<td>Observational Studies</td>
<td></td>
</tr>
<tr>
<td><strong>FINAL SCORE</strong> (highest score)</td>
<td></td>
</tr>
</tbody>
</table>
CHOLERA VACCINES: Conclusions and recommendations of the October 2009 Meeting of SAGE
As published in Weekly Epidemiological Record - 11 December 2009

SAGE reached the following conclusions and made the following recommendations.

Cholera control should be a priority in areas with endemic cholera, since cholera outbreaks can disrupt health systems.

Given the availability of 2 oral cholera vaccines (one prequalified and the other pending prequalification) and new data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in areas where the disease is endemic and should be considered for use in areas at risk for outbreaks in conjunction with other prevention and control strategies. Vaccination should not disrupt the provision of other high priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented for immediate response while the longer term intervention of water and sanitation improvements, that involve large investments, should always be put into place.

Control of endemic cholera
Specific cholera vaccination strategies about whether, when, where and how to vaccinate should not be pre-scribed to countries since the appropriate strategies will differ by country, depending on the epidemiological pattern of cholera, the capacities of the immunization programme and health system, and other local factors.

SAGE accepted the ad hoc working group's suggestions that countries consider the following options for strategies to control endemic cholera through vaccination.

a) Scope of vaccination: In cholera-endemic countries, vaccination of the entire population is not warranted. Rather, vaccination should be targeted at high-risk areas and population groups.

b) Where to vaccinate: Vaccination should be targeted at areas where 2 of the following criteria have been met: (i) culture-confirmed cholera has been detected in at least 3 of the past 5 years; (ii) an incidence rate of cholera of at least 1/1000 population in any of these years has been recorded; (iii) if population-based incidence rates are not available, high-risk areas or groups have been identified using information collected from local public health officials.

c) Groups to target for vaccination: Although all age groups are vulnerable to cholera, priority should be given to high-risk groups if resources are limited. In situations where funding is limited, the primary targets for vaccination should be preschool-aged and school-aged children. Other groups that are especially vulnerable to severe disease and for which vaccines are not contraindicated can also be targeted, such as pregnant women and people infected with HIV. Countries should also consider vaccinating older age groups if funding is available. There is no reason to expect toxicity when killed cholera vaccines are used in pregnant women.

d) Vaccine-delivery strategies: Periodic mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns. Incorporating cholera vaccination into routine vaccination schedules can be an alternative or complementary to mass vaccination campaigns (for instance, to reach young children between campaigns).

e) Frequency of vaccination: Since the documented duration of significant protection for oral cholera vaccines is 2 years, it is recommended that initial vaccination with 2 doses be followed
by revaccination every second year. Once data on the longer-term efficacy of oral cholera vaccines become available, the recommended interval between initial and booster vaccinations could be extended.

**Control of cholera outbreaks**

Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas.

The need for predictive risk-assessment tools to help countries determine when pre-emptive vaccination should be used is urgent; these tools should be developed and field-tested as soon as possible.

Given the emergence of recent, large and prolonged outbreaks (for example, in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure; this could be implemented if the local infrastructure will support it after a thorough investigation of the current and historical epidemiological situation has been completed and geographical areas to be targeted have been clearly identified. The feasibility and impact of vaccination in halting ongoing outbreaks should be documented and the findings widely disseminated.

Providing appropriate treatment to people with cholera, implementing water and sanitation interventions, and mobilizing communities should remain the mainstay control measures during ongoing epidemics.

Pre-emptive or reactive vaccination should cover as many people eligible to receive the vaccine as possible (for example, children aged ≥1 or 2 years, depending on the vaccine) and should be conducted as quickly as possible.

While specific cholera surveillance studies are not recommended for every country and setting, it is strongly recommended that surveillance of microbiologically confirmed cases of cholera be instituted (for example, via regional or subregional networks) to determine the burden of disease and impact of vaccination and other interventions.

SAGE agreed that cholera vaccines need to be placed on the priority list for WHO prequalification so that the newly licensed low-cost Shanchol vaccine (Shantha Biotechnics Ltd., India), developed specifically for use in cholera-affected countries, could be accepted for review and if successful join Dukoral (SBL Vaccine, Sweden) on WHO’s list of prequalified cholera vaccines. The prequalification of Shanchol and other cholera vaccines in the future would remove a major roadblock to the increased use of oral vaccines in developing countries.
An Investment Case for the Accelerated Introduction of Oral Cholera Vaccines

Submitted by
the International Vaccine Institute to:

The Bill & Melinda Gates Foundation

Preliminary draft, not for citation or distribution
January 28, 2010
Executive Summary

The goal of this investment case is to provide a global evidence base for investing in oral cholera vaccines (OCVs) as part of a larger strategy that includes improvements to water and sanitation. These analyses should be useful to potential donors, cholera-affected countries, and vaccine manufacturers in making evidence-based decisions regarding the use of cholera vaccines based on currently available data.

With this investment case, we aim to answer the following questions:

- What is the global burden of cholera?
- What impact does the disease have on the larger economy?
- How should cholera vaccines be targeted for high risk populations?
- Which countries are likely to adopt cholera vaccines and when?
- For specific vaccination strategies, how many cases will be averted and lives saved?
- How much will the cholera vaccination program cost?
- How can a cholera vaccination program be financed?

The development of an investment case for cholera vaccines poses a number of challenges beginning in part due to the nature of the disease, which may strike anywhere with inadequate or damaged water and sanitation infrastructure. As an example, much of the investment case was developed under the assumption that cholera is largely absent from the Western Hemisphere. However, this was prior to a large outbreak that erupted in Haiti in October 2010. The Haitian Ministere de la Santa Publique et de la Population reported that this outbreak had caused 194,095 cumulative cases and 3,819 deaths by January 16, 2011 (PAHO 2011). At this time, it is uncertain whether cholera will continue to spread in the Western Hemisphere because infrastructure throughout the Hemisphere has improved considerably since the last outbreak in the early 1990s. This is indicative of the constantly evolving threat of cholera.

The situation in Haiti also demonstrates the difficulty in targeting cholera vaccines, since the incidence and severity of disease can shift dramatically over a short time period. While most other vaccines strive to provide universal coverage, the cholera vaccination program would most likely be targeted to high risk groups, identified by age, socioeconomic status, and geography. The optimal strategies are likely to vary from country to country and will not be fully determined until disease surveillance is improved in advance of vaccine introduction. As a result, this investment case presents four different options that serve as templates for consideration. These options provide upper and lower bounds on the potential costs and public health impacts of cholera vaccination programs; however, no single approach will be optimal for all countries.

Cholera global burden

A systematic analysis of the global cholera disease burden first identified cholera-endemic countries, as well as non-endemic countries that experience periodic outbreaks. Data were collected from the WHO Weekly Epidemiological Record, postings from the ProMED disease reporting system, the Global Infectious Disease and Epidemiology Network (GIDEON) database, and published articles using PubMed. Per the WHO Position Paper (2010), cholera-endemic countries were defined as those where cases of cholera have been reported in at least
three of the past five years (ending in 2007 or 2008). The analysis identified 51 cholera-endemic countries in Africa, Asia and the Middle East, and 18 additional (non-endemic) countries where cholera occurs sporadically, but which do not meet the definition of cholera-endemic.

The annual number of cholera cases in endemic countries that seek treatment in a health facility, either as an inpatient or outpatient, are estimated from population-based cholera surveillance studies conducted in Beira, Mozambique, Kolkata, India, and North Jakarta, Indonesia in the early 2000s (Deen et al., 2008). These rates were applied to countries in the same or neighboring regional sub-groupings (defined by WHO region and by level of mortality). Incidence rates – ranging from 0.1/1,000 (in wealthier countries) to 4.0/1,000 – were then applied to the population at risk for cholera in each country. To be conservative, we assumed zero incidence for the populations not considered at risk.

The average age-specific annual incidence rates ranged from 7.3/1,000 in infants to 0.9/1,000 in adults. The percentage of cases by age group was extrapolated from Kolkata data and may not be representative of populations lacking natural immunity from previous exposure, as in the case of Haiti during their ongoing outbreak. The annual number of cholera deaths was estimated from the average annual number of cases and average case fatality rates for each WHO region/mortality strata. Nearly three million cases of cholera are estimated to require treatment in health facilities each year on average. Most cholera cases take place on two continents – Africa and Asia, with Sub-Saharan Africa and the Indian sub-continent accounting for the majority of cases.

A map of cholera-endemic countries by their overall incidence rates (per the entire population) is shown in Figure ES1. The countries with the highest incidence (≥2/1,000 for the total population) include Bangladesh and a number of countries in Central and Eastern Africa. Most cases and deaths (72%) are estimated to occur in children 14 years old and younger. The age group with the greatest number of cases (37%) is 1-4 year olds, followed by 5-14 year olds (25%).

The severity of some of these outbreaks may be linked to new variant strains of V. cholerae O1 that began to emerge in the early 2000s, and now predominate in South/Southeast Asia and parts of Africa. These strains are of the El Tor biotype, but produce the cholera toxin formerly produced only by classical strains. There is evidence from Bangladesh that these hybrid strains are more virulent and cause more severe disease than the original El Tor strains (WHO 2008; Siddique, Nair et al. 2009). This strain is also responsible for the severe outbreak in Haiti.
Cholera is one of the few vaccine-preventable diseases that significantly affects countries’ economies, particularly in such industries as tourism and food exports. Oxford Economic Forecasting modeled the impact of a cholera outbreak on the economy of a southern African country with this investment case based on assessments of Peru’s cholera outbreak on its economy in the 1990’s (Suarez and Bradford 1993) and on an analysis of the impact of a European Union ban on fish imports from East African countries (Kimball, Wong et al. 2005). The impact of a large and prolonged cholera outbreak on the economy of this African country can result in a reduction of the Gross Domestic Production (GDP) by as much as 2.9% during the first year of the outbreak and 0.5% during the second year assuming an outbreak lasts nine months. These impacts are in addition to the direct costs of medical treatment, which average about US$9-16 by WHO region when accounting for both hospitalized and outpatient cases.

**Oral cholera vaccines**

There are two oral cholera vaccines currently available, both consisting of killed whole cells of *Vibrio cholerae*. Both vaccines require two doses and have estimated efficacies of 50-66% over three years with strong safety profiles. While there are live-attenuated cholera vaccines under development, these will not be available in the market for at least five years and thus are not considered in this investment case.

The whole cell-recombinant B subunit (WC-rBS) vaccine is produced by Crucell/SBL Vaccines and is sold as Dukoral®. It consists of a mix of whole cells along with the B (binding) subunit of the cholera toxin. The vaccine is licensed for persons two years and above, and is given in two doses with an interval of one to six weeks (three doses for 2-5 year olds). While the
vaccine has a cumulative efficacy over three years of around 50%, it is much more effective during the initial six months after delivery (84%). It has been used on a demonstration or pilot basis in several post-crisis situations to preempt cholera outbreaks, including in refugee camps in Darfur, Sudan and Uganda and following the 2004 tsunami in Aceh, Indonesia. Dukoral® is prequalified by WHO and may be easily procured in developing countries.

The other oral cholera vaccine is referred to as WC O1/O139, and does not contain the B subunit. Because this vaccine lacks the cholera toxin component, it can be produced at relatively lower cost and does not require a buffer solution to administer. The first version of this vaccine, ORC-Vax®, was developed in Vietnam and has been given to more than 10 million persons between 1997 and 2008, both in high-risk areas of Vietnam and following floods. This vaccine was subsequently modified to comply with WHO guidelines for GMP. A Phase 3 trial of the vaccine in slum areas of Kolkata, India has shown that it provides 77% protection at two years following vaccination (Sur, Lopez et al. 2009) and sustained protection of 66% over three years against culture-confirmed cholera. It is currently licensed and sold in Vietnam (as mORC-Vax® by VaBiotech and in India as Shan chol® by Shantha Biotechnics. Both manufacturers plan to sell the vaccine on the international market once the vaccines become WHO prequalified. Shanchol® is expected to be prequalified by mid-2011 while mORC-Vax® is not expected to be prequalified until 2014.

Proposed vaccination strategies

This investment case proposes a two-pronged approach towards the control of cholera through immunization including: 1) introduction of cholera vaccine into immunization programs in high-risk areas of cholera-endemic countries; and 2) preemptive or reactive vaccination to prevent the occurrence or spread of cholera outbreaks both in endemic and non-endemic countries through the use of a global cholera vaccine stockpile.

Because of the cost and logistical issues associated with universal cholera vaccination, it is assumed that programs would be targeted to areas and populations categorized as high risk. These include areas where cholera cases or outbreaks have taken place in the past or areas presumed to be at high risk, such as urban slums and low-income rural areas with poor access to safe water supply and adequate sanitation. Countries may also choose to target vaccination for other marginalized populations, such as refugees and internally-displaced persons. The vast majority of beneficiaries of cholera vaccination would therefore be the poor and marginalized groups in both urban and rural areas. The whole-cell O1/O139 vaccine is not currently licensed for use in infants and thus cannot be incorporated into the routine infant EPI schedule. Since the duration of vaccine efficacy is limited, it will be necessary to revaccinate at least primary and middle-school aged children as protection wanes. For these two reasons, mass vaccination campaigns should be the most practical and effective means of delivering cholera vaccines to endemic populations, using schools, markets, and other appropriate community settings as vaccination points. These analyses incorporate the assumption that revaccination will be required after three years. As data on the fourth and fifth year of follow-up become available from the trial, the recommended frequency of revaccination could be reevaluated.

Demand forecast

A demand forecast was conducted to determine which countries would introduce cholera vaccination to control endemic disease during 2014 and 2020, and how many doses they would use each year over time. The adoption schedule is based on a model consisting of variables

Preliminary draft, not for citation or distribution
used to represent disease burden, vaccination program infrastructure, history of adopting new vaccines, and experience with cholera vaccines and cholera surveillance.

A total of 33 countries and Zanzibar, a semi-autonomous group of islands that are part of Tanzania, are predicted to introduce cholera vaccination to control endemic disease between 2014 and 2020. This represents a majority of the 51 countries identified as cholera endemic in the disease burden analysis. The remaining 18 cholera endemic countries are projected to either forego the use of cholera vaccines or adopt cholera vaccination during 2021 or later. Twelve Indian states are predicted to adopt the vaccine between 2014 and 2020.

Phase 1 is defined to include the time period from 2014-2017 in which eleven countries are forecasted to introduce the vaccine. These countries are classified as Investment 1 countries and include the early adopter countries of Bangladesh, India (selected states), Uganda, Mozambique, and Tanzania – all of which have had experience with cholera vaccine demonstration projects or clinical trials, or have expressed interest in introducing the vaccine. The remaining 22 countries are forecasted to adopt during Phase 2, which is between 2018 and 2020. These countries are defined as Investment 2 countries. Of the 33 countries included in this investment case, twenty-six (79%) are in the AFR region, five (15%) are in the Southeast Asian region, and two are in the Eastern Mediterranean region. Twenty-six (79%) of the countries are GAVI-eligible (as of 2010) and the remaining are either not currently eligible or are expected to graduate from GAVI eligibility based on their revised eligibility criteria.

The analysis includes four potential vaccination programs. In the Large Target scenario, all persons living in urban slums and rural areas lacking access to improved water sources would be targeted for vaccination. The Small Target scenario would limit vaccination to 50% of urban slum dwellers and rural residents without access to improved water supply based on the assumption that some subpopulations would be at significantly greater risk than others. For each target scenario, we present two options for targeting age groups: children 1-14 years of age, and all persons one year and above. Cholera vaccine coverage rates are estimated by country based on their current measles vaccination coverage rates. The population targeted for vaccination in the 33 target countries ranges from 113 million to 637 million, depending on the program option. In practice, each country should tailor their vaccination programs in consideration of all available data and consultations with local stakeholders.

This investment case also estimates requirements of a global stockpile that countries could use to prevent outbreaks from occurring (e.g., following extensive flooding or other natural disasters) or from spreading to new areas. The analysis assumes that stockpile vaccines would be used by both endemic and non-endemic countries to prevent outbreaks, such as following floods or cyclones, or to control currently occurring outbreaks from spreading to other countries or to new areas within their countries. Since outbreaks tend to strike all age groups, mass vaccination campaigns for outbreak control would cover all ages eligible for the vaccine. The appropriate stockpile size was estimated to be about 10 million doses based on cholera cases reported from 2000-2008 as well as operational data from the meningococcal vaccine stockpile. However, the size of the stockpile should be increased gradually as experience is gained.

Vaccine supply and pricing

There are currently three producers of oral cholera vaccines and production capacity is at present, quite limited. Crucell/SBL Vaccines is the sole producer of Dukoral®, the WC-rBS vaccine already prequalified by WHO. The current production capacity of Dukoral® is around 10
million doses per year. Shantha Biotechnics produces the O1/O139 WC vaccine marketed as Shanchol®; the current production capacity is around 1.5 to 2 million doses, but is assumed to increase to 25-30 million doses per year by 2014. The other producer of the modified O1/O139 WC vaccine, VaBiotech in Vietnam, has a production capacity of 10 million doses per year for its mORC-Vax® vaccine; however, its vaccine will not be prequalified until 2014 at the earliest.

Assuming supply capacity of prequalified Shanchol® and mORC-Vax® can expand to 40 million doses by 2014, this would be sufficient to cover the proposed stockpile and Small Target program for children ages 1-14 until 2020 at which time additional facilities would need to be constructed. For the other demand forecast scenarios, additional facilities would need to be completed by 2014-16. The greatest gap between projected supply and demand – up to nearly 300 million doses per year – would be realized if all 33 countries adopted the strategy of vaccinating all eligible ages in the Large Target areas. However, this scenario is not very likely. As countries indicate interest in introducing cholera vaccine and make plans for doing so, and as donors indicate their interest in providing financial support, more precise forecasting can be conducted to guide both current and potentially new suppliers in making decisions on whether and how to meet the anticipated demand.

Shantha has committed to a public sector price of $1.85 per dose for Shanchol®. The current price of the Vietnamese vaccine mORC-Vax® is $0.75 for the EPI program and $1.00 for the private sector. These prices may increase to meet the production and quality control requirements for WHO prequalification. In the analysis, it is assumed that the average public sector price for O1/O139 WC vaccines would decline to $1.45 per dose, starting in 2014, as projected demand increases. This estimated price reduction assumes that there will be some increases in production efficiency and economies of scale, and potentially increased competition from new producers entering the market.

Costs and financing needs

The total cost of providing cholera vaccines requires assumptions for the price paid ($1.45 per dose), freight and insurance ($0.22 per dose), delivery costs ($0.60 per dose), and vaccine wastage (5%). During Phase 1 from 2014-17, the cost of introducing the vaccine into 11 countries would be between $107 million if only children are vaccinated in the Small Target program to $599 million if all ages above 1 are vaccinated in the Large Target. As the remaining 22 countries adopt the vaccine between 2018 and 2020, the program costs increase substantially. The total costs range from $350 million for the small target for children (ages 1-14) to $1.8 billion for the large target for all ages (above 1 year) for the entire seven-year period.

Financing for cholera vaccination could come from several potential sources, including external partners and internal (government) sources. One possible source of financing is GAVI. Due to the uncertainty about whether and when GAVI will begin providing support for cholera vaccine introduction, other sources of financing should be sought as well. Potential external sources of financing could be development banks, bilateral donors, and regional donors.

In addition, governments usually provide funding for at least a proportion of the costs of introducing a new vaccine, including service delivery costs. Ministries of Health could advocate for the funding to introduce cholera vaccine in high-risk populations on the grounds that control of outbreaks is costly both in terms of program manager time and expenses required to manage these events and to treat infected persons. Local governments or local NGOs may also be interested in introducing the vaccine if their populations are living in at-risk areas. Private industry (e.g., seafood or tourism industries) may consider contributing to vaccination efforts if
they perceive that cholera outbreaks have a negative impact on the demand for their goods and services. Additionally, some health insurance plans partially or fully cover the costs of vaccines.

**Expected public health impact of oral cholera vaccines**

The introduction of oral cholera vaccine would have an important impact on morbidity and mortality. It will also result in medical cost savings as the number of cases will be reduced. The population impact of vaccination is based on a deterministic dynamic model, which estimates the population-level impact of vaccination based on data from a clinical trial in Bangladesh. This model estimates the number of cholera cases with and without introduction of cholera vaccines. In particular, it measures the impact of vaccination programs for: 1) children aged 1-14 years; and 2) all ages greater than 1 year by WHO sub-region. This model incorporates herd effects of cholera vaccination – i.e. the vaccine provides indirect protection to non-vaccinated members of the population as well as additional protection to the vaccinated. These findings have been reaffirmed in two recent studies of cholera vaccine herd protection conducted in Kolkata, India and Zanzibar. The baseline disease burden and vaccine coverage in each country is based on the results presented in the disease burden and demand forecast appendices.

The projected impacts of each of the four potential cholera vaccination programs are shown in Table ES1. During Phase 1, from 2014-17, the vaccination program in endemic countries would avert 265,000 – 641,000 cholera cases and 7,800 – 18,700 deaths depending on the vaccination programs chosen. Assuming that the program is expanded to include Investment 2 countries between 2018-20, an additional 850,000 – 2.2 million cases and 28,000 – 62,000 deaths would be averted. The cumulative cases and deaths averted via vaccination are summarized in Figure ES2, assuming both Investments 1 and 2 countries adopt cholera vaccines..Overall, the potential programs would avert between 7.7 - 18.9 million cases and 260,000 – 620,000 deaths over the period of 2014-2030. In addition, cholera vaccination programs would avert $6.5 - 16 million per year in direct medical costs once all countries have adopted cholera vaccines.

**Economic analysis**

Cholera vaccine introduction through preventive campaigns is cost-effective when compared with well-established benchmarks such as those from the 2002 World Health Report. Vaccination of children aged 1-14 years is broadly considered very cost-effective with cost-effectiveness ratios varying between $148 per DALY averted in African countries and $359 per DALY averted in Southeast Asian countries. Vaccination of all ages above 1 year is more costly per DALY averted but is still very cost-effective in many countries with an average cost-effectiveness ratio varying from $285 per DALY averted in African countries to $889 per DALY averted in Southeast Asian countries. The diminished efficiency of expanding vaccination efforts from children to all ages is shown clearly in Table ES1. While costs are about 240% greater for all ages programs relative to children-only programs, only about 18% more cases are averted. This is due to both the higher incidence rates among children and the herd protection impact of the vaccination program.
### Table ES1. Projected costs and impacts of cholera vaccination strategies

#### Large Target

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged 1-14 years</td>
<td>2014-2017</td>
<td>110</td>
<td>52</td>
<td>183</td>
<td>64</td>
<td>0.8</td>
<td>20</td>
<td>359</td>
</tr>
<tr>
<td></td>
<td>2018-2020</td>
<td>228</td>
<td>109</td>
<td>380</td>
<td>136</td>
<td>1.9</td>
<td>58</td>
<td>272</td>
</tr>
<tr>
<td></td>
<td>2021-2030</td>
<td>1,301</td>
<td>620</td>
<td>2,170</td>
<td>781</td>
<td>13.4</td>
<td>457</td>
<td>195</td>
</tr>
<tr>
<td>Total (2014-2030)</td>
<td>1,639</td>
<td>780</td>
<td>2,733</td>
<td>981</td>
<td>16.1</td>
<td></td>
<td>535</td>
<td>213</td>
</tr>
<tr>
<td>All persons aged 1 year and above</td>
<td>2014-2017</td>
<td>266</td>
<td>127</td>
<td>444</td>
<td>156</td>
<td>1.0</td>
<td>24</td>
<td>755</td>
</tr>
<tr>
<td></td>
<td>2018-2020</td>
<td>521</td>
<td>248</td>
<td>868</td>
<td>309</td>
<td>2.2</td>
<td>68</td>
<td>572</td>
</tr>
<tr>
<td></td>
<td>2021-2030</td>
<td>3,095</td>
<td>1,474</td>
<td>5,162</td>
<td>1,857</td>
<td>15.7</td>
<td>531</td>
<td>442</td>
</tr>
<tr>
<td>Total (2014-2030)</td>
<td>3,882</td>
<td>1,849</td>
<td>6,474</td>
<td>2,322</td>
<td>18.9</td>
<td></td>
<td>623</td>
<td>475</td>
</tr>
</tbody>
</table>

#### Small Target

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged 1-14 years</td>
<td>2014-2017</td>
<td>47</td>
<td>23</td>
<td>79</td>
<td>28</td>
<td>0.3</td>
<td>9</td>
<td>359</td>
</tr>
<tr>
<td></td>
<td>2018-2020</td>
<td>109</td>
<td>52</td>
<td>181</td>
<td>65</td>
<td>0.9</td>
<td>28</td>
<td>272</td>
</tr>
<tr>
<td></td>
<td>2021-2030</td>
<td>633</td>
<td>301</td>
<td>1,055</td>
<td>380</td>
<td>6.5</td>
<td>225</td>
<td>195</td>
</tr>
<tr>
<td>Total (2014-2030)</td>
<td>789</td>
<td>376</td>
<td>1,315</td>
<td>472</td>
<td>7.7</td>
<td></td>
<td>262</td>
<td>213</td>
</tr>
<tr>
<td>All persons aged 1 year and above</td>
<td>2014-2017</td>
<td>112</td>
<td>53</td>
<td>187</td>
<td>66</td>
<td>0.4</td>
<td>11</td>
<td>755</td>
</tr>
<tr>
<td></td>
<td>2018-2020</td>
<td>244</td>
<td>116</td>
<td>407</td>
<td>145</td>
<td>1.0</td>
<td>33</td>
<td>572</td>
</tr>
<tr>
<td></td>
<td>2021-2030</td>
<td>1,490</td>
<td>709</td>
<td>2,484</td>
<td>894</td>
<td>7.5</td>
<td>261</td>
<td>442</td>
</tr>
<tr>
<td>Total (2014-2030)</td>
<td>1,846</td>
<td>879</td>
<td>3,078</td>
<td>1,105</td>
<td>9.0</td>
<td></td>
<td>304</td>
<td>475</td>
</tr>
</tbody>
</table>
Figure ES2. Cumulative cases and deaths averted through cholera vaccination, Investments 1 and 2 countries

a. Large Target (urban slums and rural populations without safe water), all ages 1+ years

b. Large Target, age 1-14 years only

c. Small Target (50% of at-risk populations), all ages 1+ years

d. Small Target: age 1-14 years only
A sensitivity analysis was run to estimate whether variation in variable values would affect the results. Key drivers of uncertainty in the cost-effectiveness analysis are cholera incidence, the case fatality rate, herd protection effects, and vaccination costs. However, even if the four variables are varied by a wide range, the cost per DALY for children continues to fall within the “very cost-effective” range and falls within the “cost-effective” range for the all ages option.

Finally, the introduction of oral cholera vaccines is a good intervention for reducing health inequities since cholera strikes mainly the very poor populations in countries (i.e., those with little access to clean water, adequate sanitation and decent health services). These populations live in urban slums and rural areas with poor sanitation and access to improved water sources. Because populations at-risk for cholera have limited access to health services, persons infected with cholera are less likely to receive treatment in a timely fashion. The people most likely to die from cholera are those who don’t reach a health facility in time either because of distance, inability to pay, or social taboos (Sack et al. 2009). Many countries have proven their ability to reach even the very poor and persons with restrictive mobility with vaccination since these services can be provided through campaigns and mobile services in hard-to-reach areas without routine health services. In addition, access to water and sanitation infrastructure tends to lag for the poor relative to the wealthy. The introduction of vaccines will prevent cholera cases over the short and medium term until improvements in water and sanitation reach these disadvantaged populations.