Report of the Strategic Advisory Group of Experts (SAGE)

Geneva, 27–29 October 2004

Immunization, Vaccines and Biologicals

World Health Organization
Report of the Strategic Advisory Group of Experts (SAGE)

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<th>Description</th>
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<tbody>
<tr>
<td>AACPE</td>
<td>Ad-hoc Advisory Committee on Polio Eradication</td>
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<td>AD</td>
<td>autodisable (syringes)</td>
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<td>ADIP</td>
<td>accelerated development and introduction plan</td>
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<td>AEFI</td>
<td>adverse events following immunization</td>
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<td>CRS</td>
<td>congenital rubella syndrome</td>
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<td>DCVM</td>
<td>Developing Countries Vaccine Manufacturers</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>DQA</td>
<td>data quality audit</td>
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<tr>
<td>DTP</td>
<td>diphtheria-tetanus-pertussis (vaccine)</td>
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<tr>
<td>EMEA</td>
<td>European Medecines Agency, United Kingdom</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>ETEC</td>
<td>enterotoxigenic <em>Escherichia coli</em></td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FSP</td>
<td>Financial Sustainability Plan</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>GDP</td>
<td>gross domestic product</td>
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<td>GIVS</td>
<td>Global Immunization Vision and Strategies</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<tr>
<td>IPV</td>
<td>inactivated poliovirus vaccine</td>
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<td>IFFIIm</td>
<td>International Finance Facility for Immunization</td>
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<td>IMCI</td>
<td>integrated management of childhood illness</td>
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<tr>
<td>IP</td>
<td>intellectual property</td>
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<td>IPR</td>
<td>intellectual property rights</td>
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<td>IVB</td>
<td>Immunization, Vaccines and Biologicals (WHO Department)</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>IVR</td>
<td>Initiative for Vaccine Research (WHO Department)</td>
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<td>MDGs</td>
<td>Millenium Development Goals</td>
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<tr>
<td>mOPV</td>
<td>monovalent oral polio vaccine</td>
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<td>MVP</td>
<td>Meningitis Vaccine Project</td>
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<tr>
<td>NIBSC</td>
<td>National Institute for Biological Standards and Control, United Kingdom</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NRA</td>
<td>national regulatory authority</td>
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<td>ODA</td>
<td>official development assistance</td>
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<tr>
<td>OPV</td>
<td>oral poliovirus vaccine</td>
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<td>RAPID</td>
<td>Rotavirus Action Plan for Immunization and Development</td>
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<td>RED</td>
<td>reaching every district</td>
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<tr>
<td>RVP</td>
<td>Rotavirus Vaccine Project</td>
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<td>SIA</td>
<td>supplementary immunization activity/activities</td>
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<td>SII</td>
<td>Serum Institute of India</td>
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<td>SWAps</td>
<td>sector-wide approaches</td>
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<td>TAG</td>
<td>technical advisory group</td>
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<td>TRIPS</td>
<td>Trade-Related Aspects of Intellectual Property Rights</td>
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<tr>
<td>VAPP</td>
<td>vaccine-associated paralytic polio</td>
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<tr>
<td>cVDPV</td>
<td>circulating vaccine-derived poliovirus</td>
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<tr>
<td>iVDPV</td>
<td>immunodeficient vaccine-derived poliovirus</td>
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Summary of discussions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals

The Strategic Advisory Group of Experts (SAGE) was established in 1999 by the Director-General of WHO to provide guidance on the work of the Department of Immunization, Vaccines and Biologicals (IVB). SAGE held its sixth meeting on 27–29 October 2004 in Geneva, Switzerland. The following summarizes the principal points raised and the recommendations made by SAGE.

Global Immunization Vision and Strategies

The context in which national immunization programmes function has changed dramatically: globally, the expanded range of traditional and new vaccines used in immunization programmes is protecting more children against disease; and many more innovations aimed at reducing disease burden are in the pipeline. The Global Polio Eradication Initiative is now tackling the last remaining foci of wild poliovirus transmission and looking ahead to certification and cessation of oral poliovirus vaccine (OPV) use. Significant progress is also being made in several countries in reducing mortality caused by measles.

However, four global immunization challenges must be addressed: how to sustain the gains, both managerially and financially; how to ensure equitable access to new vaccines; how to control diseases such as avian flu, severe acute respiratory syndrome (SARS) and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS); and how to finance the more costly new vaccines currently available as well as those shortly to come forward from clinical trials. These new vaccines present an opportunity to scale up immunization activities, to reach everyone, and to increase the range of diseases prevented by vaccination.

Furthermore, the scope of the financial resources being made available through initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, or the "3x5" drive to massively increase provision of antiretrovirals by the end of 2005, is also changing the global picture. These resources meet urgent needs but simultaneously create infrastructure and administrative challenges. The neediest countries are also those least well equipped to put aid into practice. Together, these issues are driving the development of the joint WHO/UNICEF Global Immunization Vision and Strategies (GIVS) for 2005–2015.

SAGE commended the GIVS document as an important statement of intentions and a starting point for sharing ambitions among immunization partners. The document addresses the importance of immunization within the health system context, outlining opportunities for integration of immunization delivery with other primary health

1 At that time, the Department of Vaccines and Biologicals.
care interventions in a sustainable and cost-effective way. Translation of GIVS into action will require substantial additional resources and considerable advocacy. Governing bodies' orientation and endorsement will be sought through presentation of the GIVS document to the executive boards of WHO and UNICEF in January 2005 and thereafter to the World Health Assembly.

Work remains on defining the structure and format, and on agreeing to measurement and implementation parameters, including quantitative objectives, targets and milestones in further consultation with countries and partners. SAGE would be pleased to give input to such further work, and strongly endorses the process.

SAGE **recommended** that, through its regional offices, WHO should ensure a full process of consultation at country and regional level on GIVS; in early 2005, SAGE should review a revised version of the GIVS document which will incorporate its comments; the GIVS document should describe the additional accompanying documents to be developed later (i.e. guidelines for countries to prepare the strategic plan for GIVS to be fully operational); an estimation of the cost implications; and an outline of the tools that will be used to measure the process and outcomes.

**Improving access to immunization services in Africa**

SAGE noted the progress made in many African countries in raising routine immunization coverage through application of the reaching every district (RED) approach; appropriate health infrastructure is needed to sustain the gains made and reach more children. SAGE reiterated its previous recommendations on integration of other interventions with immunization delivery services. However, while noting the progress achieved, SAGE expressed concerns about the sustainability and intensity of activities required by African countries to fully maximize the RED approach.

SAGE **recommended** that WHO should advocate globally to assure the additional resources required to fully implement and sustain the RED strategy so as to ensure a stable transition from the polio infrastructure to a more integrated immunization and child health infrastructure. The RED strategy should be integrated into national plans of action for immunization with especial emphasis on implementation and expansion in low-performing countries. The WHO Regional Office for Africa should rigorously monitor the progress of the RED strategy implementation in each target country in the region, giving the required support to solve problems and document needs.

**Financial challenges for immunization services**

Financial sustainability planning provides very useful information for global-level strategic planning. The financial sustainability assessments conducted in 22 countries mid-way through the period of funding by the Global Alliance for Vaccines and Immunization (GAVI) have produced valuable data showing the increase in immunization financing, both from domestic resources and bilateral donors' support. Also highlighted were the funding gaps and the impact of those gaps on the introduction of new vaccines. Where countries are not yet financially self-reliant, especially those with very low gross domestic products, substantial international support such as the proposed International Finance Facility for Immunization (IFFIm) will be essential. The Inter-Agency Coordinating Committees will play a critical
role in assuring national financial self-sufficiency; capacity-strengthening will be critical in this regard.

**SAGE recommended** that WHO and UNICEF should work with all partners to craft an advocacy strategy for fund-raising that makes the investment case for immunization, obtaining political commitment within each country, as well as developing strategies for financing. WHO should continue to help improve countries’ ability to plan financially for immunization; increase the predictability of international funds for immunization by working with partners on new financing options and sources such as debt relief, GAVI, IFFIm, and carrying out analytical work on immunization financing; and help improve national decision-making and ownership, as well as capacity in financial management.

**Synchronous global cessation of oral poliovirus vaccine (OPV) use after Global Polio Eradication**

Following the interruption of wild poliovirus transmission globally, the continued introduction of the attenuated poliovirus strains of OPV will be incompatible with the goal of polio eradication. Individual vaccine-associated paralytic poliomyelitis cases would occur at a predictable rate (i.e. 250–500 cases per year) in addition to polio outbreaks due to circulating vaccine-derived polioviruses (cVDPV). Given that surveillance sensitivity and population immunity can be expected to decline with the reduction in external financing that will accompany global eradication, a relatively narrow window of opportunity will exist for stopping the routine use of OPV as safely as possible.

SAGE recognized, however, that OPV cessation can only occur if six stringent conditions are achieved, two of which have substantial implications for national immunization managers and programmes: the process and verification of internationally synchronized OPV cessation; and post-OPV immunization policies. SAGE also noted the importance of rapidly developing new products to facilitate OPV cessation (i.e. monovalent OPV). SAGE members reaffirmed that many low-income countries continue to expect the cessation of all polio immunization, and do not consider there to be compelling data to support universal use of inactivated poliovirus vaccine (IPV). SAGE noted the need to fully engage the broader scientific community, the developing country manufacturers and the national regulatory authorities in deliberations on future IPV use so that they might plan accordingly. Recognizing that the risk of cVDPV following monovalent OPV response could increase over time, SAGE encouraged continued work to characterize these risks and explore the potential utility of other outbreak response strategies that include IPV and, potentially, antiviral agents. SAGE reaffirmed the importance of biocontainment prior to OPV cessation.

**SAGE recommended** that, to assist its deliberations on post-OPV immunization policy, WHO should keep it fully informed of: all related policy decisions made by the oversight groups responsible for other aspects of the OPV cessation work (i.e. the Ad-hoc Advisory Committee on Polio Eradication, the Global Commission on Certification of Polio Eradication, the Biosafety Advisory Group); the evolving understanding of the nature and magnitude of the risks of circulating polioviruses following interruption of wild poliovirus transmission and OPV cessation; and the outcomes of the continuing work to model these risks over time. WHO should continue to work with manufacturers and national regulatory authorities to accelerate
access to monovalent strains of OPV for use in the vaccine stockpile needed prior to OPV cessation. WHO should work with partners to establish a mechanism for rapidly evaluating the candidate IPV vaccines that have been developed using Sabin strains (i.e. S-IPV) and, if appropriate, ensure the capacity to transfer such technology, particularly to new manufacturers of IPV. To facilitate national decision-making on long-term immunization policy, WHO should, by the end of 2005, develop explicit guidance for OPV-using countries on the impact of IPV on "post-OPV" risks and the implications of IPV use from the financial, programmatic and opportunity perspectives.

Research and development

SAGE was updated on the development of vaccines against malaria, tuberculosis, HIV, and SARS, as well as on new technology, such as the measles aerosol, and areas of accelerated development, such as rotavirus and pneumococcal vaccines.

To further strengthen WHO’s efforts in vaccine research and development, SAGE recommended that the following areas of work should be reassessed: the work on cross-cutting issues and the role of the Network of Developing Countries Regulators in supporting and advancing some of the development projects. WHO should identify which other advisory committees, apart from the one overseeing the work of the Meningitis Vaccine Project (MVP), could possibly benefit from the participation of SAGE members.

Meningococcal meningitis: the Meningitis Vaccine Project (MVP)

In 2003, SAGE had requested a follow-up presentation on conjugate meningococcal vaccine development issues. Updates were provided on: the development of a monovalent A conjugate vaccine in India; the recommendations made by the MVP clinical advisory group; the proposed timelines for the project; work with the regions; and information gathered on the distribution of Neisseria meningitidis serogroup across Africa. SAGE praised the work accomplished; the MVP presents a useful model in terms of the development of a vaccine tailor-made for Africa by a developing country manufacturer.

SAGE recommended that, at the SAGE meeting in 2005, WHO should submit a report on the epidemiology of meningococcal serogroups in Africa. WHO should particularly strive to obtain more data on the epidemiology of the meningococcal serogroup in Nigeria where currently no laboratory data are being collected by the African network.

Intellectual property rights and vaccines

The global context for vaccine research and manufacture has undergone rapid and significant change, with intellectual property rights potentially impacting many IVB goals and activities such as promotion of research and development on most-needed vaccines; the introduction of new vaccines and technologies in developing countries; and the promotion of technology transfer and competitive supply of vaccines. Solutions such as "patent pooling" may provide some answers, but much work remains to be done, for example in collecting information on the impact of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreements on pharmaceuticals and vaccine patents to come into force in 2005. IVB has a useful
role to play in collecting and disseminating information, such as the effects of intellectual property rights on access to the most-needed vaccines in developing countries, and in fostering a collaborative network.

**SAGE recommended** that, to facilitate developing countries’ access to new inventions, WHO should clearly articulate the responsibilities of both private- and public-sector intellectual property owners to consider developing-country needs in the management of their intellectual property. WHO should continue to take an active role in collecting and analysing information on how intellectual property rights may affect access to vaccines and vaccine development, with the Commission on Intellectual Property and Public Health, to ensure that these issues are reflected in the Commission’s report to be submitted in February 2006. WHO should be proactive in helping to resolve the issue of intellectual property rights over reverse genetics for influenza vaccine and generally encourage dialogue and partnership to resolve intellectual property issues for most-needed vaccines, with emphasis on the public health concerns.

**Challenges for rotavirus vaccine**

Several vaccine candidates, at various stages of readiness, are under review and testing. Two (Rotarix™ and RotaTeq™) are in late-stage development with clinical trials of efficacy and safety conducted in Latin America and Asia (Rotarix™), and in the United States, Europe, and some countries in Central and Latin America (RotaTeq™). Phase III results for both vaccines are imminent. Through the RAPID² public-private partnership convened by WHO in 2000, trials are also in progress in Bangladesh and South Africa to address the issues that are important to developing countries, such as the Expanded Programme on Immunization (EPI) schedule or OPV interaction with rotavirus vaccines. Surveillance networks globally have continued to expand, including the network in Africa which has reached 14 countries. IVB has important roles to play in supporting early-stage vaccine candidates; strengthening national regulatory authorities so they can adequately evaluate and license rotavirus vaccines; developing guidelines for production of live oral rotavirus vaccines; and examining safety issues.

**SAGE recommended** that WHO keep it informed of progress in assessing the effectiveness and safety of the vaccines both in clinical trials and in plans for post-marketing surveillance. Information was specifically requested on the methodology for intussusception surveillance, in different settings where rotavirus vaccine is most needed and would be used. In addition, WHO should continue to work with the alternative vaccine candidates and the emerging country manufacturers.

**Measles mortality reduction and rubella control**

The global goal is sustainable measles mortality reduction, with 45 target countries identified for priority action, mostly in Africa and South-East Asia. These countries are those with the weakest health systems, lowest routine coverage and 90% of the measles disease burden. The strategy for mortality reduction is: to strengthen routine immunization services through the RED approach; provide all children with a second opportunity for measles immunization; conduct surveillance to monitor progress; and assure appropriate case management. Supplementary immunization activities

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have caught many previously unreached children, but nine countries, including high-burden, high-population countries – India, Nigeria and Pakistan - have not yet started. In addition, the burden of rubella and congenital rubella syndrome must be assessed, and rubella vaccination policies and strategies need to be developed.

SAGE recommended that, at the SAGE meeting in 2005, WHO should present a report from the regions on progress with rubella vaccine introduction; a report on the optimum age for the first measles dose in the light of current research and findings; and the potential benefits, risks, regulatory issues and experience to date with the development of a combined yellow fever-measles vaccine. WHO should support efforts to implement measles mortality reduction strategies in the large, measles-endemic countries, with an ultimate aim of encouraging the two remaining WHO regions (the African Region and the South-East Asian Region) to establish measles elimination goals.

**Strategic challenges for Haemophilus influenzae type b**

Currently 88 countries have introduced Hib vaccine, including 8 African countries. There are several barriers to its introduction, including its high price, limited supply of Hib-containing pentavalent vaccine, and uncertainties about the true burden of disease in Asia. However, new data from a controlled trial in Indonesia show a substantial impact of Hib vaccine in preventing meningitis. Discussion highlighted the importance of effective communication of what is already known about vaccine impact and increasing competition among manufacturers to decrease vaccine price. WHO has an important role to play with countries in strengthening evidence-based decision-making, implementing recommended approaches, and working to raise awareness and communicate the value of the Hib vaccine. SAGE reviewed the status of GAVI funding of Hib vaccine introduction in 15 countries. The transition to self-financing in these countries has not yet been made. Supply chain issues and financing structures are important areas for resolution.

SAGE recommended that WHO should consult with countries in all regions, with particular emphasis in the WHO African Region, on their use of Hib vaccine. These consultations should aim at providing comprehensive information on existing evidence about Hib disease burden and the impact of Hib immunization in preventing meningitis and pneumonia. By the end of 2005, WHO should provide clarification on its recommendations for vaccine use in several geographical areas.

**Quality challenges: acceptability of cell substrates**

A broad range of cell substrates is available for production of biologicals including vaccines, out of which regulatory authorities for vaccine production accept only a certain number. Progress in vaccine development is currently limited by the cell types that can be used. One aspect of WHO’s role is to establish norms and standards for cell substrates for vaccines; specifications are already in place for primary, diploid and continuous cell lines.

Risk-reduction strategies are applied to all cells in the areas of good manufacturing practices and characteristics of the source materials. SAGE stressed the vital importance of safety considerations over the long term in all aspects of the
immunization programme. Review is in progress to assess the extent of theoretical risk posed by residual DNA from cell substrates. Currently, this research is conducted mainly by industry. SAGE commented that such expertise should also reside in the regulatory bodies, with research conducted by academic bodies, and this would require support. Safety and broader acceptability issues should be impartially considered.

**SAGE recommended** that WHO establish a working group to recommend and coordinate scientific studies relating to the safety of new continuous cells substrates, and to discuss their acceptability.

**Regulatory and safety challenges**

The national regulatory authorities play an essential role in regulatory and safety issues. Supported by a national regulatory system, the national regulatory authority ideally fulfils six critical functions defined by WHO: licensing, post-marketing surveillance, lot release, laboratory access, regulatory inspections and authorization/evaluation of clinical trials. The responsibility for regulation of new vaccines is increasingly borne by the receiving country (usually developing countries), rather than the producing country. This places increased responsibility on the national regulatory authorities of developing countries, which do not have the experience to make the necessary assessments. As growing numbers of candidate vaccines reach clinical trial stage, more trials are being conducted in developing countries, again making quality control demands of the regulatory authorities that they have to meet.

The Developing Countries Vaccine Regulators Network has been established in nine countries to promote and support capacity-strengthening in working towards the global use of vaccines of assured quality. WHO has also been active in promoting vaccine safety information through the Vaccine Safety Net in addition to the information disseminated through the web site of the Global Advisory Committee on Vaccine Safety (GACVS). SAGE commended WHO’s work on the strengthening and maintaining of vaccine quality, safety and regulation, as well as its capacity-building efforts with national regulatory authorities to ensure that they fully exercise their critical regulatory oversight including adequate post-marketing surveillance.

**SAGE recommended** that WHO further strengthen its work on the core functions of quality, safety and regulatory issues, continuing its capacity-building work with national regulatory authorities to ensure that they exercise all their critical regulatory functions. WHO should consider increasing the attention paid to post-marketing surveillance, and to the epidemiological capacity-building for such surveillance. This effort could also include promoting the use of regional networks of national regulatory authorities. WHO should develop a strategy to strengthen regulatory research as part of the independent assessment of product safety. WHO should continue its work towards the global use of vaccines of assured quality and strengthen its efforts to communicate the value and benefits of vaccines and their safety through resources such as the GACVS web site and the Vaccine Safety Net.

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4 http://www.who.int/vaccine_safety/en/
The sixth meeting of the Strategic Advisory Group of Experts (SAGE) to the Department of Immunization, Vaccines and Biologicals (IVB) took place on 27–29 October 2004 at WHO headquarters in Geneva, Switzerland. Dr Jean-Marie Okwo-Bele, Director of the department, welcomed participants, presented Dr Merceline Dahl-Regis as the chair of SAGE and asked the SAGE members to introduce themselves.

1. Opening of the meeting

Joy Phumaphi, the Assistant Director-General of the Family and Community Health cluster (FCH), touched on the many immunization successes including: the reduction in polio cases from 350 000 in 1988 to 784 in only six countries in 2003; a decline of 30% in measles mortality globally, and 35% in the African Region; and the rapid decline in neonatal tetanus mortality, from levels around 800 000 in the 1980s to 180 000 in 2002.

She also pointed out that vaccine development has markedly accelerated: 16 new or improved products are in the pipeline, notably including vaccine against rotavirus, which would address one of the principal contributors to childhood morbidity and mortality in developing countries. New delivery options, such as the aerosol for measles vaccine, would similarly significantly improve the situation in developing countries.

However important those advances are, the most important lesson learnt is to maintain the focus on routine immunization. Where coverage has fallen, gains made in child health are lost, and additional investment is needed to make up that lost ground. Achievements must be protected, sustained, and pushed further forward. Immunization can prevent 10–30% of global child deaths; the challenges of how to achieve that protection are reflected in the agenda items on which the advice of the expert strategic advisory group was anticipated.

Experience has confirmed the vital importance of working together, optimizing outcomes through having common approaches and a common monitoring and evaluation system. With UNICEF, WHO is working on a shared agenda for all involved in global immunization. Achievement of the health-related Millennium Development Goals (MDG) is closely linked to continued progress in control of vaccine-preventable diseases.
Joy Phumaphi appealed to the members of SAGE who are important global stakeholders and major contributors to global immunization: they are the brains behind the success who must continue to prove that immunization is the backbone of public health.


(Presenters: P. Carrasco, J-M Okwo-Bele)

The Programme Manager and the Director of IVB reviewed progress in responding to SAGE’s recommendations at its meeting in 2003 in the priority areas of innovation, immunization systems and accelerated disease control:

**Innovation:** To promote synergy between WHO standard-setting and product-development activities, broad technical consultations have been organized on each standard, including academia, regulators, and industry, soliciting additional regional input, and widely sharing drafts of written standards. Specific meetings have been organized to address the immune correlates of protection, e.g. for Japanese encephalitis. SAGE had recommended the development of a plan to describe which regional reference reagents would be developed and how to deploy and use them. That plan has been prepared, and a meeting in Thailand is to be held in November 2004 to discuss implementation of a regional reference reagent plan for the South-East Asia Region. WHO collaborating centres have agreed to support a regional resource for biological standardization. As regards work to protect vaccine supply of prequalified vaccines in situations where the national regulatory authority (NRA) is no longer functional, no such situation has arisen. Work to strengthen good regulatory practices is ongoing; an expert consultation was held in June 2004 to revise the indicators against which NRAs are being assessed.

**Immunization systems:** In response to the advice of the Steering Committee of the Immunization Safety Priority Project, the focal point for the project was retained, an environmental health engineer has been recruited to deal with waste disposal issues: guidance and policy documents have been prepared to support decision-making by countries on the most appropriate waste disposal systems. To meet the concern that safety issues should be integrated into the mainstream of IVB work, a wide range of activities now emphasize and promote safety at regional and headquarters levels.

Remarkable increases have been achieved in the use and production of autodisable (AD) syringes. UNICEF has been able to supply one AD syringe per vaccine dose to maintain quality immunization services, supported by GAVI in eligible countries through the Vaccine Fund. There are new syringe manufacturers and new AD products. Sustainability issues have to be faced after GAVI funding ceases, and safety (e.g. recapping) and waste disposal remain concerns.

Good progress has been made in training on vaccine quality and management for 35 countries, emphasizing AEFI monitoring and vaccine store management.

WHO has been working with the Global Advisory Committee on Vaccine Safety as required on investigation into issues such as suggested links between hepatitis B vaccine and multiple sclerosis (a link that was found to be unconvincing).
Accelerated disease control: Vaccination has prevented approximately 2–3 million deaths among children under five years of age in 2003.

Figure 1: Vaccination prevented 2.7 million deaths in 2003

![Deaths occurring in 2003 vs Deaths averted in 2003](chart)

*Preliminary estimates as of 25 October 2004.*

With better surveillance data, WHO will be better able to monitor progress and advocate for more support for public health interventions.

The polio eradication initiative continues to receive the highest attention. With intensive efforts South-East Asia is on track to break transmission; in the African Region, infection has been reintroduced from Nigeria and is being combated through synchronous immunization in 23 countries in western and central Africa. In Egypt, where transmission continues, there will be full-scale intensive immunization activities in 2005 (see also section 6).

Impressive results have been achieved in increasing coverage with measles vaccine and decreasing measles mortality, thanks to the good work of the measles partnership (see also section 8).

The Programme Committee for the Elimination of Maternal and Neonatal Tetanus in 2004 recommended that, in view of the lack of infrastructure, supplementary immunization activities for tetanus toxoid should be mainly targeted at districts with the lowest coverage. Elsewhere elimination can be attempted through improvement in routine coverage and integration of health services for marginalized children.

Good progress has been made in the use of current antigens; whereas, in 2001, 18 countries had DPT3 coverage of below 50%, by 2003 this had been reduced to 12 countries, all in the African Region, and half of them in conflict-affected zones (see also section 4). The problem of unreached children is still acute, particularly in the African, South-East Asian and Eastern Mediterranean Regions, but effective strategies are in hand to correct this in all regions.

Between 2001–2003, 22 additional countries have introduced vaccine against hepatitis B into their routine immunization programmes, many supported by funding from GAVI and the Vaccine Fund. The goal is to have all eligible countries introducing
hepatitis B vaccine by 2007 (eligibility being determined by their having reached 50% coverage with DPT3).

IVB has been extensively involved in research on vaccines against rotavirus and pneumococcus, HIV, meningitis A, tuberculosis, and devices for measles delivery (see also section 7).

After this review, Dr Jean-Marie Okwo-Bele presented current strategic directions within the department:

The Global Immunization Vision and Strategies (presented in more detail in section 3) calls for a major scaling up of immunization activities to reach everyone. Specifically, it aims to prevent the deaths of another 1–2 million children by 2015 through the new and currently available vaccines. To translate this vision into practice at country level there is a need for additional funding. Through GAVI, there are pledges of frontloading future development assistance to finance vaccines and system-strengthening needs in eligible countries. However, funds expected from the International Finance Facility for Immunization (IFFIm) are a fraction of the US$ 34 billion that are needed by 2015 for countries to achieve a two-thirds reduction in vaccine-preventable diseases. In the 2006–2007 WHO budget, the IVB area of work ceiling has been established at US$ 380 million. However, the planned transfer of funding to regional activities and the anticipated decrease in funds for polio post-eradication will demand a revisiting of core functions at headquarters and realignment of activity implementation. Following from the 2002–2005 strategic plan, a new plan will be formulated for SAGE to review at its next session in 2005. The plan will draw substantially on GIVS, with activities following three overall directions: research and development; quality, safety and sustainability; and immunization services within the health sector.

Discussion

The following is a consolidated account of the principal themes explored both in plenary and in camera.

Management: SAGE commended WHO on the significant progress made since 2003, which reflected the outstanding leadership provided by former director Daniel Tarantola and the smooth transition to new management. Much of the success of the last five years is due to the work done in championing vaccines and raising the profile of immunization globally.

Funding: There is a potential tension between the driving need for an integrated approach and the reality of targeted funding, which needs to be addressed as the process evolves. There will be a very substantial increase in overall funding, through the IFFIm and the increased funding now being experienced by the Vaccine Fund. Although it was originally the expectation that bilateral mechanisms would predominate with multilateral mechanisms feeding into that stream, in fact that scenario is reversing, which has implications for sustainability and long-term financing.

The background to the IFFIm is that UK analyses showed current funding to be inadequate to achieve the MDGs. A pilot project has been selected – immunization – to test the financial model, which capitalizes on the commitment of many countries
to increase the percentage of GDP dedicated to development aid, and converts pledges of future aid to current funding. The choice of immunization as the pilot project is a recognition of the achievements to date but confers increased visibility and still greater accountability. The resources are additional, not a substitute. It is essential to make it known that additional efforts to build secure health systems globally are having a positive impact at the country level. Advocacy will be important to elicit regular contributions from bilateral partners or through IFFIm as well as to strengthen the messages about the financial allocations needed.

Implications of the 2006–2007 budget directions: The budget for immunization is the largest among technical programmes but will be lower than for the previous biennium. The substantial decrease in budget for headquarters’ activities for 2006–2007 has led to a re-evaluation of core functions and an identification of functions that should be devolved to regions. SAGE warned that WHO must be careful not to diminish its role where issues are accelerating, for example in vaccine development. Examples of core capacities are: policy, strategy, planning, norms and standards, linkages with the research community, regulation and quality monitoring. Implementation, training, and elements of monitoring could be examples of suitable elements for decentralization. Furthermore, SAGE stressed that WHO’s ability to deliver must not be compromised by budgetary constraints and requested assurances that quality is a key criteria of the way forward, although with no proliferation of staffing. SAGE asked to see the plan of work (the Strategic Plan) for IVB for 2006–2007, which should clearly show where the changes have been made and articulate the role of WHO in immunization, with reference to the Global Immunization Vision and Strategies document (see section 3 below).

3. Global Immunization Vision and Strategies (GIVS)

(Presenters: J-M Okwo-Bele, WHO, P. Villeneuve, UNICEF)

The Global Immunization Vision and Strategies document presents to all immunization partners a unifying vision of what needs to be accomplished in the field of immunization by 2015. Including WHO, UNICEF and the Centers for Disease Control and Prevention (CDC), 18 partner agencies have contributed to the development of the GIVS document. Although not intended as a detailed strategic plan, it describes key activities to guide all countries in the formulation and implementation of their immunization programmes. It will be supplemented as it evolves by other documents giving guidance on planning and implementation. Following SAGE’s critical review and any revisions needed, the aim is to have the document accepted by the executive boards of WHO and UNICEF and endorsed by the World Health Assembly in 2005.

GIVS outlines the following goals to be attained in 2015 or earlier by all contributors to immunization and product development:

- **Coverage:** Every person eligible for immunization included in national programmes will be offered immunization with quality vaccines according to the established national schedule.

- **Intermediate coverage goal:** In every country, by 2010, at least 90% of children under one year of age will be fully immunized, with at least 80% coverage in every district or equivalent administrative unit.
• **Access to new vaccines**: Immunization with newly introduced vaccines will be offered to the entire eligible population within five years of the introduction of these new vaccines in national programmes.

• **Mortality and disease reduction**: Global childhood mortality and morbidity due to vaccine-preventable diseases will be reduced by at least two thirds compared to 2000 levels.

• **Sustainability and systems strengthening**: All national immunization plans will be formulated and implemented in ways that link them explicitly with sector-wide human, financial and logistic plans and ensure that activities will not have to be scaled back due to shortage of human resources, funding or supplies.

Specific measurable benchmarks and targets will be set by each country in 2005–2006 to attain the above global goals, and effective monitoring and evaluation systems will provide the evidence base needed for policy forming, programme development and impact assessment.

To achieve these goals, the document outlines three principal strategic areas: protecting more people in a changing world; introducing new vaccines and technologies; and linking immunization to other interventions. Together with these, two areas with cross-cutting themes are defined: immunization in the context of health systems, and global interdependence in a number of areas specific to immunization.

**Protecting more people**: Currently, about 16 million children under one year of age are still not being immunized.

**Figure 2**: Estimated number of unimmunized children\(^a\), under one year of age, by year and WHO region, 2000–2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Number (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>19.0</td>
</tr>
<tr>
<td>2001</td>
<td>19.3</td>
</tr>
<tr>
<td>2002</td>
<td>16.9</td>
</tr>
<tr>
<td>2003</td>
<td>15.7</td>
</tr>
</tbody>
</table>


\(^a\) Infants missed by immunization services = surviving infants minus immunized infants; immunized infants = maximum coverage of DTP1, BCG, MCV and POL3.
Current epidemiology shows that there is still a long way to go to ensure that all districts can provide DPT3 coverage to at least 80% of children. The first strategic area therefore aims to achieve at least four contacts per year, everywhere, targeting older age groups, and using campaigns as appropriate.

**Introducing new vaccines and technologies:** There is a good range of candidate vaccines. Products to protect against rotavirus, HPV and pneumocococcus are close to introduction. Work still needs to be done to assess the disease burden and convince decision-makers of the benefits of introducing the vaccines. It is imperative to reduce the time lag currently seen between licensing and wide-scale introduction. The aims are to empower country decision-making, make the vaccines available, and develop new vaccines for the disadvantaged.

**Linking immunization to other interventions:** Vaccination should be considered as one aspect of a “package” of interventions for child health and not implemented as a vertical programme. The aim is to achieve greater efficiency and impact. For example, work has been done to link vaccination campaigns to delivery of bednets for malaria control, and recent consultations in Ethiopia on child survival packages have highlighted the intervention for child survival and relevant implementation strategies to scale up coverage.

**Immunization in a health system context:** The performance of immunization services and systems largely depends on the strength of the health system as a whole. The aim of this cross-cutting area is to create a sustained enabling environment focused on the resolution of system-wide barriers, and to maximize the synergy between immunization services and other health services.

Key barriers include limited political and financial commitment. There is increasing fragmentation of public health initiatives worldwide with a proliferation of activities. Harmonization of these initiatives will bring efficiency gains. Key success factors include effective decentralization policies and strategies, and strengthening accountabilities at all levels but particularly at regional and district levels, and political will.

**Global interdependence:** GIVS aims to create an awareness of the interdependencies that exist, and to strengthen the partnerships that will work to overcome obstacles that go beyond domestic policy action. This applies for example to the development and production of vaccines, which need to take account of varying disease profiles and volume requirements. Developing countries still rely heavily on international assistance for immunization services and co-financing strategies are needed to reduce the financial barriers experienced.

Improved forecasting of demand for vaccines is essential to avoid potential shortfalls in supply and to encourage appropriate manufacturing and contracting plans. This also has a strong bearing on the funding required for immunization planning. In instances where a vaccine has only one manufacturer there is no price competition to encourage reduction in costs. Approximately 95% of vaccines provided by UNICEF are bought through external funding, not paid for by recipient governments.

SAGE’s guidance was sought on the way forward, in terms of the companion documents suggested, such as guidelines on the linking of other interventions with
immunization, human resources planning, vaccine supply strategies etc. Global targets and indicators need to be refined, and plans made on how to use the GIVS document to inform national and regional plans.

Discussion

The following is a consolidated account of the principal themes explored both in plenary and in camera.

**Support for the initiative:** SAGE praised the document as an important statement of the department’s intentions and a starting point for sharing ambitions with its partners. SAGE will be pleased to give input to further work, and endorses strongly the process started by WHO and its partners in taking on the work to prepare the GIVS document.

Despite its limitations as a strategic document, there is a value in piecing together the varied elements to create a consolidated vision and to explore a framework for future work among the many different actors. The timing of the GIVS document presents a leadership opportunity for WHO and UNICEF that must be taken. Immunization is envisaged and accepted as a central part of interventions to promote development and should provide a leading edge for child interventions. WHO and UNICEF should convene and coordinate across all these different areas.

**The country-level perspective:** The driving impetus is from "bottom up", giving more emphasis to individual country-level decision-making than to global targeting. SAGE however recognized that it is an aspect of WHO’s normative function to set out quantified global objectives. The need to consult extensively at country level was emphasized, taking the appropriate time to make sure that governments’ vision of what is needed is reflected.

**Measurement/implementation issues:** SAGE was critical of the lack of indicators and measurement tools in the strategic elements of the GIVS document. Clear mortality and disease reduction targets must be put in place to illustrate the cost of not immunizing, at both country and global levels. Measurability is agreed to be important and again needs to be linked to sustainability (measurement over time). Within an overall concern about the identification of appropriate goals of the vision, especially disease-burden reduction goals, a specific challenge is to identify measurable goals for older-age vaccination programmes. The metric for success is most often the mortality rate for children aged below five years. The newer vaccines such as HPV and hepatitis B will have no impact on these data and therefore lack an evidence base for advocacy and country decision-making. Within the context of discussion of vaccine research, SAGE observed that operational research should also be given due attention in the GIVS document.

**Integration:** The real opportunities for new funding that currently exist provide the context for the development of the GIVS document. However, there are also huge international initiatives for other health interventions, such as for HIV/AIDS, tuberculosis and malaria. These represent important opportunities if the vision in the document is implemented, services are considered in a coherent way, and countries can use these funds for strengthening. It is important to look at harmonization with partners in disease-specific initiatives and make this explicit in the document.
The issue of which other health interventions to integrate with immunization is not straightforward. SAGE suggested that WHO engage actively in dialogue with the global level management of the other interventions including the integrated management of childhood illnesses (IMCI). Critical assessments should be made of achievements and failures in immunization programmes and unmet needs defined. Historically, programmes have been more successful in some regions than others. This should not happen with GIVS. To avoid this “fate” a spearhead programme of integrated interventions could be tested, for example in a sub-Saharan African country, with assessment after three to four years.

**Advocacy:** SAGE agreed that more needed to be done to communicate the value of immunization. This issue should be emphasized in the GIVS document. Credibility is very important. Once polio eradication is accomplished, it provides clear evidence of the gains that can come through immunization. Changes in vaccine supply and funding over the last few years have brought a shift in opportunities in public health; immunization can be put very high on countries’ agendas. However, unless the “affordability barrier” is broken through, it will not be possible to move forward into the future of new vaccines.

**Safety and quality:** SAGE asked WHO to consider how to integrate safety more thoroughly into the document, looking beyond safety of administration, at the safety of the products themselves, and monitoring the safety of their use.

**Access:** Access to vaccines should be a specific goal in the document. The gap between when a vaccine is available and when it is actually introduced into the national programme should be discussed and included (see paragraph above, Advocacy). A mechanism by which equitable access to the vaccine stockpiles proposed under strategy 24 in the document should be included. An interregional strategy is needed for infectious disease control that recognizes that artificial boundaries around regions have perhaps constrained progress – for example in polio eradication – and do not reflect equitable access for all populations.

**Human resources brain drain, training and sustainability:** SAGE acknowledged that there is a crisis in human resources that needs to be addressed. Sustainability is an important issue for the future. Empowering people to be active in immunization systems is an important part of building a sustainable system. In emergency situations, where populations are displaced, infrastructure disrupted or destroyed, health workers can no longer exercise their profession. The financial losses, threat to family security etc. may force them to leave the country. It was suggested that immunization activities could serve as a vehicle to maintain health workers, assuring some continuity in health-care services and securing the needs of their families. This would play a major role in retaining health workers in their own countries.

**The role of expert advisory bodies:** International advisory bodies such as SAGE can play an important role in oversight of strategic directions to make best use of increased resources and to ensure there is a consistency of approach to decision-making, analyses, technical advice and messages. It will be important to streamline the work of different subcommittees to get the maximum input from experts in the context of the framework.
Making the most of the global resources: SAGE commented that the sustainability of financing was not well enough developed within the document. WHO is in the process of reviewing funding streams and assessing the main areas of work to reduce the visible gaps. The International Financing Facility will also provide an opportunity to reduce funding gaps. A "sea change" has taken place in public health whereby the scale of funding available is counted in billions not millions of dollars. This has implications also for the management and the effectiveness of financing, for example, dealing with the known issue that insufficient money goes to district-level service delivery.

Monitoring and evaluation: The opportunities and substantiation for country decision-making would come through strong monitoring and evaluation, supported by efficient and comprehensive surveillance systems. The 10-year timeframe for the GIVS document was discussed, from 2005 to 2015, with a midpoint at 2010 for evaluation, review, and adjustment where necessary. A question was raised over the place of monitoring within data-driven decision-making in the scope of the vision, and what was being done to support data-driven decisions at the local level, for example through the "reaching every district" strategy and through expanded monitoring and surveillance.

Recommendations:

- Through its regional offices, WHO should ensure a full process of consultation at country and regional level on GIVS.

- In early 2005, SAGE should review a revised version of the GIVS document, which will incorporate its comments.

- The GIVS document should describe the additional accompanying documents to be developed later (i.e. guidelines for countries to prepare the strategic plan for GIVS to be fully operational); an estimate of the cost implications; and an outline of the tools that will be used to measure the process and outcomes.

4. Improving access to quality immunization services in Africa: Challenges and ways forward

(Presenter: D. Nshimirimana)

The challenge presented is to revive stagnating EPI coverage in the African Region. Immunization services suffer from a history of underfunding, poor programme management and a lack of evidence-based decision-making. The reaching every district (RED) approach aims to improve access to and quality of immunization services at service delivery through five operational components.

1) Re-establishing outreach activities: This addresses the high numbers of unimmunized children in priority districts, using district microplans, community maps and target population distribution. Activities include securing financing and logistics and delivering integrated services including vitamin A supplementation.
2) **Supportive supervision:** Standardized tools have been developed for use at different supervisory levels, with district and provincial health officers including active surveillance as part of their responsibilities and providing supportive supervision to district health teams.

3) **Community involvement:** This improves access to quality EPI services through involving the community in planning outreach services, mapping target communities, tracing defaulters, training volunteers and generally mobilizing local resources.

4) **Data for action:** Programme management and performance data collected monthly are used to guide the activities of district teams, involving surveillance officers, with quarterly meetings to review data and agree on priority activities.

5) **Planning and managing resources:** The strategy emphasizes the best use of limited resources, using district microplans and prioritizing activities for communities with the highest numbers of unprotected children.

In 2003, 30 of 46 countries increased the proportion of districts reaching 80% DPT3 coverage. Ethiopia presents particular challenges: consistent under-investment in EPI, difficult terrain, high population, and competing priorities such as civil war and drought. Of the 85 zones, 13 with a particularly serious profile (e.g. poor access, high rates of unvaccinated children) were selected for implementation of the RED approach. The opportunities for RED implementation include high political commitment to EPI, improved cold chain and distribution, recruitment and deployment of more EPI officers by WHO and UNICEF, better resource mobilization by a range of partners, better integration of surveillance and routine EPI, and use of communication channels and advocacy (such as the local religious leaders) to raise the profile of immunization.

The RED strategy has had a clear impact, quickly reaching the national average for DPT3 coverage from a low starting point.

In 2004 RED is being implemented in 20 countries in the region, positively influencing coverage despite obstacles. Polio-funded infrastructure and staff have been a major contributor to the success of RED, and the sustainability of the projects will depend on maintaining support for human resources, and material and financial capacity at district level. It will be important to strengthen the links between immunization and the delivery of integrated packages of interventions using the RED strategy. Long-term challenges to increasing coverage mean that WHO must tackle advocacy, fund-raising and sustaining human resources.

**Discussion**

The following is a consolidated account of the principal themes explored both in plenary and in camera.

**Infrastructure strengthening:** It was agreed that there is a great opportunity to access very substantial funding if, as expected, approximately half the funds allocated to countries from the International Financing Facility are to go to infrastructure
development. To achieve the aim of financial sustainability, WHO must help countries to make the RED approach an integral part of their national immunization plans, then use those plans as a basis for funding applications. The approach could very usefully be raised at GAVI meetings and viewed as a key tool, like DQA etc., for use by the whole immunization community as a way of strengthening health infrastructure.

**Improved access:** The RED approach, which improves access to EPI services, is a means of accelerating progress towards the ultimate goal of improved access to basic health services, particularly at district and subdistrict level. Once this improvement in infrastructure has been achieved, access will increase for all programmes. Experience from the Region of the Americas supports the strategy of institutionalizing tools such as the RED approach into plans of action and provides support for the practice of regular supervisory follow-up to sustain momentum and progress.

**Outreach services:** In Ethiopia, the majority of the strategies to overcome the challenges of the terrain were achieved by a combination of mobile and outreach administration rather than by the routine fixed post.

**Human resources:** Outreach services are a fundamental part of service delivery in most countries. The most important aspect of this process is assuring people’s mobility, on motorcycles etc., which requires the sort of “front-loading” financing being proposed in the IFFIm. This however in turn needs rigorous maintenance management or the investment is wasted. Schemes to invest in infrastructure must include both capital and relationships in public/private and outsourcing partnerships to assure maintenance and long life from the transport provided.

For the last 20 years, the immunization programme in the Eastern Mediterranean Region has been mainly dependent on regular mobile outreach activities rather than fixed post. Pakistan’s experience of training female health workers has the potential to improve maternal and child health services.

In most poor African countries the money to support development programmes is from external sources; the country contribution is to pay staff, although these salaries are inadequate to motivate staff and need “topping up”. The current child mortality rates in Africa demand such a solution, even if it is temporary, and not ideal. SAGE noted that the need to provide viable salaries for critical health workers is a central issue for progress.

**District-level data:** SAGE praised the emphasis on the use of district-level data in making decisions and capitalizing on the experiences and contributions made by the polio eradication programme in supporting the provision of routine care. There is great need for a stable transition in activities for the skilled trained local workers produced by the polio eradication campaign. Polio staff are already involved in implementing the RED strategy in countries, and the polio infrastructure is being used in surveillance of other communicable diseases.

Presently relatively few countries are implementing the strategy. If it is to be scaled up to make the difference that is needed, the budget would need to be greatly increased. There is a real need for countries to recognize and make this commitment to get the necessary levels of coverage.
Recommendations:

- WHO should advocate globally to assure the additional resources required to fully implement and sustain the RED strategy so as to ensure a stable transition from the polio infrastructure to a more integrated immunization and child health infrastructure.

- The RED strategy should be integrated into national plans of action for immunization, with especial emphasis on implementation and expansion in low-performing countries.

- The WHO Regional Office for Africa should rigorously monitor the progress of the RED strategy implementation in each target country in the region, giving the required support to solve problems and document needs.

5. Financial sustainability planning: update on the process

(Presenter: P. Lydon)

The financial sustainability planning process has been an important area of growth for GAVI and WHO. To date it has provided very useful information for global-level strategic planning and policy-making for immunization. Drawing on the lessons learnt to date is important and timely in the light of the development of the global immunization vision and strategies, and new phases of GAVI.

When GAVI began in 2000, it sought to rejuvenate immunization efforts by helping the poorest countries to introduce vaccines against hepatitis B and Hib and to strengthen immunization systems with performance-based funding. Unlike many previous global initiatives, GAVI provided multiyear commitments.

The success of the initiative depends partly on the realization of four financing assumptions: first, that vaccines against hepatitis B and Hib will become cheaper in the long term; second, that GAVI resources will be additional to existing and future investments for immunization; third, that the GAVI push will catalyse more funds for immunization by governments and partners, and finally, that the financial responsibility for these new vaccines would be assured, once the multiyear GAVI commitments drew to an end – otherwise known as the financial sustainability process.

To address the concerns about the sustainability of its actions, at the midpoint in the funding timeframe, each country being supported by GAVI has to prepare a financial sustainability plan (FSP). The plan’s objective is to motivate the country to articulate clear strategies and identify options for future financing of their programmes in order to manage the transition of responsibility as GAVI inputs are phased out. By 2004, 22 countries had developed such plans. Analysis of their data allows the original funding assumptions of GAVI to be tested against reality and highlights the issues and implications for future immunization efforts, particularly in the context of the GIVS, IVB strategic directions, and the future GAVI design.

Reduction in vaccine prices: So far the movement in vaccine prices has not been favourable. For monovalent hepatitis B the price has decreased slightly since 2000 (to less than US$ 0.50 per dose). For hepatitis B combined with DTP the trend is
upwards of US$ 1–1.50 per dose and the vaccine combination including Hib is up to
US$ 3.60 a dose. No favourable movement in pricing is expected until 2007–2008
when additional suppliers will contribute to increased competition and downward
pressure on vaccine prices. A consequence of these high prices is that, those countries
that have introduced hepatitis B and DPT in combination have, on average, doubled
their programme costs. Where the pentavalent vaccine has been introduced,
programme costs have tripled. It should be noted that while the largest cost driver is
the vaccines, the cost of non-vaccine inputs has risen following the introduction of
these new products.

**Additionality of GAVI funding and catalytic funding:** So far there is no evidence
that GAVI is replacing national funding. In fact, governments are continuing to
support immunization and even anticipating a modest rise in their support. On the
other hand, future funding commitments from other development partners have not
materialized. This is partly due to the fact that most development partners are
institutionally unable to make multiyear commitments and that few mechanisms exist
for them to do so. It is, therefore, difficult for GAVI to catalyse – as anticipated –
additional funding from development partners. The result of this is that substantial
funding gaps are projected in the 22 countries as of 2007: about 64% of the resource
needs are unmet (as an aggregate).

While the picture is daunting, some of it reflects the fact that countries have tended
to be optimistic when projecting their future resource requirements and cautious
when forecasting future funds. Finally, the current financing gaps reflect current
prices of vaccines and without factoring in the impact of implementing the financing
strategies that countries have outlined in their FSP.

**Sustainability:** Based on the above that reflects an aggregate picture, financial
sustainability seems far from assured. There is considerable variation among the
22 countries as regards their degree of success in generating longer-term funds. In
Guyana and Uzbekistan the governments have been most successful in raising the
resources needed to sustain vaccine purchase into the future. They have strong political
commitment, and the funding gap is very small. In other countries there is a huge
challenge to sustainability, and this needs to be addressed by funding partners if the
immunization targets and objectives are to be met.

**The consequences:** Not meeting the financial sustainability challenge will come at a
cost. If the funding gaps projected currently for 2004–2008 are not filled in the
22 countries, 6.4 million children will not be reached with DTP3. This will mean
that an additional 210 000 vaccine-preventable deaths would not be averted in the
22 countries. However, to carry out the projected plans would be a good investment,
at a cost-per-life saving of US$ 543.00. In terms of investment from the national
governments, this level of expenditure would equate to between 2–20% of a health
budget (depending on the macro-economic fundamentals of the country and the type
of new vaccine introduced).

The lessons learnt from the FSP process in countries have highlighted a number of
issues with implications for future immunization efforts and IVB strategic directions.

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1 For further information see the WHO Bulletin: Special issues on the economics of immunization;
and the WHO immunization financing website at http://www.who.int/immunization_financing
It is critical that support to countries continues to be provided to (1) improve countries’ ability to plan financially for immunization (e.g. by helping countries to develop an FSP or a comprehensive multiyear plan for immunization, including costing and financing elements); and (2) increase the predictability of international funds for immunization (by working with partners of new financing options such as debt relief, GAVI, IFFIm analytical work on immunization financing); to help improve national decision-making and ownership (by educating countries on the financing options open to them and supporting country choices through risk/benefit assessments etc); and capacity-building in financial management (by developing guidelines, tools, training materials with partners’ support).

Discussion

SAGE noted the alarming contrast between the original plan and the present reality but recognized that there were both positive and negative points to be drawn from the presentation. There is much that can be done to address the issues that the mid-term assessments have thrown up, especially now that the position has been so clearly articulated.

Integration/reduced costs: It is important to separate the vaccine-specific costs from the costs of infrastructure specific to vaccines and to generic infrastructure. The level of generic costs is important in making the case for the mutual benefit to be derived from integrated interventions. An analysis of these aspects is given in the background document for the meeting, in the special issue of the WHO Bulletin on the economics of immunization prepared under the auspices of GAVI and the financing taskforce, and in the web site on immunization financing.1

The role of combined interventions in potentially lowering costs is an urgent research area. If resources are to increase very substantially, it will be essential to link immunization to other activities, even if this means delaying some targets in order to get integration off the ground earlier. Vaccine-specific costs might be met through technical assistance or through creating benefits for the manufacturers that would facilitate technology transfer for new vaccines. Research into this area would support a definition of WHO’s role. Middle-income countries that are self-supporting also contribute to vaccine demand/supply.

SAGE praised the articulation of the problems and quantification of need, which is in advance of other programmes. It is very useful to know what the vaccines cost and what the roles are. It is important to recognize that the vaccine pricing is affected by the fact that supply is a monopoly. In one to two years there should be a dramatic reduction in the cost of products as other manufacturers of DTP/Hep B and DTP/Hib come online. The traditional perspective on financial sustainability is that it equates to what national governments can provide. IFFIm offers a solution that differs from the ethical standpoint that the importance of saving lives through immunization goes beyond the importance of sustainability.

Lessons learnt: Where countries are already nearly self-sufficient in vaccine supply, GAVI funds could be redirected from them to more needy countries. It would be useful to learn why those countries have done so much better than others.
International voice: Each year about US$ 300 billion is spent by the major industrialized nations on industry subsidies. The total ODA flows are around US$ 70 billion. Marginal changes in the first figure would profoundly affect the terms of trade of many of the developing countries. The international health community should speak on the terms of trade and therefore support the ability of countries to pay. All partners should be convinced that immunization provides the best cost-benefit ratio in public health, using all channels, including publication in international scientific journals. The convergence of GAVI with the Vaccine Fund should lead all partners to co-own the necessity of contributing increasing resources.

Commitment among partners: There must be solidarity and commitment among parties, to prevent resources being increased in some areas at the expense of others with no overall increase. The bilaterals at country level must be reintroduced into the process, putting more emphasis on managing the processes at country level, such as the use of debt relief. Stronger national Inter-Agency Coordinating Committees (ICCs) will help in this.

Reduction in vaccine price: China, India and Indonesia should be helped to produce more vaccines and so increase vaccine supply to the Asian subcontinent. Economists should be asked to comment on the fact that the global market economy appears to be having a negative effect on the programme.

Manufacturers: The relationships between technology, supply and production are an important factor in the future of vaccines. The bulk of the vaccines are combination vaccines that are currently only made available by one manufacturer, but this will change in the future. It is important to understand the whole chain of development and marketing of vaccines and think more broadly about how partners can expedite the increase in volume and get to price decreases faster. There is a need to think about access to technology, to expand the supply base and to make products more affordable, thinking about intellectual property, regulatory structure support, and support for clinical trials. The vaccine market has become much healthier in the last two or three years, with fewer shortfalls in supply due to the increases in production and quantities from developing countries as well as re-entry of manufacturers from industrialized countries. It is important to keep up the efforts made at donor and country level in forecasting, planning and good communications with manufacturers.

Recommendations:

- WHO and UNICEF should work with all partners to craft an advocacy strategy for fund-raising that makes the investment case for immunization, obtaining political commitment within each country, as well as developing strategies for financing.

- WHO should continue to help improve countries’ ability to plan financially for immunization; increase the predictability of international funds for immunization by working with partners on new financing options and sources such as debt relief, GAVI, IFFIm, and carrying out analytical work on immunization financing through the immunization financing database; and help improve national decision-making and ownership, as well as capacity in financial management.
6. Synchronous cessation of oral poliovirus vaccine (OPV) use after Global Polio Eradication

(Presenters D. Heymann, B. Aylward)

Of the six "pre-requisites" or conditions for OPV-cessation, two require particular oversight and guidance to national managers by SAGE: the actual process of synchronous OPV cessation and stock destruction, and the use of IPV. SAGE guidance on the development of the products for OPV cessation is also sought (e.g. monovalent oral poliovirus vaccines types I, II, III, and an inactivated poliovirus vaccine developed with Sabin strains).

**Rationale for OPV cessation:** There are unacceptable risks from continued oral poliovirus vaccine after wild poliovirus interruption: vaccine-associated paralytic polio (VAPP) and circulating vaccine-derived polioviruses (cVDPVs). The scale of the VAPP risk is 2–4 cases per million birth cohort. There have been four outbreaks due to cVDPVs since the late 1990s: in Hispaniola (2000), in the Philippines (2001), in Madagascar (2002) and in China (2004). Each outbreak had small numbers of cases and limited transmission. In addition to these risks, continued OPV use could, very rarely, give rise to the prolonged excretion of VDPVs by individuals with severe primary immunodeficiency syndromes. There are 17 well documented cases of iVDPVs including three "long-term" excretors (e.g. > four years, all of whom were in developed countries, probably due to better health care). These risks have underpinned an international consensus to stop routine OPV use after wild poliovirus interruption. Other risks following the interruption of wild poliovirus transmission include the release of a wild poliovirus from an IPV manufacturing site, a laboratory accident or bio terrorism. The Expert Consultation on Vaccine-derived Polioviruses in 2003 concluded that, post interruption of wild polioviruses, "the continued use of OPV will compromise the goal of a polio-free world".

**Timing:** Cessation of OPV for routine immunization must occur while population immunity and surveillance sensitivity are high. Currently, the minimum period envisaged between interruption of wild poliovirus transmission and OPV cessation is three years, with a maximum of five years. Confirmation of interruption of wild poliovirus transmission will come from the Regional Certification Committees.

**Prerequisites for OPV Cessation:** For OPV cessation to go ahead there must be: confirmation of interruption of wild poliovirus transmission; appropriate containment of all stocks of poliovirus and potentially infectious materials; global surveillance and notification capacity (the revised International Health Regulations may include polio); a monovalent OPV stockpile and response mechanism; synchronous cessation of trivalent OPV use and documented destruction of stocks; and finalization of post-OPV immunization policy at the national levels. Countries can decide whether or not to administer IPV or IPV combinations following OPV cessation, however WHO will not make a universal IPV recommendation given the current balance of risks. It is estimated that 150 countries will be using OPV at the time of cessation. A specific framework is being developed for national policy-makers on the rationale, pre-requisites and timelines for OPV cessation (target May 2005). When appropriate, national guidelines will be developed for the actual process of OPV cessation. Work is ongoing with manufacturers to ensure clarity on the timeframes. The wider context of immunization programmes is being kept in mind, in terms of the combinations being used, e.g. with pertussis.
**Epidemiology:** In India, polio transmission is now localized in a limited number of districts in Uttar Pradesh and Bihar; in Pakistan it is primarily the Sindh, with transmission also continuing in the North-West Frontier of Pakistan and the Punjab. In Afghanistan there have been three cases to date and in Egypt only one case.

*Figure 3: Polio cases since 1 January 2004*

It is believed that transmission can be interrupted in these countries by mid-2005. In some of these areas, especially in Egypt and India, coverage is already over 90% but gaps remain among minority population groups. In Africa the suspension of polio immunization activities in Nigeria resulted in a major epidemic in that country and Niger, and the re-infection of 12 others. In Burkino Faso, Chad, Côte d’Ivoire and Sudan polio transmission has now been re-established. In response, in sub-Saharan Africa 80 million children have been targeted for synchronized immunization in 23 countries. Polio transmission could still be interrupted in Africa by end-2005.

**Risks following interruption of wild poliovirus transmission:** The primary risk in the "pre-OPV cessation" era will be ongoing wild virus transmission that was missed due to surveillance gaps, and VAPP. During the three-year period immediately after OPV cessation the primary risk will be circulating VDPV (cVDPVs). Following that period, the primary risks become wild virus re-introduction and iVDPV (although it is believed that the former risk is minimal if the conditions of containment are in place). Key work is ongoing to model and quantify the risks to countries of cVDPV emergence during OPV cessation. This work suggests that, globally, there is a 60–70% chance that a cVDPV will emerge during the 12 months immediately following OPV cessation. IPV use would not eliminate this risk, for a number of reasons, and could only reduce it in some areas. Managing the "OPV cessation" period is a major focus of work with countries, with the aim of minimizing the risks and being able to respond rapidly where there is a cVDPV. An appropriate vaccine stockpile and strategy is being prepared. Current modelling suggests that cVDPV emergence is the largest risk (although still small) with the risks of iVDPV and wildvirus re-introduction being substantially smaller. Areas with particularly high
population density, low immunization coverage and suboptimal sanitation may be the highest risk areas for cVDPVs. These known risk areas might need to be targeted with specific strategies in advance of OPV cessation (e.g. pulse immunization to hyperimmunize the population; stockpiles pre-positioning).

**Decision points:** For national managers there will be three decision points: how OPV cessation will be implemented and stock destruction verified; the strategy for responding to cVDPVs during OPV cessation (and possible wild poliovirus reintroduction afterwards due to containment failure); and what role IPV might play in post-OPV national immunization policy.

**IPV introduction:** WHO is working with countries to improve international and national understanding of the technical, operational and financial implications of introducing IPV, as well as to highlight the fact that the future polio risks are not eliminated through IPV use.²

Of particular importance is the need to ensure IPV is not regarded as a simple “add-on” vaccine. For example, there is currently no widely available combination vaccine that includes both IPV and whole-cell pertussis; this is a particularly important consideration for low-income countries being funded by GAVI, which would have to use completely new vaccines. Based on current prices and combinations, a switch to IPV could increase immunization programme costs by up to twentyfold.

**Vaccine products required for OPV cessation:** WHO is working very closely with industry and national regulatory authorities to develop monovalent OPV (mOPV) – including mOPV-licensing requirements – accelerate access to monovalent OPV vaccine, and secure financing for an mOPV stockpile. Candidate trial lots have already been produced for Sabin IPV and accelerated development processes are under consideration.

SAGE input was sought in particular on additional work that could be done by WHO in readiness for the period of OPV cessation.

**Discussion**

The following is a consolidated account of the principal themes explored both in plenary and in camera.

**The objectives of the programme and the role of SAGE:** WHO reiterated the objectives of the polio eradication programme: the interruption of poliovirus transmission and the cessation of the use of immunization against polio. There is sufficient, compelling evidence for the policy decision to stop the use of OPV for routine immunization, when the appropriate conditions have been achieved. The

² Various publications have been prepared:

role of IPV in some settings is still under discussion, with much work ongoing in this area under the oversight of the AACPE. SAGE’s role as an advisory body, looking at the broad directions in the topic areas, and giving guidance on whether WHO has identified the problems and solutions correctly, was revisited, in the light of formulating recommendations. For example, it may be premature for SAGE to give an opinion or to make substantive recommendations on the issue of IPV, since the results of the work initiated by the AACPE are not complete. However, SAGE must be kept well informed on this critical area and be involved in decision-making given the broader implications for routine immunization programmes.

The magnitude of risk: There is a non-zero risk of cVDPV when OPV administration stops. There is, however, a higher “non-zero” risk over time if OPV is not stopped, based on what is expected to happen with routine immunization programmes and populations of unreached children. Immediately after OPV immunization stops there is at most a 60% chance that one vaccine-derived virus outbreak will occur globally (in any one country the risk would be substantially smaller, the actual magnitude depending on population size, coverage, etc). By the second year, that risk will drop to 3% and in the following year, to 1% based on the current model assumptions. By using IPV, it may be possible to reduce that risk by at most half (at the national level, the actual impact would depend on the country, routine immunization coverage, etc). Work is ongoing to quantify the consequences of a future polio outbreak if IPV is or is not used in routine immunization (e.g. how many people might be affected). It was noted that changes in the immunological profile of a population in 10–20 years’ time should be borne in mind in this work. Also, it was noted that the coming years may be the only opportunity to look at IPV use in outbreak settings. There must be very tight criteria for the introduction of attenuated strains in response to an outbreak in the post-OPV era, to minimize the probability of generating a cVDPV (although that the risk is expected to be very small as out of the 10 billion doses already administered, only four cVDPVs have emerged). The existence of that risk, however, means that WHO is taking a very comprehensive approach.

Country-level decision-making on IPV use: Countries that have recently eradicated polio expect to be stopping the use of OPV. WHO will not make a universal recommendation to use IPV. Each country will determine its own post-OPV cessation policy. Many criteria need to be satisfied before a new vaccine is introduced. Some developed countries, e.g. the United States, will continue to use IPV indefinitely, some perhaps in response to the suggestion that poliovirus may be used in future in bio terrorism. In western Europe, countries that already use IPV will continue to use it into at least the medium term. The new member countries of the European Union will probably also follow that decision.

Production of IPV: In general, for those countries which do use IPV, WHO would like to promote eventually the sole use of Sabin strains, although there are substantial issues to resolve about protective efficacy, industrial scalability etc. Once those issues have been resolved, WHO would look at preferential purchasing of Sabin IPV to promote its use. Many issues remain to be resolved with manufacturers, regulatory authorities and the biosafety community. There is some confusion among the developing country manufacturers as it is understood that there will be demand for IPV from developed countries, yet OPV cessation is likely to take place before any such new IPV product can be prepared by these producers. These manufacturers are potentially very important to the future of vaccine production. WHO confirmed its
close collaboration with manufacturers (e.g. annual meetings on these issues), sharing information of projected scenarios and timeframes to facilitate their planning and production, and committed to doing more in that direction.

**Secured poliovirus samples:** Currently 152 countries have initiated a survey of institutions that are holding wild polioviruses or potentially infectious material and 103 countries have supplied those inventories to WHO. More than 200,000 facilities have been searched worldwide, of which no more than 757 hold wild virus or potentially infectious materials. Post-eradication, certain laboratories may elect to retain poliovirus samples in secure conditions. This is expected to be the subject of a resolution by the World Health Assembly in 2006.

**Stockpiles:** Although modelling has been done for settings of high IPV coverage, there has been consideration that, in the event of a catastrophic outbreak, a stockpile of attenuated vaccine should also be maintained. It is not clear yet what would be achieved by the use of IPV in outbreak settings and input would be welcomed.

**Consensus/cooperation:** Three key issues must be agreed internationally. The cessation of OPV use must be synchronous and conducted in a very short timeframe; there must be concurrence on the level of containment for all polioviruses (i.e. agreement reached on wild poliovirus and Sabins); and there must be international restriction on, and criteria for, the reintroduction of attenuated strains in the event of a circulating poliovirus.

**Recommendations:**

- To assist its deliberations on post-OPV immunization policy, WHO should keep SAGE fully informed of: all related policy decisions made by the oversight groups responsible for other aspects of the OPV cessation work (i.e. the Ad-hoc Advisory Committee on Polio Eradication, the Global Commission on Certification of Polio Eradication, the Biosafety Advisory Group); the evolving understanding of the nature and magnitude of the risks of circulating polioviruses following interruption of wild poliovirus transmission and OPV cessation; and the outcomes of the continuing work to model these risks over time.

- WHO should continue to work with manufacturers and national regulatory authorities to accelerate access to monovalent strains of OPV for use in the vaccine stockpile needed prior to OPV cessation.

- WHO should work with partners to establish a mechanism for rapidly evaluating the candidate IPV that have been developed using Sabin strains (i.e. S-IPV) and, if appropriate, ensure the capacity to transfer such technology, particularly to new manufacturers of IPV.

- To facilitate national decision-making on long-term immunization policy, WHO should, by the end of 2005, develop explicit guidance for OPV-using countries on the impact of IPV on “post-OPV” risks and the implications of IPV use from the financial, programmatic and opportunity perspectives.
7. Research and development

7.1 Update on the global research and development agenda

(Presenter: M-P. Kieny)

A brief outline of the topics covered in the Global Vaccine Research Forum\(^3\), held in collaboration with GAVI, was given.

**Malaria:** Very recently, for the first time a vaccine has been demonstrated to protect young children against severe malaria. In the study, protection against the first and only episode of fever and parasitaemia was only 30%, but protection against severe malaria was 57%. It is debatable whether this vaccine can have an impact in the field, however, the clinical trial in Mozambique showed that efficacy was better in children aged 1–2 years than 2–4 years, so it might perhaps be considered for integration into EPI. As the focal point of the malaria vaccine funding agencies group, WHO has coordinated a meeting to set up technology "roadmapping" for malaria vaccine to accelerate its development and introduction, and continued its involvement in the development of a particular candidate vaccine in Shanghai, China, sponsoring a clinical trial. The malaria vaccine initiative at PATH may take this on further, given its immunogenicity results.

**Tuberculosis:** BCG vaccine gives protection to infants and children against severe disseminated forms of tuberculosis, but does not prevent primary infection. Prevention from BCG vaccine wanes with age, allowing some infected teenagers and adults to develop overt disease. A new vaccine is needed. More than 200 vaccine candidates have been tested in animal challenge experiments and three have entered phase I clinical trials: a recombinant BCG, an adjuvanted protein subunit vaccine and a vaccinia virus construct. The latter has completed its first safety trial in the UK, with excellent immunogenicity. Three more candidates (a recombinant BCG, an adenovirus-based construct and an adjuvanted protein subunit vaccine) are entering early clinical trials in 2005. Success in clinical efficacy trials of any of these may mean a new vaccine licensed by 2013–2015. WHO’s role is to accelerate development, facilitating actions in preclinical and clinical evaluation, production and control, vaccine introduction and advocacy. BCG continues in importance, both for its effective prevention of childhood TB and in the future as the priming component of a new TB vaccine, with the novel product being used to boost BCG-induced immunity. Further genetic characterization is needed; a working group has been established with NIBSC (a WHO collaborating centre) that will review results and make recommendations for production and control of BCG vaccines addressing strain identity, potency, standards and storage.

**HIV:** Results so far are disappointing; the latest trials of gp120 vaccine in Thailand indicates no protection. A phase III trial will investigate its efficacy as a booster after priming with a live vector (canarypox) to induce T-cell immunity. IAVI’s lead candidate vaccine has also produced disappointing results. Multiple vaccine concepts are being developed in parallel, such as the work on the adenovirus construct as a potential HIV vaccine, and a revival of candidate vaccines intended to induce neutralizing antibodies. Supported by bilateral agencies, WHO has strengthened

\(^3\) Report available at: http://www.who.int/vaccine_research/about/gvrf/en/
the African AIDS Vaccine Programme, promoting regional and international collaboration to ensure appropriate scientific and ethical standards of HIV vaccine-related research and clinical trials. WHO has consulted extensively on policy issues in HIV vaccine development.

**Pneumococcus:** A new pneumococcal conjugate vaccine has been found to prevent X-ray-confirmed pneumonia. Published results range from 21–30% efficacy in California and South Africa, with little difference in efficacy between these epidemiologically diverse populations. Data from the United States following introduction of a 7-valent vaccine has shown a dramatic decline in the incidence rates of invasive pneumococcal disease and the elimination of the disparity in disease rates among black and white children. These data suggest that the disease reduction effect would be even more dramatic in developing countries, which carry a high burden of disease. Recent data show that replacement does occur, but not substantially. There is a significant increase in non-vaccine types but this does not offset the substantial decrease of invasive disease due to vaccine type strains. Furthermore a significant herd immunity effect is seen in the unimmunized population 5–17 years, with a 50% reduction of invasive disease in the group. In addition, parents and grandparents of vaccinated children also showed reduced disease rates. Additional efficacy data is expected in 2005 from trials in the Gambia and the Philippines. Other candidates are in development, including a re-formulated 11-valent conjugate and a common protein vaccine. WHO’s activities are geared to address key uncertainties, for example evaluating alternative, more cost-effective vaccination schedules.

**Measles aerosol:** The objective of this partnership with the American Red Cross and CDC is to develop and license at least one method for respiratory delivery of currently licensed measles vaccines. The aims are: to obtain a vaccine that is cheaper, safer and easier to use than the current form; to evaluate at least three devices for aerosol delivery; and to assess a dry powder method for entry into initial studies. After determining the output and particle sizing of the benchmark classical Mexican device, new delivery devices are measured against this reference. A number of preclinical studies have been completed. These include safety, immunogenicity and toxicology, evaluated in cynomolgus monkeys and bench-testing of candidate delivery devices. Three devices have been selected for clinical testing, based on performance characteristics, usability, vaccine potency reduction, and the willingness of the company to collaborate long-term. The three delivery devices – unvented, breath-activated, and ultrasonic – will enter clinical trials in India (phase I safety, three sites, each with one device) and Mexico (phase II immunogenicity and safety, one site, all devices). The Mexico study will also assess the risk of environmental contamination, evaluate devices for contamination and cross-infection, and conduct economic analysis. The objective of the economic analysis, using measles as a case study, is to develop and validate a list of standard criteria by which to judge the need for the introduction of new vaccines. All of the projects’ activities are well on schedule.

**SARS vaccines:** WHO is working with the Chinese national regulatory authority to design a procedure to approve SARS clinical trials in their country, consulting with the broader community on animal models to test vaccine, specifying the requirement to test vaccine in the absence of a SARS epidemic. WHO has been involved in the initiation of a phase I clinical trial of an inactivated SARS vaccine in China, in close collaboration with the NRA, with WHO as a reference in terms of animal models, providing assistance in protocol writing and reviewing the Informed Consent form.
The trial has finished, with no safety issues, and the immunogenicity analyses are ongoing. In the absence of SARS outbreaks there will be little IVR involvement, although it will work on outlining the ethical and regulatory conditions for testing the efficacy of a pandemic vaccine in the presence of such a pandemic.

**Collaboration with ADIPS:** This report responds to SAGE’s request in 2003 for more information on the accelerated introduction and development plans. The plans cover pneumococcal and rotavirus development. Staff have been recruited, funding received and a collaboration agreement reached. Activities began in August 2003 on provision of information to enable national decision-makers and others to make evidence-based decisions regarding the use of vaccines, and to accelerate the availability of affordable new vaccines appropriate for use in developing countries.

**Other new vaccines:** Only a certain number have been reported on to SAGE, although work continues with vaccines against HPV, Japanese encephalitis, shigella, dengue and ETEC. A report on this work will be presented in 2005.

**Discussion**

**WHO’s role with ADIPS:** IVR is the focal point, but almost all the teams in IVB are involved in some aspect of ADIP. There is very close collaboration, with weekly contact. WHO participates in all ADIP activities, including the development of overall goals, objectives and workplans, participating in evaluating the protocols submitted, and identifying those to go for funding. Specific “top-up” funding is given for particular research projects. ADIP works with other teams where they have particular areas of expertise, such as in the establishment of global disease-burden estimates, establishing criteria for production and quality control of vaccines, and regulatory pathways. ADIP’s mission is focused on the accelerated introduction of vaccines in late phases of development and does not encompass development of vaccines in the earlier phases of development. WHO works with ADIPs in the area of surveillance, and also outside the ADIPs with other manufacturers of rotavirus vaccine, for example in developing countries.

**BCG and TB vaccine development:** Although the achievement of sterilizing immunity would be optimal, the aim presently is to cover 95% of the non-immunodeficient population with vaccine that allows them to suppress outbreak of the disease during their lifetime. The regularly-reviewed EPI policy recommendation for BCG is to continue the use of the vaccine as it prevents severe TB in some, but not all children who have been immunized. There should be no BCG booster doses. Should countries, based on cost-effectiveness considerations, decide to discontinue the use of BCG, WHO recommends applying the criteria defined by the International Union against Tuberculosis and Lung Disease (IUATLD). The criteria essentially refer to the requirement for an efficient case-notification system against a background of very low national prevalence figures for all forms of TB. SAGE commented that, as BCG does not prevent infection with tuberculosis, it would be an important long-term goal to develop a vaccine that can achieve this.

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4 A fuller account of WHO’s collaboration with ADIPs is given in the CD-ROM of the SAGE meeting, see “Progress” folder.
Measles aerosol: Studies have shown one strain (Edmonston Zagreb) to retain its potency better during nebulization although different options are still being explored and the science behind the variations further investigated. Following extensive consultation and studies it appears that the minimum dose that should be delivered/presented is at least 1000 pfu. Following SAGE and other advisory groups GLP-compliant animal immunogenicity and safety and toxicology studies were conducted, where animals were given five times the human dose. There was extensive evaluation of all body tissues, particularly of brain and olfactory tissues and a search for presence of the virus throughout the central nervous system. No virus was isolated except in the lungs and there was no micro or macro histopathological change in the brain or central nervous system. With support from different expert groups a protocol for the evaluation of contamination has been developed to satisfy international regulatory requirements regulations. This will be applied during the studies in Mexico. All the nebulisers selected for trial have designs that avoid the risk of cross-infection and contamination. Enquiries on projected costs per dose formed part of the selection process for delivery devices of the aerosol vaccine. Only those who confirmed that the pricing would be similar to injectable vaccine (US$ 0.20 per dose) were included in the preselection of devices. The majority of the nebulisers being tested will be single vial use, with the vial and the nebulizer being discarded after use or after six hours following vaccine reconstitution, whichever comes first.

NRAs are assessed against a set of indicators that allow determination of capacity, and provide a basis for strengthening. Such assessments allow a producer to submit product for prequalification by the NRA. In Mexico the NRA has a very strong system for the evaluation and regulatory oversight of medicines and drugs, although nothing specifically for biologicals. The areas of licensure and lot release still need strengthening. The measles aerosol project is making efforts to ensure that the studies and the licensure documentation fulfil international standards and is exploring mechanisms to assist the national regulatory authorities including support from the recently formed NRA network.

HIV vaccine: Collaboration with the Global Vaccine Enterprise is ongoing, for example, intensifying surveillance activities for isolation and characterizing strains of circulating HIV. There are also activities in regulatory and ethics areas, strengthening clinical trial sites. WHO does not itself engage in research and development of HIV vaccine, instead facilitating as impartial broker. WHO has a seat on the Board of the European Developing Country Clinical Trial Partnership (a new European Union mechanism) and in that capacity discusses strategies and ways forward.

Ethics in paediatric vaccine trials: In 2002, WHO organized a consultation in Ghana on the precautions needed for evaluating vaccine in paediatric populations in countries with a high disease burden. A further consultation on ethical aspects of intervention is planned for 2005 on standards of care and intervention in cases of severe disease during clinical trials, perhaps in connection with HIV infection.

Avian influenza: WHO is promoting the development of vaccines that are not based on MI Glutemin but on the M protein of a virus, setting up standard methods and establishing the endpoints to evaluate the immunogenicity of the vaccine.
Factors in co-morbidity: The IVB team structure supports work between disease specialists on "common pathway" issues such as whether vaccine against influenza has a role in diminishing co-morbidity with pneumonia or RSV, a link that has been demonstrated in some research. At present there is little synergy with work on nutrition and diarrhoea.

Serotype distribution: SAGE praised the impact of the pneumococcal vaccine in the United States’ market but queried whether additional serotypes would be needed to increase the coverage of that vaccine for the serotypes prevalent in developing countries. Work has been done on serotype distribution in different areas. A meeting in London in November 2004 will address this specifically to determine, inter alia, whether the 7-valent vaccine can be used in other countries. The most advanced alternatives to the conjugate vaccines are the protein vaccines, which are not serotype-specific. WHO has only limited funds to support research on these vaccines and is using these for a consultation to develop guidelines for determining the clinical efficacy of the new products in a situation where effective vaccines already exist. The Children’s Vaccine Program at PATH has received a grant from the Bill & Melinda Gates Foundation to support development of candidate pneumococcal protein vaccines.

IVR budget: The overall research budget is US$ 21 million including staff and activities, of which US$ 7 million are staff costs. With additional funds more could be done to support the development of rotavirus alternative candidates and to support work on a malaria vaccine.

Recommendations:

- The following areas of work should be reassessed: cross-cutting issues and the role of the Network of Developing Countries Regulators in supporting and advancing some of the development projects.

- WHO should identify which other advisory committees, apart from the one overseeing the work of the Meningitis Vaccine Project, could possibly benefit from the participation of SAGE members.

7.2 Update on the Meningitis Vaccine Project (MVP)
(Presenter: M. LaForce)

In 2003 SAGE requested a follow-up presentation on conjugate meningococcal vaccine development issues. SAGE members have become more active in the Meningitis Vaccine Project (MVP), with four members joining the MVP Expert Panel. SAGE has been represented at all advisory meetings since June 2003.

Product development: A consortium has developed a monovalent A conjugate vaccine through the Serum Institute of India (SII). The development model looks at raw materials, manufacturer and the conjugation model with MVP coordinating work. The target price is US$ 0.40 per dose. Since June 2003, the conjugation method has been transferred to SII, the vaccine has been made and successfully tested, the product has been endorsed by an expert panel, clinical lots for phase I trials have been released by SII and for toxicological studies, and the Clinical Advisory Group has reviewed
and made recommendations on the plan to qualify the vaccine. The conclusions about the product are that the starting materials are consistent with the quality expected for Meningitis A, PS and TT vaccine components; there is no reason to doubt the safety of the conjugate on the current data; the SII conjugate produced good immunogenicity in mice, elicited clearly better antibody response than plain polysaccharide, and one lot in particular gave very good murine bactericidal antibody titres. The vaccine has been manufactured and sample packaging is under development.

Clinical Advisory Group: The group was convened in September 2004 and made a series of recommendations on the vaccine clinical development plan. These recommendations concerned the documentation of timelines and feasibility of field studies; the determination of key decision points for each trial; the presentation of the composition and role of the Data Safety Monitoring Board for each study; the planning of carriage studies; the addition of an infant pilot trial and the performance of a detailed review of potential control vaccine candidates.

Projected timeline: Clinical lots of the Meningococcal A conjugate vaccine were released by SII in August 2004, and toxicological studies will be finished in November 2004. A dossier is expected to be submitted to the India NRA for phase I testing in November 2004, and the study should begin in the first quarter of 2005. Phase II studies will begin in Africa in the last quarter of 2005.

Serotype distribution: Thanks to the partnership with the WHO/AFRO Multidisease Surveillance Centre (MDSC) in Ouagadougou, there is now information on the serotype distribution across Africa. In 2001, out of 40 000 cases of meningitis, there were fewer than 100 bacterial isolates where it was possible to type the organism. By 2003–2004 this had grown to 2000–3000 isolates annually. In 2004, 83% of all meningococcal isolates from acute bacterial meningitis were serogroup A strains.

Discussion

Vaccine pricing: A core component of the MVP product development strategy has been to achieve a final transfer price for a conjugate meningococcal vaccine for sub-Saharan Africa to meet recommendations from senior African public health officials to price the vaccine at less than US$ 0.50 per dose so that vaccine purchase can be funded from current bilateral arrangements.

Surveillance of strains: Nine countries participate in the advanced surveillance supported by the Multidisease Surveillance Centre (MDSC) in Ouagadougou. There is very little information on Nigeria. Collection and laboratory verification of data have greatly improved since 2001. DR Congo – traditionally not considered part of the "Meningitis Belt" – had in 2004 the leading number of reported cases of acute meningitis. Meningitis "A" is largely a disease of sub-Saharan Africa; the last major epidemic was seven years ago with almost 200 000 cases. Serogroup "C" now represents less than 1% of all isolates gathered (from 20% 10–15 years ago). W135 and C have been responsible for outbreaks, but A causes the vast majority of large-scale epidemics in hyperendemic countries.

Administration schedule: The experiences of the UK in introducing the vaccine against Meningitis C have been very influential. MVP plans two strategies: mass
immunization of 1–29 year olds in sub-Saharan Africa; and a two-dose under-one year strategy with the first immunization at 14 weeks and the second at 9 months. These strategies will be evaluated in the phase II trials. The phase I trial in India is a safety study for adults, at 10 micrograms.

**SAGE involvement:** Two members participate in the work of the Clinical Advisory Committee (in addition to two other members who participated in meetings to decide on candidate vaccine) and provide feedback on the work done. Interaction has been productive: the excellent work done by MVP presents a useful model in terms of the contractual manufacture of a conjugate vaccine by a developing country manufacturer and the challenges to make such vaccines available.

**Recommendations:**

- At the SAGE meeting in 2005, WHO should submit a report on the epidemiology of meningococcal serogroups in Africa.
- WHO should particularly strive to obtain more data on the epidemiology of meningococcal serogroup in Nigeria where currently no laboratory data are being collected by the African network.

### 7.3 Intellectual property rights and vaccines

*Presenter: M. Kaddar*

**Changing world scene:** In 1997 SAGE was of the view that intellectual property (IP) could be expected to encourage research and development and technology transfer, and would not present a barrier to vaccine access. Since then there has been considerable international debate on the public health implications of trade agreements. The 2001 Doha Declaration on trade-related aspects of intellectual property and public health attempted to find a balance. The World Health Assembly in 2003 then asked for an investigation into the implications of the new regulations, with a commission on IP being established in February 2004, to report to the WHO Executive Board in January 2006.

**Impact of IP on IVB work:** IP issues impact many IVB goals and activities such as promotion of research and development on most needed vaccines, the introduction of new vaccines and technologies in developing countries, and the promotion of technology transfer and competitive supply of vaccines. The work to develop a SARS vaccine is indicative of the problems that can result from IP: a large number of patent applications are being filed, there are overlapping and competing claims that may take years and legal processes to resolve, posing a challenge to vaccine manufacturers and potentially delaying or otherwise impeding the development of a vaccine.

**One vaccine, multiple patents:** To develop a product requires multiple steps in research and production, each of which could lead to a patentable innovation. Where there are multiple producers, each has to negotiate the patents with different actors.

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5 World Health Assembly resolution WHA56.27 on Intellectual property rights, innovation and public health, available at: [http://www.who.int/governance/en/](http://www.who.int/governance/en/)
to be able to proceed with the vaccine. If one patent holder decides to offer an exclusive license, the other producers are unable to develop the vaccine without developing new technology. "Patent pooling", is a practical solution that is being explored in the context of SARS vaccines and that may also be relevant for other vaccines such as malaria where, for one antigen there are more than 200 patents.

**TRIPS:** In 2005, when the TRIPS agreement enters into force in developing countries for pharmaceuticals and vaccine patents, there may be a number of products that become restricted, with impact on global access, availability, and affordability, especially for developing countries.

**Conclusions of the meeting on intellectual property rights and vaccines in developing countries:** The meeting was held in Geneva in April 2004 to facilitate information exchange among participants from industrialized and developing country manufacturers, public-private partnerships, public sector research institutions, international organizations and nongovernmental organizations.

Conclusions included that intellectual property rights (IPR) provide incentives to innovators and encourage investment by providing a temporary monopoly for their holders. IPR have not had a major impact on limiting access to existing vaccines in the past. However, there is concern that in future, patents may limit access to recent vaccines because of the multiple layers of IP and the potential for blocking of development. The meeting also discussed IP management and technology transfer, agreeing that the TRIPS agreement makes provisions to encourage technology transfer but there are not clear obligations, and no precise mechanisms for this. It is not clear whether market forces and incentives alone are sufficient to develop priority vaccines and promote technology transfer. Mapping of the situation and management of IP were agreed to be crucial, as there is a lack of expertise in developing countries, and there is concern among certain producers that IPR may have an impact on production of combination vaccines. However, positive benefits might be gained from the new models of research and development, where the public sector is involved to ensure the rights of developing countries.

**IVB’s role:** SAGE’s guidance was sought on the appropriate role for IVB in terms of documenting and analysing the issues, perhaps taking the lead in providing information, referrals, and capacity-building to countries, developing interventions to address adverse impacts on access and on research and development, and encouraging dialogue and partnership between all stakeholders to develop priority vaccines and facilitate access to them. IVB’s contribution to the field of IP and beyond the legal aspect was important, especially in terms of orphan vaccines and in terms of global access to technology transfer and knowledge. The broader community interested in issues such as ensuring access to products and the science, includes NIH and the Rockefeller Foundation.

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*The presentations, proceedings and background documents are available at: [http://www.who.int/intellectualproperty/events/vaccines-meeting](http://www.who.int/intellectualproperty/events/vaccines-meeting)*
Discussion

Public institutions: Public institutions hold many intellectual property rights (IPR). In the past such institutions have issued exclusive licenses to pharmaceutical companies in return for royalties. This does not always provide a return to taxpayers. SAGE commended NIH’s approach to IP and suggested making an explicit statement stressing to public sector institutions the need to consider the needs of the poor and of the developing world when patenting a product. There is a clause in TRIPS for compulsory licensing and government use that may be used.

Patent pooling: Without adequate IP protection companies cannot be expected to make the investment in developing the technologies or vaccines of the future. However, IP can impede progress through the associated complexities. Concerns have been expressed about potential difficulties in implementation; however, if patent pooling can be done it would be good step forward. A strong driver is needed to engage the actors and WHO can play a useful convening role in this.

WHO’s role in IP: SAGE strongly encourages WHO to take an active part in the Commission on Intellectual Property, expanding the perspective beyond drugs and antiretrovirals, to ensure that in 2006 vaccines are on the agenda supported by a strong consensus on the relationship between access and IPR. Technical, legal, ethical, political and health information should be aired. WHO should gather strong evidence of the negative or positive effects of IP on the most needed vaccines in developing countries. That evidence should be reported to SAGE and to the Commission in 2005. The effects of IP and the patent status of important vaccines could be tracked in selected countries and the results mapped. Interventions to address any negative impacts need to be developed. SAGE’s support was sought to put in place a collaborative network and encourage increased technical resources and the provision of expert advice. WHO should provide information and advocacy to producers, NRAs etc., and generally foster access to technical information.

Recommendations:

• To facilitate developing countries’ access to new inventions, WHO should clearly articulate the responsibilities of both private and public-sector intellectual property owners to consider developing-country needs in the management of their intellectual property.

• WHO should continue to take an active role in collecting and analysing information on how intellectual property rights may affect access to vaccines and vaccine development, with the Commission on Intellectual Property and Public Health, to ensure that these issues are reflected in the Commission’s report to be submitted in February 2006.

• WHO should be proactive in helping to resolve the issue of intellectual property rights over reverse genetics for influenza vaccine and generally encourage dialogue and partnership to resolve intellectual property issues for most-needed vaccines, with emphasis on the public health concerns.
7.4 **Challenges for rotavirus vaccine**  
*(Presenter: D. Steele)*

Rotavirus is ubiquitous and every child will receive a rotavirus infection; however, approximately one in sixty will be hospitalized. Approximately 500 000 children die from rotavirus annually, with deaths concentrated in sub-Saharan Africa and the Asian region. The global agenda for rotavirus vaccine research was set in 2000, looking at: the burden of disease studies in developing countries; laboratory surveillance of rotavirus strains; the epidemiology of intussusception; the rapid development of new rotavirus vaccines; parallel trials in developing countries; and the support of NRAs.

**Burden of disease surveillance networks:** In collaboration with RVP and CDC, regional networks are in place in Latin and Central American regions, African and Asian regions, and a network is in process in the Eastern Mediterranean Region. The networks provide information on the hospital-based burden of disease; surveys of health service use; cost estimates of diarrhoeal disease; laboratory strain characterization, creating regional laboratories in each network; and intussusception surveillance.

**Epidemiological toolkit:** In collaboration with CDC a range of documents have been prepared for the networks, including protocols on hospital-based burden of disease, health service utilization, intussusception, and cost estimation.

**Epidemiology and pathogenesis of intussusception:** A report has been prepared to provide a global picture of intussusception.7

**Development of vaccines:** There are many vaccine candidates, at different stages of readiness, offering great promise for the future.

### Table 1: The second generation of live oral rotavirus vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</th>
<th>Inventor</th>
<th>Principle</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLR</td>
<td>Lanzhou</td>
<td>Bai</td>
<td>Lamb – monovalent</td>
<td>Licensed in China</td>
</tr>
<tr>
<td>Rotarix™</td>
<td>GSK</td>
<td>Ward/Bernstein</td>
<td>Human – monovalent&gt;65 000</td>
<td>Licensed in Mexico</td>
</tr>
<tr>
<td>RotaTeq™</td>
<td>Merck</td>
<td>Clark/Offit</td>
<td>Bovine-human RV reassortant pentavalent</td>
<td>&gt;65 000 enrolling</td>
</tr>
</tbody>
</table>

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Table 2: The third generation of rotavirus vaccines in development

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</th>
<th>Inventor</th>
<th>Principle</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine UK reassortants</td>
<td>NIH</td>
<td>Kapikian</td>
<td>Bovine-human RV reassortant</td>
<td>Efficacy trial DCVM required</td>
</tr>
<tr>
<td>Rhesus tetravalent</td>
<td>NIH-BioVirX</td>
<td>Kapikian</td>
<td>Rhesus-human RV reassortant</td>
<td>In negotiation</td>
</tr>
<tr>
<td>Indian neonatal</td>
<td>Bharat</td>
<td>Indo-US Consortium</td>
<td>Human-bovine RV reassortant</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Australian neonatal</td>
<td>BioFarma</td>
<td>Bishop/Barnes</td>
<td>Human – monovalent</td>
<td>Phase 1, 2 DCVM required</td>
</tr>
</tbody>
</table>

There are three licensed vaccines, none of which is being used by the global community: Rotashield® was licensed by FDA in 1998, Lanzhou Lamb Rotavirus was licensed in China in 2000, and Rotarix™ was licensed in Mexico in July 2004. Rotashield® was withdrawn by the manufacturer shortly after being introduced in the US, before evaluation had been completed in African or Asian infants (where most infection is occurring), because of problems with intussusception in the US. A license has now been obtained for production of this vaccine outside the US. Clinical efficacy trials will need to be performed with this new “Rotashield®” to determine if it is comparable in preventing serious hospitalizing illness due to rotavirus. Both the immunogenicity and clinical efficacy of RotaShield® were lower in developing countries than in the developed countries. To date more than 700,000 doses (single dose regimen) of Lanzhou Lamb Rotavirus have been administered in China. The Institute is also trying to create a reassortant vaccine and different Chinese manufacturers are in consultation with NIH to acquire the NIH reassortant bovine rotavirus strain.

Two candidates are in late-stage development, each of which represents different approaches to vaccine design. The GSK Biologicals G1P[8] “Rotarix™” is a human rotavirus attenuated through tissue culture passage to create a monovalent vaccine, drawn from the most widely occurring strain globally to protect against infection. The Merck vaccine, “RotaTeq™” is an animal rotavirus strain, biologically attenuated, further attenuated through tissue passage for administration to humans. The vaccine consists of five strains, with the necessary antigens to elicit neutralizing antibodies to circulating human rotavirus strains.

**Efficacy results of late-stage candidates:** In efficacy trials in Europe Rotarix™ and RotaTeq™ showed comparable immunogenicity and efficacy data to Rotashield in the same population. In other trials in Latin America with Rotarix™, the results were a little lower but again comparable to the results of Rotashield in the same population. Currently large-scale safety and efficacy trials are being conducted in 12 countries in Latin America and 8 in Asia with Rotarix™. Although several cases of intussusception were reported, the data shows that they were evenly distributed between vaccine and placebo groups. The Dominican Republic and Mexico have granted national licenses to GSK for Rotarix™. On the other hand, RotaTeq™ is under evaluation in a large-scale safety and efficacy trial in the US and Europe, with
some subjects recruited in Central and Latin American areas. In the more than 70,000 infants in the trial, several cases of intussusception were reported but none in the window after vaccination. The Data Safety Monitoring Board is reviewing the data and results may be available by the end of the year.

Other early-stage candidates follow both the bovine reassortant strain model and the monovalent human neonatal strain with collaboration ongoing for technology transfer to developing countries for production.

**WHO initiatives for vaccine development:** Following the recommendation of the Global Agenda for Rotavirus Vaccine Research in 2000 that parallel vaccine trials be held in developing countries, a public-private partnership (RAPID) was convened by WHO in 2000 for parallel vaccine evaluation in Africa and Asia. Trials are ongoing in Bangladesh and South Africa to address issues that are important for developing countries, such as the EPI schedule; polio vaccine interaction with rotavirus; the dose regimen for infants; and the safety of live oral rotavirus vaccine in HIV-infected infants. Phase III efficacy trials are planned to start in 2005.

There are significant differences between developed and developing countries in the epidemiology of rotavirus infection: the disease infects children in developing countries earlier, infection occurs year-round, there is a high diversity of strains, co-infections and co-morbidity are common, and mortality is much higher. In general, live oral vaccines have performed less well in the developing world.

Discussions are ongoing between WHO and the Rotavirus Vaccine Programme at PATH with Merck, to conduct similar clinical trials with the Merck reassortant bovine-human rotavirus vaccine in developing countries in Asia and Africa.

The rotavirus ADIP (RVP) will only work with the late-stage candidates with the following attributes (as defined by GAVI): positive safety and efficacy data; credible manufacturer; en route to immediate phase III and market introduction.

WHO has important roles to play beyond the framework of the RVP, which includes supporting the early vaccine candidates, (e.g RV3 with BioFarma); strengthening NRAs so that they can adequately evaluate and license rotavirus vaccines; developing guidelines for production of live oral rotavirus vaccines; and looking at safety issues.

**Developing country manufacturers:** Emerging vaccine manufacturers potentially play a significant role: their entry into the market with other vaccines has already brought the prices of these vaccines down, and greatly increased supply. Their involvement with rotavirus candidates could be important.

**Regulatory issues:** WHO has established a developing-country vaccine regulators network that will help with review processes in countries where there is no functioning NRA. This new regulatory pathway could help with pre-qualification.

**SAGE role:** The advisory body is a very valuable resource as it has a broad cross-cutting view of the programme and is able to provide a broad view and input as counterpart to the highest level specialist technical advice given to each priority vaccine area. SAGE provides important policy considerations related to research and development, which greatly strengthen the effort.
Discussion

Surveillance issues: Events in the US with Rotashield showed that sample sizes needed to be large, although the definition of that size was not easy and had further complications in the context of parallel studies. Discussion between Merck and GSK with the FDA, based on figures of the attributable risk at the time of the withdrawal of Rotashield, led to the selection of a 60 000 minimum sample size. It is now known that the attributable risk is greatly less than the first figures of 1 case per 2500 vaccinees and is suggested to be 1:11 000 by more recent data. Thus even sample sizes of 60 000 are unlikely to answer the question of intussusception risk and it appears likely that only post-marketing surveillance will address the questions. The type of surveillance system needed to ascertain these adverse events, both in clinical trials and post-license, has been carefully considered by GSK and Merck. The license in Mexico was granted before the intussusception data associated with the GSK trial was available to the NRA.

The GSK multiple-site survey of safety and efficacy has a "double capture system" with a hospital-based surveillance in the sites where the study was taking place, to capture any cases of intussusception, in addition to an independent team surveying hospitals for cases. Confidence limits were set for the sample sizes that limited the number of cases of intussusceptions detected before the study was unblinded.

Laboratory-based networks: In 1998 a laboratory-based network was started in Africa, growing to 14 countries. The network is mainly hospital-based and focused on research. It is hoped to manage the network through the Regional Office for the African Region, which would provide a useful link to ministries of health. Discussions have recently been held with the Regional Office for the Eastern Mediterranean to set up a similar network there. In Asia there is collaboration with CDC and the Children’s Vaccine Program on surveillance involving 36 hospitals in nine countries, with support from the ministries of health. Intussusception surveillance is not linked to the networks.

National regulatory authorities: The Technical Advisory Group, shortly to make country evaluations in the Region of the Americas, should also review the strengths/weaknesses of the NRAs, for example in Cuba, a member of the global network of NRAs. The question was raised of how to take forward the work of the NRAs, through, for example, assessing their work through the regional offices which have the capacity to carry out assessments of vaccine management in countries.

Update on NIH bovine reassortant vaccine: An exclusive license has been granted in North America and Europe; it is also the intention to grant a license to two companies in India, three institutions in China and one in Brazil. A very different approach has been taken to IP in this instance, looking at the geographical needs of institutions with respect to rights to use the technology. Through consultation with stakeholders, depending on the market forces in operation, the approach is exclusive, co-exclusive or non-exclusive. The approach is to license it directly to institutions in mid-level emerging markets in developing countries to have it produced locally.

The Rotavirus Vaccine Project: A suggestion was made that RVP might consider extending its criteria to look at the new rotavirus vaccines with a view to adapting practices from the Meningococcal Vaccine Project to support introduction of one of the new vaccines where it was most needed.
Recommendations:

- WHO should keep SAGE informed of progress in assessing the effectiveness and safety of the vaccines both in clinical trials and in plans for post-marketing surveillance.

- Information is specifically requested on the methodology for intussusceptions-surveillance, in different settings where rotavirus vaccine is most needed and would be used.

- WHO should continue to work with the alternative vaccine candidates and the emerging country manufacturers.

8. Measles mortality reduction and rubella control

8.1 Update on progress and recent developments

(Presenter: B. Hersh)

Reduction targets: In 1999 there were an estimated 875 000 measles deaths globally. Half were in Africa, 30% in South-East Asia. Global targets have been set to reduce the under-five mortality rate by two thirds by 2015, and to reduce measles deaths by 50% by end 2005 compared to 1999 levels. Of the six WHO regions, four have established regional goals for measles elimination (the Americas (2000), Europe (2010), Eastern Mediterranean (2010) and Western Pacific (2012) regions). The current global goal is not eradication, but sustainable measles mortality reduction.

Priority activities: WHO and UNICEF have identified 45 countries for priority measles reduction activities. They are mostly in Africa and South-East Asia and accounted for about 95% of measles deaths in 2000. All except one country is GAVI eligible. The strategy for sustainable measles mortality reduction8 seeks as a foundation, to strengthen routine immunization services through the RED strategy; provide all children with a second opportunity for measles immunization; conduct surveillance to monitor progress; and assure appropriate measles case management (vitamin A and antibiotics as necessary).

Global meeting for sustainable measles mortality reduction and immunization system strengthening: There were over 250 participants at the WHO-UNICEF meeting in South Africa in October 2003, including senior ministry of health representatives from the 45 priority countries, partner agencies and WHO and UNICEF regional staff. Progress and obstacles were discussed and a declaration was agreed on working together to strengthen routine immunization systems, and on achieving and possibly surpassing the 2005 goal.

Role of GAVI: A principal recommendation of SAGE in 2003 was to encourage the “fullest possible collaboration of GAVI in supporting the objectives of sustainable measles mortality at country level”. In April 2004 WHO submitted a “measles

investment case" to the GAVI Board, advocating increased GAVI engagement in measles mortality reduction activities in Africa. The result was an award of US$ 37 million over five years for "catch-up" campaigns and US$ 13 million for introduction of a routine second dose of measles vaccine in selected countries.

**Insufficient coverage:** Routine measles vaccine coverage in the 45 countries is approximately 65%. That is an increase from 1999 when coverage was only 59%. This chronically low coverage has allowed the measles virus to circulate, killing thousands of children each year.

**Figure 4: Average measles vaccination coverage, 2000–2003**

The 45 countries are those with the weakest health systems and lowest routine coverage.

**Supplementary immunization:** In the priority countries between 2001 and 2004, 28 have conducted nationwide catch-up campaigns targeting children 9 months to 14 years old; 8 countries have conducted subnational SIA; and 9 countries have not yet started (including India, Nigeria and Pakistan – polio-endemic, high-population countries with a very high measles burden). Between 1999 and 2004, over 280 000 000 children have been vaccinated against measles, mostly in catch-up supplementary campaigns, but increasingly also in follow-up campaigns.

**Measles vaccine security:** In 2002–2003 there was a crisis in supply of single-antigen measles vaccine whereby demand virtually equalled supply. This has been rectified, but is a major issue for the future.
Measles vaccine is relatively inexpensive: US$ 0.12 per dose. There are four major vaccine manufacturers that supply measles vaccine to UNICEF, but the overwhelming majority comes from one producer, which raises vulnerability issues. UNICEF has worked with manufacturers to increase availability through 2006, with the result that prices have increased.

Surveillance: Building on the polio infrastructure, a global measles/rubella laboratory network has been developed to provide testing of suspected cases to confirm diagnosis. There are currently 690 laboratories in the network, including subnational laboratories, national laboratories, regional reference laboratories and global specialized laboratories. Most of the funding and personnel comes from the countries themselves, with WHO providing technical support and laboratory reagents.

Estimating the global measles burden is a challenge; surveillance is incomplete in many countries; those with the highest burden do not conduct measles mortality surveillance. To confirm that the goals set have been reached, there must be accurate data. WHO has developed a model to estimate measles mortality levels and trends that uses country-specific indicators such as coverage data from both routine and supplemental immunization activities, vaccine-effectiveness, and case fatality ratios. The latter is the most sensitive parameter.9

Decreasing measles mortality: Globally, based on provisional estimates, there were approximately 530,000 measles deaths in 2003, representing a 39% reduction compared to 1999. The measles deaths in the African Region have been reduced by 49% over the past four years, impacted by increased routine coverage and supplementary immunization activities. It is expected that the 2005 measles mortality target will be met and likely surpassed. A global goal for eradication does not appear to be imminent, since polio has not yet been eradicated. To support continued success WHO must: strengthen routine immunization, assure country ownership of the activities with financial sustainability, and work on integration of measles mortality reduction with other priority health interventions.

Decreasing measles morbidity: Numbers of confirmed measles cases in countries where campaigns have increased measles vaccine coverage show dramatic reductions in morbidity, for example in Ghana, Kenya and Malawi. The experience of the Americas shows that it is possible to interrupt indigenous transmission of measles. The last indigenous case was reported in November 2002 with one small outbreak in Mexico 2003–2004 due to imported measles virus.

Integration with malaria interventions: Many of the countries that are high-risk for measles are similarly high-risk for malaria. Efforts have been made to integrate activities. Insecticide treated bednets are very effective for reducing under-five mortality from malaria but are bulky to transport: planning and logistics are critical to overcome this.

Rubella: the trend shown in the Region of the Americas, is that, as the incidence of measles decreased and laboratory testing improved, rubella appears to "emerge". In 2003, the Americas established a regional goal to eliminate rubella by 2010.

The laboratory network has revealed a high burden globally of rubella and congenital rubella syndrome (CRS) globally affects an estimated 100 000 infants annually. The primary purpose of the rubella vaccination is to prevent CRS (rubella infection in the first three months of pregnancy gives a 85% risk of CRS birth defects). However, the vaccine must be used appropriately. Where there is low chronic routine rubella vaccine coverage there is an increase in the average age of rubella infection, thereby increasing the risk of CRS. As with the introduction of any new vaccine, a full and careful assessment must be made before introducing rubella vaccine. The emergence of rubella must be assessed and policy developed. This will be a major issue for the African Task Force on Immunization (TFI) to discuss in December 2004.

There is an increase in the number of countries using rubella vaccine, from 65 in 1996 to 110 to 2003. Two regions have rubella goals: the Region of the Americas has a goal for rubella elimination by 2010 and the European Region has a goal to reduce CRS incidence to less than 1 case per 100 000 live births by 2010.

Discussion

Coverage plateau: SAGE noted that there had been little evidence of increased coverage overall in the last decade. This is of very considerable concern, given that there are still high-population, high-disease-burden countries, such as Pakistan, producing quantities of measles virus, which were not apparently being tackled. The three priority countries (India, Nigeria and Pakistan) represent about one quarter of the global population. The children can be accessed; this has been seen in the polio campaigns. The measles vaccine is very inexpensive. SAGE questioned why those children could not be reached, at least once. In reply, WHO cited the efforts of GAVI, the RED strategy, the identification of target countries, and work commenced there: these are positive steps. Not enough has been done yet, but an important start has been made. There has been a major drop in deaths from measles, to which the supplementary campaigns have contributed.

Leaving the worst until last: One SAGE member speculated that experience from the polio eradication initiative suggests that, had the most difficult areas been dealt with first, rather than last, eradication might have been achieved earlier. It might be better to refocus the measles strategies, tackling the worst, most high-burden countries first. WHO is working with the governments of India, Nigeria and Pakistan to turn their attention to measles. Without their commitment, it will not be possible. However, polio remains endemic in these countries. Discussions on measles have been held with EPI managers in these three countries; an assessment has been made in Pakistan, and work done in several states in India on measles. Measles has been brought under control using these strategies in other difficult countries, such as Afghanistan and Angola. Campaigns have been conducted in Iraq, and are being planned for Djibouti, Somalia and Sudan. There are political reasons why certain countries have not been reached, not technical. Eventually even high-burden countries will be able to set elimination targets. This may eventually pave the way for global measles eradication (there was not consensus on this point).

Strengthening routine immunization: Measles activities are part of EPI, not a separate activity or vertical programme. WHO works as an integrated team, with countries, with GAVI, and other partners through the RED strategy to improve coverage, conduct microplanning and monitoring at every district.
Routine second dose: Countries like Canada, Finland and the United States have been able to eliminate measles without mass campaigns. High routine coverage of two doses is an appropriate elimination strategy. It would not be appropriate in countries with low coverage. Where a country has a high routine coverage with the first dose, the second dose could be really useful. Once high coverage and low incidence is established, an increase in the age of vaccination could be considered, from 9 months to 12 months, at which age there is higher vaccine effectiveness. In the future, a routine second-dose schedule would offer opportunities for add-on interventions, such as bednet distribution. It is a long-term strategy, and as such countries must be able to assure consistently high coverage of both doses either through routine immunization or periodic follow-up campaigns.

There are several vaccines suitable for giving at nine months: the question was reiterated of a possible second dose of meningococcal A vaccine at this point, as well as for yellow fever, and measles. WHO suggested that GAVI, or the IFFIm, may be able to support this with a new ADIP.

Surveillance: Surveillance is acknowledged to be one of the most important aspects of an elimination strategy. Standard case definitions and surveillance guidelines have been developed and are being adapted and implemented by the regions. Moreover, the global laboratory network is now evaluating the possibility of using saliva samples or blood spots on filter paper to confirm measles diagnoses.

SAGE questioned whether the surveillance systems at country level were adequate to assess the burden of rubella. Some special studies need to be done in countries looking specifically at the burden of CRS and immunity profiles of women of child-bearing age to assess the risks of rubella outbreaks.

Issues in data collection: Estimation of mortality is always problematic, particularly in data-poor countries. Every effort is made to validate data. The method used by WHO to estimate measles mortality levels and trends constantly cross-checks against surveillance data in countries, to check that estimations from the model are in line with what is being reported from surveillance systems in different countries. The most sensitive parameter in the model used by WHO is the estimate of the case fatality ratio. WHO is improving data, through new, extensive, community-based studies.

Measles/yellow fever vaccine: At a previous meeting it had been suggested that a combined measles/yellow fever vaccine be prepared for sub-Saharan Africa. A study to assess demand was to be conducted. In Brazil, measles and yellow fever vaccines have been administered simultaneously to a small group, with very good results. However, when the test group was enlarged, competition between the vaccines was revealed: measles seroconversion was lowered. Although a combined vaccine is feasible, and formerly existed, a programmatic decision would need to be made, balancing cost and effect. Also, a very broad long-term study would be needed before embarking on simultaneous vaccination, given the questions raised over its effects.

Vaccine supply: UNICEF confirmed that there is currently sufficient vaccine supply but that efforts are being made to increase the number of vaccine suppliers.
Vaccination of pregnant women: Since 1998 Brazil has vaccinated almost 40 million women against rubella. Results of a study on this are to be published in November 2004, showing that the vaccine appears to have no adverse effect in the infants born to women who were inadvertently vaccinated early in their pregnancy. These data provide additional evidence to demonstrate that rubella vaccine administered early in pregnancy does not cause CRS.

Aerosol applications: The use of the aerosol technology to administer rubella vaccines as well as measles is an important area currently being investigated to avoid creating an orphan product of single-antigen aerosol measles vaccine. A consultation has already been held on this. Aside from further safety and immunogenicity issues that remain to be conducted, preliminary studies in Mexico of MMR and MR aerosol vaccines show similar immunogenicity and safety profiles to those of subcutaneous injection. In the first quarter of 2005, work will begin to develop the full plan and carry out initial studies.

Recommendations:

- At the SAGE meeting in 2005, WHO should present a report from the regions on progress with rubella vaccine introduction; a report on the optimum age for the first measles dose in the light of current research and findings; and the potential benefits, risks, regulatory issues and experience to date with the development of a combined yellow fever-measles vaccine.

- WHO should support efforts to implement measles mortality reduction strategies in the large, measles-endemic countries, with an ultimate aim of encouraging the remaining two regions (the WHO African Region and the WHO South-East Asia Region) to establish measles elimination goals.

9. Challenges around vaccines

9.1 Issues for the global prevention of invasive *Haemophilus influenzae* type b diseases

*Presenter: P Zuber*

Hib introduction: The use of Hib vaccine has increased substantially since 1997 from 25 countries to 88 by the end of 2003, including 8 African countries. There are several barriers to introduction: uncertainties about the true burden of disease limit decision-making on vaccine use and cost-effectiveness. Limited vaccine supply and high price present additional challenges.

In industrialized countries: Hib vaccine introduction was based on demonstrated incidence of laboratory-confirmed meningitis cases. This represents only a fraction of the true burden of disease. Many countries have limited capacity to confirm the diagnosis. Severe pneumonia is an important cause of mortality in many developing countries and demonstration of impact on pneumonia is important for decision-making. However, the lack of a test for laboratory confirmation of Hib pneumonia makes estimation of burden difficult. Current estimations of the global burden of Hib infections vary greatly, with mortality ranging from 200,000–700,000 annual deaths with the burden of Hib pneumonia mortality contributing to the wide range in the estimates.
**Epidemiology:** The literature on confirmed meningitis incidence indicates a very low incidence of invasive Hib disease in Asia. However, several methodological limitations due to the limited use of cerebrospinal fluid culture and use of antibiotics prior to specimen collection have consistently raised the possibility that those studies underestimated the true incidence of meningitis. Data from Africa, the Americas, the Middle East and Oceania suggest higher incidences. In Western Europe, data indicating middle incidence was considered sufficient justification for immunization.

**The impact of Hib vaccine:** Two important studies have recently been completed in Dhaka, Bangladesh and Lombok, Indonesia. In the Lombok study on meningitis incidence among vaccinated and unvaccinated children aged 2–23 months, the laboratory-confirmed vaccine-prevented incidence was low (14 cases per 100 000 children less than two years of age). The statistically significant reduction in cases of meningitis with spinal fluid inflammation suggests that the true burden of Hib meningitis is four to five times greater than that measured by laboratory confirmation alone.

**Review panel findings:** Based on the Lombok data and other recent studies, a panel to review Hib disease burden in Asian countries met in Bangkok, Thailand in January 2004 and recommended that countries considering Hib vaccine introduction should look at the possible burden of disease, starting with syndromic surveillance of meningitis and trying to estimate the proportions attributable to Hib through a few facilities with improved laboratory capability. Four possible approaches to estimating the Hib burden were suggested, depending on country circumstances and resources: rapid assessments, population-based surveillance, case-control and prospective cohort studies of vaccine effectiveness.10

**Cost-effectiveness:** With imprecise burden data it is even harder to estimate the cost-effectiveness of vaccine introduction. WHO has therefore developed guidelines for estimating the cost effectiveness of Hib vaccines.11

Six cost-effectiveness studies have been published from developing countries and one from an economy in transition. The overall conclusion of most of the cost-effectiveness studies in developing as well as in developed countries, is that Hib vaccine introduction is cost-saving to society and in most cases also to the health sector.12 While the assignment of a money value to a life lost is sometimes the determining factor for this conclusion, a few studies illustrate that the vaccine is cost saving when "only" future treatment costs saved are included. In all the economic evaluations published so far, the effect of Hib vaccination is only evaluated according to invasive Hib disease. While most studies include all types of invasive Hib disease, some are only assessing the effect on Hib meningitis.

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10 Review panel on *Haemophilus influenzae* type b (Hib) disease burden in Bangladesh, Indonesia and other Asian countries, Bangkok, 28–29 January 2004, see http://www.who.int/wer/2004/wer7918/en/


**Product limitations:** The pentavalent vaccine is presented in two-dose vials that require large volumes of storage (three times more than the 10-dose DPT/Hep B). The lyophilized version has to be reconstituted with a liquid component. The price remains high, at US$ 3.60 per dose. Supply is through a single manufacturer, and has been insufficient until now to provide vaccine to all GAVI-approved countries.

**Vaccine cost:** The use of the expensive Hib vaccine has dramatically changed the cost of vaccine programmes (see also section 5 on financial sustainability planning). In most African countries, vaccine procurement is the main component in the programme. The challenge of funding vaccine programmes is greatest in donor-dependent countries.

**Lessons learnt:** Studies of Hib introduction in South Africa, Tanzania and Uganda have reinforced the important lesson that, even with demonstrated and convincing data on disease burden, Hib vaccination will not be introduced/maintained unless supply is 100% assured; prices decline substantially; and decision-makers are personally interested in introducing and sustaining the vaccine.

**Future activities:** WHO will work with countries to strengthen evidence-based decision-making. This will include ensuring that:

- In Asian and Eastern European countries, additional studies are conducted to measure the extent of undiagnosed Hib infection, implementing the approaches recommended by the Bangkok panel.

- In Africa, improved communication of existing evidence on Hib disease burden and vaccine impact is developed.

- A vaccine product menu is made available to national managers, allowing them to understand all the programmatic implications of vaccine product characteristics.

- An increased number of suppliers becomes available, as several countries are working on multivalent products including Hib through technology transfer.

- Financial sustainability planning efforts are pursued, with shared responsibility for financing agreed.

- Documentation of the impact of the Hib vaccine is obtained systematically, looking at the immunization system, disease incidence and adverse events. This will also allow for problems to be addressed, issues and solutions documented, and the experience communicated to local stakeholders and other countries.

The original 1998 WHO statement on Hib vaccine does not clearly indicate where Hib should be used based on existing evidence. The proposed agenda should allow, by the end of 2005, clarification of recommendations for several important parts of the world while allowing the ability of countries that could be benefit from Hib vaccination to introduce it in a sustainable way.
Recommendations:

- WHO should consult with countries in all regions, with particular emphasis in the WHO African Region, on their use of Hib vaccine. These consultations should aim at providing comprehensive information on existing evidence about Hib disease burden and the impact of Hib immunization in preventing meningitis and pneumonia.

- By the end of 2005, WHO should provide clarification on its recommendations for vaccine use in several geographical areas.

9.2 Update on GAVI Hib recommendations
(Presenter: D. Fleming)

Hib provides good examples of the issues around financing, supply, delivery of services and surveillance that have been discussed by SAGE.

Review: After four years, only 15 of 38 countries have been approved and chosen to introduce Hib. Some are now reaching the end of the five-year cycle of Vaccine Fund financing but have not arranged a transition to self financing. A mid-course assessment of the Hib policy is warranted, perhaps with corrections. A task team has been set up by GAVI, to look at programme issues, forecasting, procurement and supply issues, and immunization financing.

A country consultation process has started with three groups of countries: those which have introduced or decided to introduce Hib vaccine; those with a known high Hib burden yet to decide, and those with an unclear disease burden. Feedback indicates problems with lack of recognition of the problems, lack of perceived priority, lack of local data and lack of finance to sustain programmes.

Discussion

Lessons learnt from the United Kingdom’s introduction of meningitis C vaccine:
The UK introduced a meningitis C conjugate vaccine, which was essentially a very similar product (a protein conjugate with a polysaccharide). The product was originally developed primarily for the UK, but uptake expanded to other countries. The price has fallen every year in which the UK has contracted for it in the last five years, and is now a fraction of the original level. The difference may be in having three competing suppliers whereas there is no competition in the pentavalent market.

Lessons learnt from introduction of vaccine against hepatitis B: A study has been made of the characteristics of countries that adopted hepatitis B vaccine, in which there were two clear important factors: infrastructure (as indicated by the percentage of coverage rate for DPT at the time) was ten times more important than the disease burden); and the cost of the vaccine relative to the GDP of the country. In a predictive model, it was possible to establish which countries would be likely to accept the vaccine. This correlates quite well with the picture seen now with Hib. However, even lowering the price shows very little uptake in the sub-Saharan countries because of the lack of infrastructure.
**Vaccine cost:** A choice was made to introduce a vaccine that has higher technological barriers to entry than others (the pentavalent vaccine). There are few manufacturers that own the production for all five of the components. Dealing with sub-suppliers adds to the cost. A "menu of options" would be important. If the objective is the lowest possible cost of Hib vaccine, economies of scale could be obtained. Different costs are associated with preferred presentations e.g. a single measles dose produced by the same manufacturer would cost US$ 0.75–US$ 0.90 per dose, instead of US$ 0.14 for a ten-dose vial. Competition is going to be part of the solution: an increase in the number of manufacturers will introduce competition and price decreases, however, depending on the price threshold, it may also be necessary to look at different presentations.

**Fundamental issues:** The issues are: what is the disease burden and what does it cost to prevent it? The crux of the programme is how to address these two points. It is easier to address the clarification of the disease burden while financing is the harder aspect. Achieving a decline in the vaccine price is the most important factor in achieving accelerated introduction of vaccine.

**WHO's role:** Communicating value. Most experts believe that the burden of Hib disease is higher in Africa than in Europe, North America or many other parts of the world. That information has not been communicated to the African decision-makers. WHO should actively address this information deficit by developing a comprehensive information package for national decision-makers. Hib is “invisible” to many decision-makers in Africa, unlike hepatitis B, where blood screening provided evidence, or meningococcal A infection, that is responsible for spectacular outbreaks. The current WHO position paper does not provide sufficient guidance on the use of Hib vaccine (“In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included as appropriate to national capacities and priorities in routine infant immunization programmes”).

### 9.3 Quality challenges: acceptability of cell substrates

**Presenter: D. Wood**

Through reviewing a specific challenge to quality in the areas of acceptability of cell substrates, advice was sought from SAGE on the wider issue of how to assure the public’s right to an independent assessment of the safety of the vaccines. The specific issue is that there is a broad range of cell substrates available for production of biologicals including vaccines. However, the range of substrates accepted by regulatory authorities for vaccine production is limited.

**WHO’s role:** WHO establishes norms and standards for all aspects of vaccine production and quality control including the cell substrates used for manufacture of virus vaccines. These take the form of written standards (the WHO Technical Report Series) setting out specifications to assure safety, quality and efficacy of vaccine products. These written standards facilitate integration of sound science into regulations.

**Specifications are already in place for three types of cell substrate:** primary, diploid and continuous cells. Risk-reduction strategies are applied to all cells in the areas of good manufacturing practices (e.g. no prior handling of animals or infectious materials)
and characteristics of the source materials (e.g. cells of neurological origin are not used).

**Trends in cell substrate acceptability:** The progression has been from primary cells to diploid cells, to a few lines of continuous cells (all of which are used currently). Consensus on the acceptability of each cell type has taken on average a decade or more to achieve, primarily because of safety concerns. In the last few years, much work has been done by vaccine manufacturers on expanding the use of continuous cell lines. Additional cell lines are under consideration in order to expand the range of vaccines available. Many current candidate vaccines are being developed in cell lines that are not widely accepted by regulatory authorities. They may, however, ensure the availability of vaccines that cannot be grown in currently accepted cells, or improve the yield of some existing vaccines.

**Management of potential risks from the new cell lines:** There are three categories of risk: unwanted contaminants such as viruses and other transmissible agents; growth-promoting proteins; and cellular DNA. The aim of regulations is to put mechanisms in place to manage and minimize these risks. Potential infectious agents are screened through a combination of tests that have to be carried out on all products, and manufacturing processes have to be validated to exclude potential introduction of adventitious agents (including re-examination when new agents are discovered). Cell banks are extensively tested for infectious agents. The risks from growth-promoting proteins are considered negligible as they are essentially transient, are rapidly inactivated and are not considered to replicate. An area of more concern is where cell substrates contain residual cellular DNA that might result in a transfer of unwanted biological activity to vaccine recipients. There is good evidence that the limits for cellular DNA set for Vero cells assures safe products. The key issue for SAGE to consider was whether this risk reduction strategy is sufficient for the new cell substrates under investigation.

**Vaccine cell substrate conference:** Risk assessments and studies were reviewed at a conference co-sponsored by the International Association of Biologics and the US NIH in June 2004. Studies presented at the meeting showed that the potential adverse effects of continuous cell DNA had not been detected in model systems; that the present manufacturing processes support reduction of cellular DNA below theoretical risk levels; and that DNA inactivation methods can be incorporated into the manufacturing processes. The consensus of the conference was that the risk-benefit equation was favourable to using new continuous cell substrates and WHO was requested to facilitate international consensus on specifications for vaccines produced in these cells. The conference also recommended various follow-up studies, e.g. on dose-response studies to determine the relationship of DNA dose to biological activity.

This type of research is going on in industry but should be supplemented by additional coordinated research by academics and regulatory authorities. The infrastructure and support for this type of research, especially in the regulatory authorities, is either lacking or under threat. It would be inappropriate for all the expertise in these areas to reside with industry.

**SAGE’s role:** Advice is needed on how WHO can help build or retain capacity in regulatory research to address vaccine quality challenges such as the theoretical
safety risks associated with residual cellular DNA. SAGE advice was also sought on WHO plans to develop consensus among regulatory agencies on specifications for risk reduction, and to communicate the risks and benefits effectively to researchers, manufacturers, regulators and users.

**Strategies:** WHO could establish a working group to recommend and coordinate scientific studies to answer specific questions relating to potential risks from residual cellular DNA; ensure that safety and broader cell substrate acceptability issues are impartially considered, through referral to the Global Advisory Committee on Vaccine Safety; and, if warranted by the new data, propose a revision to the WHO norms and standards for cell substrates.

**Timeframe:** With appropriate support, the necessary experiments could be conducted over a two to three year period.

**The benefits/potential returns on involvement:** There would be an authoritative and credible analysis of the risks and benefits of using new continuous cell substrates. If international consensus is reached on appropriate specifications, vaccines produced in such cells would be more rapidly available. Expertise would be preserved for regulatory research in NRAs; and validated cell seeds could be made widely available to vaccine developers – as has already been done with the WHO Vero cell bank.

**Discussion**

**Industry support for coordinated activities:** There is a lot of support from the industry to collaborate in a coordinated manner on cell substrates. Many vaccines under development require specialized cell lines. It would benefit everyone to centralize expertise in a forum where data can be presented and guidelines set up.

**Need for safety:** The new approaches outlined have significant implications and should be pursued in conjunction with broad safety considerations over the long term and with extensive testing. In 2003 SAGE had asked WHO to review mainstreaming safety into all the activities of the programme. This must also be clearly stated in the GIVS document.

**Risk assessment:** SAGE was in agreement that work on risk assessment should be pursued.

**Research requirements:** Currently progress is limited by the cell types that can be used. Vero cells are available, but it would useful to have other options also. There are finite limits of stocks of some cell substrates that are currently widely accepted, such as MRC-5 cells, which is another reason why new cell substrates will be needed. Many technologies exist to analyse the risks of use of new types of cell types and novel substrates, such as from plants and insects.

**Communication of new developments in vaccine production:** WHO should foster informed decision-making by the public through provision of information on vaccines. Communications must take account of the particular sensitivities in the information on the developments in continuous cell substrates.
Recommendation:

- WHO should establish a working group to recommend and coordinate scientific studies relating to the safety of new continuous cells substrates, and to discuss their acceptability.

9.4 Regulatory and safety challenges

(Presenter: N. Dellepiane)

WHO’s objective is that 100% of vaccines used in immunization programmes are of assured quality, i.e. they conform to two essential criteria. These are: regulatory oversight by an independent authority that is capable of exercising the six critical regulatory functions defined by WHO; and the absence of any unresolved quality-related problems.

Functions: In addition to a national regulatory system, supported by legislation, the regulatory authority should be able to fulfil the following functions: licensing; post-marketing surveillance; lot release; laboratory access; regulatory inspections; and authorization/evaluation of clinical trials.

Priority countries: Countries are categorized according to the extent of the support required:

a) Although all countries need to have some regulatory system, the 83 countries that receive their vaccines through the UN agencies have the least need for regulatory functions to be in place because the vaccines supplied by the UN are all prequalified by WHO (which takes care of some of the regulatory needs). These countries need to be able to license the vaccines and monitor their safety and efficacy through a post-marketing system.

b) In addition to the above basic regulatory functions, the 61 countries that procure vaccines directly also need to be able to perform "lot release" and have "access to laboratory" testing.

c) The 48 countries that produce vaccine for domestic use or for export purposes must meet all functions.

Capacity-building: This effort has primarily been focused on producing and procuring countries. Regulatory authorities are assessed using a published tool that identifies the weaknesses and gaps in the regulatory system. An institutional development plan is developed on the basis of the findings. This usually includes a training component, provided by the Global Training Network on Vaccine Quality. Reassessment is done regularly to reinforce the cycle of improvement. Since 1998, 52 NRA assessments have been conducted.

Prequalification of vaccines: WHO provides advice to United Nations agencies on the quality, safety and efficacy of vaccines, focused on ensuring that vaccines meet the needs of the programmes. Once the vaccines have successfully passed the prequalification process they are flagged for acceptability for purchase. Vaccine quality monitoring is continuous. The evaluation process includes: a review of documentation;
the testing of samples to assess the consistency of the production; and a visit to the manufacturing facility. Because of its nature, the vaccine evaluation process has become an effective means of verifying the effectiveness of regulatory enforcement by NRAs, and for identifying appropriate training to address their weaknesses.

The countries that procure through the UN system receive vaccines of assured quality. Almost 60% of the producing countries get vaccines of assured quality, as do 15% of the producing countries. This is a substantial improvement but much remains to be done.

**New challenges:** The responsibility of regulating new vaccines is falling increasingly on developing countries, not the producing countries. This is a challenge for the regulatory authorities of the recipient countries, which do not have the experience and skills to assess the data and dossiers. The NRAs must therefore acquire new skills.

Although the quality of the trials should be guaranteed, clinical trials are being run in any country irrespective of the strength or capabilities of the NRA.

There is an exploding demand for evaluations of new vaccines, with 40 products in the pipeline for 2004–2006. Critical indicators have been defined by experts to ensure the level of functionality of national regulatory systems as a pre-requisite to the evaluation of vaccines for export. Developing-country vaccine manufacturers have an increased role in making products available for the international community. This brings additional requirements to produce reliable safety information.

**WHO’s response to challenges:** To overcome constraints related to the regulatory oversight of novel vaccines, a new area of work has been established, for the development of new regulatory pathways. The Developing Countries Vaccine Regulators Network has been created (nine countries) to promote and support the strengthening of the capacity of these NRAs to evaluate clinical trial proposals and clinical trial data, through the exchange of expertise and relevant information. Regional networks and task forces are also being promoted to facilitate clinical trial approval, monitoring and evaluation. An option is now available, to pursue a Scientific Opinion issued by the European Medicines Evaluation Agency, which would enable vaccines produced exclusively for use in developing countries to be assessed by the EMEA even though they will not be licensed in Europe.

Following the 2003 SAGE meeting recommendations, the prequalification and NRA assessment procedures have been reviewed and revised by experts: critical indicators have been defined for NRAs that regulate vaccines for international supply. With regard to the prequalification procedure, changes include: simplification of the site visits; extension of the interval between re-assessments; and the possibility of fast-track process under certain circumstances. Priorities have been set regarding the vaccines that will undergo prequalification. Furthermore, increased efforts are being made to improve the speed and quality of communication on vaccine safety. In this regard, funding for NRAs is a critical issue and GAVI immunization service funds may be a feasible source for this purpose.
The Global Advisory Committee on Vaccine Safety (GACVS) hosts a web site\(^{13}\) on which relevant reports are disseminated in all the official UN languages and regular updates given on topics of mutual concern. This web site hosts a network of sites, the "Vaccine Safety Net\(^{14}\), which links to a range of web sites providing vaccine safety information in compliance with criteria of good information practices assessed by WHO.

**Discussion**

SAGE expressed its support for the work being done to support vaccine regulation and prequalification with the objective of increasing the number of high-quality, safe vaccines available to countries.

**Web site:** The information pooling represented by the new website is a valuable resource for stakeholders in vaccines all over the world.

**Regulatory networks:** The aim is to facilitate clinical trials, premarket. The network can also support post-marketing safety.

**NRA strengthening:** A strategy should be in place to support the NRAs as identified.

**Recommendations:**

- WHO should further strengthen its work on the core functions of quality, safety and regulatory issues, continuing its capacity-building work with national regulatory authorities to ensure that they exercise all their critical regulatory functions.

- WHO should consider increasing the attention paid to post-marketing surveillance, and to the epidemiological capacity-building for such surveillance. This effort could also include promoting the use of regional networks of national regulatory authorities.

- WHO should continue its work towards the global use of vaccines of assured quality and strengthen its efforts to communicate the value and benefits of vaccines and their safety through resources such as the Global Advisory Committee on Vaccine Safety web site and the Vaccine Safety Net.

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\(^{13}\) [http://www.who.int/vaccine_safety/en/](http://www.who.int/vaccine_safety/en/)

Annex 1: Agenda

Wednesday, 27 October 2004

Chair: Merceline Dahl-Regis
Rapporteur: Silvia Bino
IVB: Julian Bilous

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<th>Time</th>
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<tr>
<td>8:00</td>
<td>Participants registration</td>
<td>Security; Liane Gross (IVB)</td>
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<td>8:30</td>
<td>Opening of meeting</td>
<td>Joy Phumaphi, ADG/FCH</td>
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<td>9:15</td>
<td>Welcome to participants</td>
<td>Jean-Marie Okwo-Bele, Director, IVB; Peter Carrasco (IVB)</td>
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<td>10:00</td>
<td>Highlights of 2003–2004 achievements, including report on progress with 2003 recommendations</td>
<td>J-M Okwo-Bele (IVB) &amp; Pascal Villeneuve (UNICEF)</td>
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<td>10:30</td>
<td>Coffee break</td>
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<tr>
<td>10:30</td>
<td>Global Immunization Vision and Strategies (GIVS)</td>
<td>J-M Okwo-Bele (IVB) &amp; Pascal Villeneuve (UNICEF)</td>
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<tr>
<td>12:30</td>
<td>Lunch</td>
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<td>14:00</td>
<td>Improving access to immunization services in Africa</td>
<td>Déo Nshimirimana, Regional Adviser (IVB/AFRO)</td>
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<td>15:00</td>
<td>Financial Challenges for Immunization Services</td>
<td>Patrick Lydon (IVB)</td>
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<td>16:00</td>
<td>Polio Eradication</td>
<td>David Heymann &amp; Bruce Aylward (POL)</td>
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<td>17:00</td>
<td>Session of SAGE members</td>
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19:00: Reception at WHO – Restaurant de France
### Thursday, 28 October 2004

**Chair:** Merceline Dahl-Regis  
**Rapporteur:** Claire Broome  
**IVB:** Michel Zaffran

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<th>Time</th>
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<tr>
<td>09:00</td>
<td>Research and Development</td>
<td>Marie-Paule Kieny, Director, IVR</td>
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<td>• Update on global R&amp;D agenda</td>
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<td>• Update on the Meningitis Vaccine Project</td>
<td>Marc Laforce, Director MVP/PATH</td>
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<td>10.15</td>
<td>Intellectual property rights and vaccines</td>
<td>Miloud Kaddar (IVB)</td>
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<td>11:00–11:30</td>
<td>Coffee break</td>
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<td>11:30</td>
<td>Challenges for rotavirus vaccine</td>
<td>Duncan Steele (IVB)</td>
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<td>12:30 – 13:15</td>
<td>Lunch</td>
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<tr>
<td>13:15</td>
<td>Session of SAGE Members</td>
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<td>14:00</td>
<td>Measles Mortality Reduction &amp; Rubella Control</td>
<td>Update on progress and recent developments</td>
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<td>14:45</td>
<td>Challenges around vaccines</td>
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<td>• Issues for the global prevention of invasive Haemophilus influenzae type b (Hib) diseases</td>
<td>Patrick Zuber (IVB)</td>
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<td>• Update on GAVI Hib Recommendations</td>
<td>David Fleming (Chair, GAVI Hib Working Group)</td>
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<td>16:00–16:30</td>
<td>Coffee break</td>
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<td>16:30</td>
<td>Quality challenges: acceptability of cell substrates</td>
<td>David Wood (IVB)</td>
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<td>17:30</td>
<td>Regulatory and safety challenges</td>
<td>Nora Dellepiane (IVB)</td>
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<td>18:30</td>
<td>Closure of meeting</td>
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### Friday, 29 October 2004

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<th>Time</th>
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<tr>
<td>09:00</td>
<td>In-camera session of SAGE members</td>
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<td>11:00: Adjournment</td>
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Annex 2:
List of participants

Members of the Strategic Advisory Group of Experts:

Dr Marie-Thérèse Obama Abena, Vice Dean, In Charge of Research and Cooperation, Faculty of Medicine and Biomedical Sciences, University Teaching Hospital Center, Yaounde, Cameroon

Dr Jarbas Barbosa da Silva Jr., Director, CENEPI/FUNASA, Setor de Autarquias Sul, Quadra 4, Bloco N, Sala 600, Brasília - DF, Brasil, CEP 70058-902, Brazil

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Dr Silvia Bino, Director, Institute of Public Health, Rr. Rreshit Collaku, P.23/1/1/21, Tirane, Albania

Dr Claire V. Broome, Senior Adviser, Centers for Disease Control and Prevention (CDC), Integrated Health Information, Office of the Director, MS D68, 1600 Clifton Road, N.E., Atlanta, GA 30333, USA

Dr Hae Wol Cho, Director General, National Institute of Health, 194, Tongil-Lo, Eunpyung-Gu, Seoul, 122 701, Republic of Korea

Dr Supamit Chunsuttiwat (could not attend), Director, Division of General Communicable Diseases, Ministry of Public Health, Tiwanon Road, 11000 Nonthaburi, Thailand

Dr Merceline Dahl-Regis (Chair of SAGE), Chief Medical Officer, Ministry of Health, PO Box N-3730, Nassau, New Providence IS, Bahamas

Dr Elaine Esber, Chair of the IFPMA Biologicals Committee, Executive Director, International Medical Affairs, Merck Vaccine Division, Merck & Co. Inc., Sumneytown Pike WP 97A-325, P.O. Box 4, West Point, PA 19486, USA

Professor Mariano Esteban, Director, Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas (CSIC), Ministerio de Ciencia y Tecnología, Campus de la Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Professor Peter I. Folb (could not attend), Professor of Pharmacology, Medical Research Council, P.O. Box 19070, Tygerberg 7505, Cape Town, South Africa

Dr Akira Homma, Representative of the Developing Countries Manufacturers Network, Director, Bio Manginhos, Oswaldo Cruz Foundation, Av Brasil 4365, Rio de Janeiro, 21045-900, RJ, Brazil
Dr Alenka Kraigher, Epidemiologist, Institute of Public Health, National Coordinator for Communicable Diseases and EPI, Trubarjeva 2, 1000 Ljubljana, Slovenia

Dr John La Montagne (could not attend), Deputy Director, NIAID, Building 31, Room 7A03, National Institutes of Health, 31 Center Drive, MSC 2520, Bethesda, MD 20892, USA

Professor Francis Nkrumah (also TFI chair AFRO), Noguchi Memorial Institute of Medical Research, University of Ghana Medical School, P.O. Box LG 581, Legon, Ghana

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Dr Lucky S. Slamet, Deputy for Therapeutic Products, Narcotic, Psychotropic and Addictive Substance Control, Directorate General of Food and Drug Control, Ministry of Health, National Agency of Drug and Food Control, Jalan Percetakan Negara No. 23, Jakarta Pusat 10560, Indonesia

Dr Kai Zhao (could not attend), Senior Researcher, Vaccinology, Beijing Institute of Biological Products, Sanjianfang, Chaoyangqu, Beijing 100024, People’s Republic of China

Advisers:

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Dr Georges Peter, Div. of Pediatric Infectious Diseases, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02903, USA

Professor Arthur Lawrence Reingold, Head, Division of Epidemiology, School of Public Health, University of California, Berkeley, 140 Warren Hall, MC 7360, Berkeley, CA 94720-7360, USA

Dr Daniel Tarantola, 10 rue des Jargilières, 01210 Ferney-Voltaire, France

Chairs of the Polio Task Force on Immunization (TFI) and the Polio Technical Advisory Groups (TAGs) in WHO Regions:

TFI Chair African Region: **Professor Francis Nkrumah** – contact details see SAGE Members section

TAG Chair American Region (could not attend): **Dr Ciro de Quadros**, Director, International Programs, Sabin Vaccine Institute, 1718 Connecticut Ave., N.W., Suite 700, Washington DC 20009, USA

TAG Chair Eastern Mediterranean Region: **Dr Mohammed Suleiman Ali Jaffer**, Director General of Health Affairs, Ministry of Health, P.O. Box 393, 113 Muscat, Oman

TAG Chair European Region (could not attend): **Dr Nick A. Ward**, Stowford Meadow, Langtree, Torrington, Devon EX38 8NU, United Kingdom

TAG Chair South-East Asian Region: **Dr Prayura Kunasol**, Senior Advisor, Department of Communicable Diseases Control, Ministry of Public Health, Tivanon Road, Nonthaburi 11000, Thailand

TAG Chair Western Pacific Region: **Dr Isao Arita**, Chairman, Agency for Cooperation in International Health (ACIH), 4-11-1 Higashi-machi, Kumamoto-city, Kumamoto 862-0901, Japan

Representatives from other agencies and institutions:

AMP/Institut Pasteur:

**Dr Brad Gessner**, Scientific Director, AMP/Institut Pasteur, 25, rue du Dr Roux, 75724 Paris Cedex 15, France

Aventis:

**Dr Shawn Gilchrist**, Senior Medical Advisor, Corporate Public Policy, Aventis Pasteur, 2 avenue du pont Pasteur, 69367 Lyon Cedex 07, France

Bill & Melinda Gates Foundation:

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**Dr Douglas Holtzmann**, Senior Program Officer, Infectious Diseases, Global Health Program, Bill & Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98102, USA

**Dr Regina Rabinovich**, Director, Infectious Diseases, Global Health Program, Bill & Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98107-5136, USA

**Dr Sally Stansfield**, GAVI Working Group Member, Associate Director, Global Health Initiatives, Bill & Melinda Gates Foundation, 1551 Eastlake Avenue East, Suite 100, Seattle, WA 98102, USA
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GAVI Secretariat:

**Dr Mercy Essel Ahun**, Principal Officer, Country Support, Global Alliance for Vaccines and Immunizations, c/o UNICEF, Palais des Nations, 1211 Geneva, Switzerland

**Dr Tore Godal**, Executive Secretary, GAVI Secretariat, c/o UNICEF, Palais des Nations, 5-7 avenue de la Paix, 1211 Geneva 10, Switzerland

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