Report of the meeting of the Scientific Advisory Group of Experts (SAGE)

Geneva, 9-11 June 1998
The Global Programme for Vaccines and Immunization thanks the donors whose unspecified financial support in 1997 has made the production of this document possible.


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# Glossary

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
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<tr>
<td>AFP</td>
<td>acute flaccid paralysis</td>
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<td>BCG</td>
<td>bacille Calmette-Guérin (vaccine)</td>
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<tr>
<td>CAMR</td>
<td>Centre for Applied Microbiology and Research</td>
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<td>CCM</td>
<td>cold chain monitor card</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CRS</td>
<td>congenital rubella syndrome</td>
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<td>CVI</td>
<td>Children’s Vaccine Initiative</td>
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<td>DANIDA</td>
<td>Danish International Development Agency</td>
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<td>DAP</td>
<td>Action Programme on Essential Drugs, WHO</td>
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<tr>
<td>DT</td>
<td>diphtheria-tetanus (vaccine)</td>
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<td>DTP</td>
<td>diphtheria-tetanus-pertussis (vaccine)</td>
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<tr>
<td>EMC</td>
<td>Division of Emerging and other Communicable Diseases Surveillance and Control, WHO</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization, WHO</td>
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<tr>
<td>GNP</td>
<td>gross national product</td>
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<td>GPV</td>
<td>Global Programme for Vaccines and Immunization, WHO</td>
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<td>Hib</td>
<td>haemophilus influenzae type b</td>
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<td>HRB</td>
<td>Division of Human Resources Development and Capacity Building, WHO</td>
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<td>HSR</td>
<td>health sector reform</td>
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<td>IMMYC</td>
<td>Steering Committee on the Immunology of mycobacteria</td>
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<td>IND</td>
<td>investigational new drug</td>
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<td>IPR</td>
<td>intellectual property rights</td>
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<td>IVI</td>
<td>International Vaccine Institute</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<td>JICA</td>
<td>Japan International Cooperation Agency</td>
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<td>MHC</td>
<td>major histocompatibility complex</td>
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<tr>
<td>MMR</td>
<td>mumps, measles, rubella</td>
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<tr>
<td>MR</td>
<td>measles, rubella</td>
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<tr>
<td>NIBSC</td>
<td>National Institute of Biological Standards and Control</td>
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<td>NID</td>
<td>national immunization day</td>
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<td>NIH</td>
<td>national institutes of health</td>
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<td>NUT</td>
<td>Nutrition Programme, WHO</td>
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<td>OPV</td>
<td>oral polio vaccine</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<tr>
<td>DFID</td>
<td>Department for International Development</td>
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<tr>
<td>PMC</td>
<td>Pasteur Mérieux Connaught</td>
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<tr>
<td>PsaA</td>
<td>pneumococcal surface adhesin A</td>
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<tr>
<td>PspA</td>
<td>pneumococcal surface protein A</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>RRV-TV</td>
<td>live oral tetravalent rotavirus vaccine</td>
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<td>SAGE</td>
<td>Scientific Advisory Group of Experts</td>
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<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TBT</td>
<td>technical barriers to trade</td>
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<tr>
<td>Td</td>
<td>tetanus and diphtheria toxoids, with reduced diphtheria content for adults</td>
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<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases, WHO</td>
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<td>TF</td>
<td>typhoid fever</td>
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<tr>
<td>TRIPS</td>
<td>trade-related aspects of intellectual property</td>
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<tr>
<td>TT</td>
<td>tetanus toxoid</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>UNICEF</td>
<td>United Nations Children's Fund</td>
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1. Introduction

The third formal meeting of the Scientific Advisory Group of Experts (SAGE) for the Children’s Vaccine Initiative (CVI) and the Global Programme for Vaccines and Immunization (GPV) was held in Geneva on 9-11 June 1998. The list of participants, the agenda, the list of documents and the terms of reference are given in Annexes I, II, III and IV respectively. Over 20 presentations were given and wide-ranging discussion took place. The recommendations that emerged are detailed in this report.

Dr J.W. Lee, Director of GPV and Executive Secretary of CVI, welcoming the participants, said that at the time when a new Director-General of WHO was about to take office it was appropriate to reflect on and plan for the future. CVI had developed a strategic plan regarding the vaccines that would be available in the future, while GPV and UNICEF were beginning a strategic planning initiative with a view to accelerating the delivery of immunization in the poorest countries. It was to be hoped that this initiative would involve all who comprised the global immunization partnership in its widest sense.

The first task was to reach the unreached. In many countries, particularly in sub-Saharan Africa, immunization coverage was unsatisfactory, and it was not conceivable that the traditional approaches would significantly improve matters. The unreached include people living far from fixed immunization sites and those who did not use immunization services for religious, ethnic, political or socio-economic reasons. The polio eradication campaign had shown that such people could be reached.

Management had to be improved. Each country needed a well-trained and effective programme manager with public health expertise. The management of managers needed to be improved by providing them with training, incentives and adequate resources.

It was vital to maintain the function of immunization programmes even though their structure might change as health reform proceeded. Immunization managers had to be trained so that they could remain effective advocates for immunization despite changing roles, and immunization coverage had to be taken as a critical indicator of the performance of health reform.

The potential existed for immunization to save twice as many lives as at present through the use of new vaccines. Regrettably, hepatitis B vaccine was still not accessible in many of the poorest countries, and the question arose as to how Hib, rotavirus, pneumococcal and important enteric vaccines would be incorporated into their programmes. New financing mechanisms had to be developed which would allow the introduction of new vaccines into immunization programmes in developing countries.
It was necessary to give increased attention to sustaining public confidence in immunization, especially as the media tended to focus on uncommon serious side-effects or to attribute side-effects to immunization when in fact there was no causal relationship.

Dr Lee said the meeting would hear about progress in the activities of the Expanded Programme on Immunization, Vaccine Research and Development, Vaccine Supply and Quality, and CVI. Polio eradication was at the top of the list of targets to be achieved. Measles, neonatal tetanus, hepatitis B and yellow fever were very important, and vitamin A and Hib had been added to the effective interventions to which a firm commitment had been given. Surveillance activities and the work on safe injections had been greatly accelerated and would be further strengthened.

Training was being offered to national control authorities, local producers, and those procuring vaccines in order to ensure that safe, potent and effective vaccines were administered. Self-sufficiency in vaccine supply was being promoted through the development of sustainable financing models and affordable pricing strategies, and efforts were being made to lower the technical barriers in the way of accessing technologies for new vaccines.
2. Progress in implementing 1997 SAGE recommendations

A number of short reports were presented in written or oral form regarding the implementation of the recommendations formulated by the SAGE a year earlier.

2.1 New vaccines

2.1.1 Pneumococcal vaccines

Conjugate vaccine trials: VRD is participating in the advisory committee of the randomized double-blind study on the efficacy of a 9-valent pneumococcal conjugate vaccine in infants in Soweto, South Africa, funded by Wyeth Lederle Vaccines and Pediatrics (WLVP). Using the WLVP vaccine in the Gambia, VRD will be coordinating another double-blind, individually randomized study lasting four years with 15,000 infants in each group.

Maternal and neonatal immunization: A review was conducted of all published and unpublished studies involving the immunization of pregnant women with pneumococcal polysaccharide vaccine. This review was intended to lead the way to a comprehensive meeting examining the two vaccine-related strategies for the control of pneumococcal disease in early infancy: maternal immunization and neonatal or early infant immunization. A maternal immunization study will be proceeding in Bangladesh and VRD will review a proposal for the evaluation of neonatal immunization.

Common protein vaccines: Most of the work continued to focus on three candidate proteins, pneumolysin, pneumococcal surface protein A (PspA) and pneumococcal surface adhesin A (PsaA). There may be an important role for these proteins in the context of conjugated polysaccharide vaccines as carriers or presented in mixture with conjugates.

2.1.2 New tuberculosis vaccines

As a number of candidate vaccines approach the end of their pre-clinical evaluation, IMMYC is streamlining its efforts downstream in the vaccine development process.

Animal models: A lack of laboratories where animal experiments involving virulent challenge can be performed presents a serious bottleneck to the development of tuberculosis (TB) vaccine. IMMYC has established a network of laboratories that can perform these assays in a reliable, standardized fashion. Over the last year, two new laboratories have been approved: CAMR in Salisbury, England, and the Central TB Research Institute in Moscow (Russia).
Immunological parameters of protection: As well as allowing preliminary comparisons of candidate vaccines, a reliable immunological correlate would also give a handle on parameters such as dosage and vaccination route. IMMYC has participated in the creation of a network of laboratories in Brazil, Ethiopia, Morocco and Pakistan for the evaluation of immunological parameters as markers of protection against TB.

Clinical trials: IMMYC has prepared a proposal for the organization of comparative international multi-centre phase I/II clinical trials of TB candidate vaccines and is currently elaborating a guideline document to help developers of new vaccines in future efficacy (phase III) trials.

2.1.3 Single-dose tetanus vaccines

Preclinical testing: All but one of the immunogenicity and quality control studies on selected formulations from collaborators have been completed. The last pre-clinical study, concerned mainly with the reproducibility of former results, was finalized at the end of summer 1998.

Clinical testing: Discussions on IND files have proceeded with potential collaborators in the USA and Europe, and Asian manufacturers are being contacted with the assistance of Professor Tikki Pang. In parallel, the NIH and FDA will be collaborating with the Steering Committee to expedite the process leading towards clinical trials.

2.1.4 Rotavirus vaccines

It is intended that the live oral tetravalent rotavirus vaccine (RRV-TV) derived from rotavirus isolated from a rhesus monkey and developed by the US National Institutes of Health together with Wyeth Lederle will be licensed in the USA in mid-1998. Licensing in Europe is expected next year.

VRD is funding:

- Surveillance studies to establish the disease burden of rotavirus in countries and areas where vaccines are likely to be introduced early or where vaccine trials are being considered.
- A regional network of surveillance for rotavirus morbidity and strain characterization in seven African countries (Cameroon, Kenya, Nigeria, South Africa, Tunisia, Zambia, and Zimbabwe). Botswana, Malawi and Namibia may participate later.
- Clinical trials in Africa (Guinea-Bissau) and Asia (Bangladesh, India) assessing the immunogenicity of different regimens of administration (e.g., neonatal dose together with BCG) and the efficacy RRV-TV.

2.1.5 Vaccines against some major cancers associated with infection

SAGE previously noted the need to encourage both the public and private sectors to make more efforts to develop safe, effective and accessible vaccines against globally recognized important diseases.
A meeting will be held in Geneva in autumn 1998 to review the current status of the development of a vaccine against human papilloma virus (aiming at the prevention of associated cervical cancer), and to set up a specific plan of action. In parallel, two research institutions (the German Cancer Research Centre in Heidelberg and the Ludwig Institute for Cancer Research in Lausanne) are in the process of being designated WHO Collaborating Centres and will serve as resources for the impending related activities.

2.1.6 Vaccine effectiveness trials

Two WHO Collaborating Centres for the Clinical Evaluation of Vaccines in Developing Countries have been established:

- The Epidemiology Branch of the National Institute of Child Health and Human Development, USA. To date, field trials have been focusing on enteric pathogens. Collaborative studies have been conducted in seven developing countries and substantial training support is being provided for scientists from Viet Nam.

- The Communicable Disease Epidemiology Unit at the London School of Hygiene and Tropical Medicine, England, whose 1997 report summarizes a large portfolio, including studies on trial design, modelling and such analytical aspects of epidemiology as immuno-epidemiology. Studies are being conducted on some 15 vaccines. Collaborative studies have been conducted in 11 developing countries.

During the past year, the vaccine probe method for assessing disease burden was applied in a retrospective study of Hib vaccine efficacy in Santiago, Chile, by Dr R. Lagos and colleagues. The study demonstrated that children who received two or three doses of Hib vaccine had a 34% reduction in lobar pneumonia with effusion or bronchial breathing (95% CI: 7%-53%).

A paper describing the establishment of the GPV Vaccine Trial Registry and reporting its findings was published in the Bulletin of the World Health Organization. VRD has received many requests for copies, indicating strong worldwide interest. The Registry, which is currently being updated, documents a major increase in the number and scope of vaccine trials conducted since the formation of GPV in 1994.

Two randomized controlled field effectiveness trials of the bivalent (01-0139) killed oral cholera vaccine produced in Viet Nam are in progress. The first, initiated in March 1997, is a placebo-controlled evaluation of a two-dose primary series followed by boosting at two years in 300 000 persons aged 12 months or more in Nha Trang, Viet Nam. The second, which began in March 1998, is an open evaluation of a two-dose series followed by yearly boosting in ca. 280 000 persons aged 12 months or more in Hue.

The feasibility and acceptability of the killed, oral rBS-WC vaccine against cholera in a camp for southern Sudanese refugees located in Adjumani District, Northern Uganda, have been tested. It was concluded that delivery of this oral vaccine in refugee settings was feasible and widely acceptable when done pre-emptively, i.e., before a cholera epidemic occurred. Mounting such a campaign in response to a
cholera epidemic was not, however, recommended, because of the need for significant logistical and human resources.

### 2.2 Disease control

#### 2.2.1 *Haemophilus influenzae* type b vaccine

The SAGE previously noted that 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. In geographic regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of this problem. Since then, five Hib disease burden studies in Bulgaria, the Dominican Republic, Guatemala, India, and Poland have been put in progress. Each two-year study is examining the incidence of meningitis due to Hib in children aged 0-5 years in a well-defined population. A sixth Hib disease burden study is under development in collaboration with the European Regional Office to be carried out in one of the countries of the former Soviet Union. There has been enhanced communication among interested partners to co-ordinate implementation and periodic updating of the CVI Hib agenda. A meeting was held to update burden-of-disease and technical introduction issues in March, and a planning meeting on financing and supply in late 1998. A brief written update of progress was presented.

Dr de Quadros noted that ten countries in PAHO were already conducting routine Hib immunization, which, by 1999, would be available to 90% of the population in the Region of the Americas. He referred to the vaccine as “the most rapidly adopted ever”.

Sir Gus Nossal noted the tremendous progress in the introduction of Hib vaccine. Surveillance studies were being planned in Asia by IVI and funded by industry. Dr Kane said a lot had been learned over the last year about the introduction of new vaccines, and compared the speed of introduction of HBV (slow), Hib (faster) and rotavirus (already started, and expected to be even faster).

#### 2.2.2 Vitamin A

The 1997 SAGE meeting endorsed the principle of administering vitamin A with vaccines. In October 1997, GPV received a grant from the Canadian International Development Agency for incorporating the administration of vitamin A into immunization services. Subsequently, activities have been undertaken with a view to helping countries to deliver the vitamin in conjunction with routine immunization, national immunization days and measles treatment.

Dr Broome and Dr Cochi questioned how the impact of vitamin A supplementation with immunization would be measured. Only process indicators were possible for measuring impact during national immunization days. Longer-term impact during routine immunization was described as predominantly the province of the WHO Nutrition Programme, which would fulfil this role in collaboration with EPI. Serum retinol, breast-milk retinol, retinol-binding protein and night blindness surveys would all be used, particularly at chosen sites. It was anticipated that the Micronutrient Initiative grant would enable basic research to be conducted into finding improved measures of impact.
Dr de Quadros reported that six countries in the Region of the Americas in need of vitamin A supplementation had incorporated its delivery into their national vaccination campaigns.

2.2.3 Yellow fever

Although the SAGE had not made recommendations on yellow fever in the last few years, the secretariat felt it important to bring the SAGE up to date with important developments in 1998. There has been a dramatic re-emergence of yellow fever, outbreaks having occurred in Benin, Bolivia, Brazil, Burkina Faso, Colombia, Gabon, Ghana, Kenya, Liberia, Nigeria, Peru, and Sierra Leone between 1992 and 1997.

Based on adjustments for underreporting it is estimated that 200 000 yellow fever cases occur each year, almost all of them in sub-Saharan Africa. Possible reasons for underreporting include the occurrence of the disease in remote areas, the difficult clinical differentiation and lack of access to virology laboratories, and the reluctance of countries to report because of the associated stigma and the financial cost of intervention activities.

The Yellow Fever Technical Consensus Meeting was held in Geneva on 2-3 March 1998, hosted by EMC and GPV. It addressed the dramatic resurgence of outbreaks and reviewed the strategies for prevention and control activities.

Yellow fever has markedly lower immunization coverage than other diseases. This arises because of poor public awareness about the gravity of the disease and inadequate surveillance systems for the identification of outbreaks. An important sub-regional meeting in Dakar during June 1998 was attended by eight Ministers of Health from countries affected by yellow fever. This was an opportunity to influence government decisions and to work with the donor agencies that were also present.

It was suggested that regional development banks be invited to the next SAGE meeting so that they could present their donor priorities and strategies. It was felt that more technical officers were urgently needed in yellow fever control at country level.

Dr de Quadros reported that on 14-15 May 1998 a meeting was held in Peru with over 40 participants from the six countries of the Region of the Americas where yellow fever was endemic. Those attending included vector control specialists, vaccine producers, epidemiologists, laboratory personnel and EPI managers. In response to the recommendations made, catch-up vaccination campaigns aimed at all residents in the affected areas will be conducted and yellow fever vaccine will be included in the routine vaccination programmes. Furthermore, vector control activities will be strengthened in all urban areas where Aedes aegypti is present and yellow fever surveillance will be intensified in coordination with measles, rubella and dengue surveillance, taking advantage of the laboratory network for measles eradication.

2.2.4 Measles

The SAGE previously noted that CVI and EPI should analyze the disease burden of measles, the cost and effectiveness of different measles control and eradication strategies, the way measles eradication activities can complement other disease control
activities, and the benefits of measles eradication including its impact on health systems development. CVI and EPI have worked jointly on a methodology for estimating measles disease burden. Estimates of the number of susceptible individuals, measles cases and deaths were made at global and country level, using a model that incorporates measles case reports, vaccination coverage and demographic data. Further refinements of the model are being made in order to accommodate country and regional heterogeneity.

In collaboration with the Communicable Disease Surveillance Centre in the United Kingdom, measles cases and coverage data from selected countries were used for the development of simple methods whereby immunization managers could be assisted to estimate measles susceptibility levels. Preliminary evaluation of the costs and benefits of different measles control/elimination strategies in the European Region was conducted.

2.2.5 Vaccine vial monitors

SAGE previously noted that GPV should pursue its efforts to ensure that VVMs are fixed on OPV vials procured directly by developing countries from either international or local producers, and should encourage countries to collect data to monitor the impact of VVMs in routine immunization programmes and NIDs.

**Progress in fixing VVMs on OPV vials**

- **Progress in countries producing or filling OPV:** One of the activities that has been undertaken with a view to providing support to manufacturers and their national control authorities who wished to adopt VVMs was to develop a testing protocol indicating whether VVMs met the specifications consistent with the properties of the OPV being produced. BioFarma has ordered a million VVMs for use with OPV. DFID has bought 17.75 million VVMs for India to supply all four local OPV producers. India has told all manufacturers to supply VVMs but will be testing only for the next year. NIH Pakistan is reported to have ordered 0.5 million VVM labels for OPV. Contacts have been made with several other countries, including Egypt and Iran, and plans have been made to contact Russia and Viet Nam. We conclude that local vaccine producers can be influenced to add VVMs, particularly if their EPI desires it.

- **Progress in countries procuring OPV:** Unless requested otherwise UNICEF suppliers were asked to ensure the availability of VVMs on all OPV they supply for public immunization programmes. We are promoting the use of the UNICEF tender to set specifications on presentation and labelling, including the use of VVMs, for countries buying vaccines directly. We are also promoting this action in procurement workshops.

Information received from PMC and Chiron (there has been no response to date from the other UNICEF OPV suppliers) indicates that a huge number of OPV vials were sold in 1997 with VVMs (over 330 million doses from PMC alone). We know of two major groups that are not requesting VVMs on OPV: PAHO and the Eastern Mediterranean countries. In addition, countries buying OPV in monodose presentation are not requesting VVMs, which is not unexpected.
UNICEF (including orders through JICA and DANIDA) is the main purchaser. Most of the countries procuring directly appear not to be requesting VVMs, and we need to work harder on this. The key is to convince immunization programme managers of the utility of VVMs. This has proved useful when working with local producers, and PATH’s work along these lines is to be commended. We could probably persuade the commercial manufacturers to help in this effort if we could provide them with convincing data on the utility and impact of VVMs.

**Technet Consultation 1998**

The 1998 Technet consultation, held in Copenhagen on 16-20 March, reviewed progress with vaccine vial monitors (VVMs). Papers covering the following subjects were presented:

- Laboratory tests on OPV potency and VVM change (NIBSC, UK). Impact data from Turkey, Nepal, Bhutan, and southern Sudan covering the use of OPV both in routine programmes and on national immunization days.
- VVMs in countries producing or procuring OPV.
- Summary of field experiences (1981-1992) with VVMs.
- World Wide Web VVM forum.

The following recommendations were adopted:

- VVMs on vials of OPV are a valuable addition to immunization services, enabling health workers to decide whether or not the vaccine should be used. Technet recommends that appropriate VVMs be introduced as soon as possible for all vaccines.
- The utilization of a VVM for OPV should be enhanced to assure vaccine quality at the point of use and to improve the management of vaccine delivery.
- Because VVMs accurately depict only the heat exposure of the vials they are on, OPV VVMs should not be used as a substitute for evaluating the heat exposure of any other vaccines. Other monitors (e.g., CCM, Stopwatch) should be used until VVMs are available for other vaccines.

The meeting also defined the following priority activities for implementation of the above recommendations:

- Enhancing the utilization of OPV VVMs:
  - Training
  - Supervision
  - Use of VVMs for management of vaccine delivery
  - Further studies
  - Expanding VVM use to countries procuring OPV directly
Introducing VVMs for all other vaccines: Three categories of vaccine stability were defined for which VVMs need to be developed:

- Highly stable vaccines: toxoids and hepatitis B vaccine
- Vaccines with medium stability: BCG, yellow fever and measles vaccines
- Vaccines with moderate stability: pertussis (whole cell), including DTP vaccines

Dr Ali Jaffar requested clarification on the quality of the VVMs that would be used by local producers. He was advised that, so far, only one VVM supplier produced the VVM as part of the vaccine label. The supplier had to meet strict specifications laid down by WHO.

Recommendations

After the presentations on progress to implement the disease control aspects of the 1997 SAGE recommendations and subsequent discussions, recommendations were made concerning yellow fever and vitamin A:

**Yellow fever**

SAGE notes with concern the continued high number of outbreaks of yellow fever, a disease still leading to a large number of deaths, and for which there is no specific treatment. The vaccine is safe, highly effective, provides long-lasting protection after a single dose, and is available to developing countries for only US$ 0.17 per dose. The vaccine has been recommended by WHO for inclusion in the national immunization programmes of countries at risk since 1991. SAGE is pleased to note that, faced with the spread of Aedes aegypti mosquito vector in the Americas, during the past year, all countries at risk in the Americas added yellow fever vaccine to their immunization programmes. SAGE notes with concern that in Africa, progress has been very slow in introducing yellow fever vaccine.

The SAGE recommends that:

- For those countries at risk of yellow fever in Africa, accelerated efforts be made to include the vaccine in national programmes, to improve disease surveillance, and to provide a rapid response to outbreaks. Additionally, where feasible, WHO should explore the possibility of including vector control.

**Vitamin A**

SAGE strongly supports the initiative to administer vitamin A with immunizations delivered after six months of age in areas where vitamin A deficiency is a significant public health problem. This is recognized as a major opportunity for improving child survival. The vitamin A supplements should be given to the mother at any immunization contacts up to six weeks post-partum or to the child from six months of age onwards.
The SAGE recommends that:

- A joint plan between the GPV and the Programme of Nutrition (NUT) be developed to evaluate the impact of vitamin with immunization on health status.

2.3 Supply and quality of vaccines

2.3.1 Quality of vaccines

SAGE previously noted that countries should take responsibility for the quality of the vaccines they use, at the appropriate level, according to the source of vaccine. Although the number of countries exercising all necessary national control functions appropriate for their vaccine source has not increased, more functions are being performed better by countries. Assessment has been facilitated by the development of indicators with refinements based on inputs from 29 countries.

SAGE previously noted that donors and governments should insist on the existence of national systems to ensure vaccine quality before support is given for vaccine production. In Pakistan the donors have united to urge the development of the national control authority and the use of UNICEF-procured vaccines until it is in place. In the Philippines, TDR has channelled funds to develop the national control authority so that new technologies can be developed. VSQ is conducting a study on the financial support donors have given to vaccine production. The results will be used to develop advocacy to refocus the support. VSQ is also conducting a survey of donors who have funded vaccine production in the past, and the outcome will provide a basis for backing national control authority development whenever support for vaccine production is envisaged.

SAGE previously noted that monitoring the performance of critical national control functions should include an evaluation of the quality with which they are performed. Independent assessments made for this purpose will need increased resources, both human and financial. It is essential that national control authorities be independent of production and have the authority to enforce their decisions. Indicators for assessing the performance of national control functions have been developed with inputs from 29 countries. These have been used to assist 18 countries to do self-assessments of their national control authorities since the 1997 SAGE meeting and to use the results for developing plans to improve the functions, including training and technical inputs. This process has become an important aspect of the selection of trainees for the Global Training Network and of monitoring its impact. VSQ will be exploring more formal ways to monitor this assessment process in 1998.

SAGE previously noted that efforts should be made to promote the harmonization of requirements for vaccines as countries develop their national control systems. In addition, countries embarking on vaccine procurement are encouraged to include product and packaging specifications already in use for vaccine procured through UN agencies. This recommendation is being implemented in collaboration with UNICEF and CVI. A meeting was held in the summer of 1997 to discuss concepts of harmonization of requirements. BLG is now undergoing a review in which consideration will be given to the development of requirements so that they can be better harmonized. Procurement workshops are now emphasizing the importance of specifications and those used by UNICEF are being provided.
SAGE previously noted that the Global Training Network had an excellent potential for including vaccine quality in its activities but additional funding will be needed to ensure optimal impact. There will be a presentation to the MIP on the progress of the Global Training Network. However, it should be noted that the DFID has generously supported this activity with a donation of over £1.2 million in 1998.

SAGE previously noted that efforts should be made to promote the harmonization of requirements for vaccines as countries develop their national control systems. In addition, countries embarking on vaccine procurement are encouraged to include product and packaging specifications already in use for vaccine procured through UN agencies. This recommendation is being implemented in collaboration with UNICEF and CVI. A meeting was held in the summer of 1997 to discuss concepts of harmonization of requirements. BLG is now undergoing a review in which consideration will be given to the development of requirements so that they can be better harmonized. Procurement workshops are now emphasizing the importance of specifications and those used by UNICEF are being provided.

SAGE previously noted that laboratory networks, perhaps on a regional basis, can serve as resources to countries lacking appropriate laboratory services. The proficiency of the laboratories in testing should be monitored and assured. Laboratory networks in the Americas and South-East Asia met again this year. Plans for networks in other regions are being developed. Proficiency testing has been started and we have received a new proposal to co-ordinate this globally.

Dr Nossal and Dr Cochi requested clarification on progress concerning vaccine supply and quality issues in China. In collaboration with WPRO staff, VSQ recently assessed national control authority functions in China and collaboratively developed an institutional strengthening plan for which government approval is necessary in order that implementation may proceed. Questions of supply raised by the start of production in the new facilities of the China Vaccine Project will present difficulties, as the new products will be much more expensive to make and finance for locally produced vaccines will be an issue.

In response to a question by Dr Holmgren on the use of regional laboratory networks as a means of avoiding duplication of effort in the development of vaccine testing laboratories, Dr Milstien agreed that this approach had been worked on by WHO for several years. Laboratory networks exist in the Americas and South-East Asia Regions but as yet they are not providing testing services for countries. It is necessary to assure countries that laboratories are consistently capable of providing testing services. The accreditation of laboratories, as with the Polio Laboratory Network, is a potentially useful approach. Proficiency testing could form part of the basis for accreditation. Dr Schild asked which vaccines would be the first to undergo proficiency tests, and was told that pertussis and measles vaccines had been chosen after discussion with experts in the field.
2.3.2 World Trade Organization

SAGE previously recognized the importance of the World Trade Organization (WTO) agreements relevant to vaccines: the Agreement on Technical Barriers to Trade (TBT) and the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS). SAGE commended the proactive work of GPV and CVI in their efforts to understand the ramifications of these treaties on vaccine supply and quality as well as on the availability of new vaccines. SAGE recommended that VSQ and CVI should jointly develop an information package for regional and national decision-makers to promote understanding of technology transfer and licensing. SAGE also recommended that VSQ and CVI continue their work to ensure that the public sector is adequately informed about the intellectual property and economic aspects of the vaccine industry.

The impact of WTO on GPV’s work was the subject of a presentation to the Expert Committee on Biological Standardization which is being prepared for publication both within and outside WHO. The report of the Bellagio meeting has been published and will provide an important part of an information package on technology transfer and licensing. CVI has commissioned a paper on IPR. A study of the legal needs of viable vaccine producers has been commissioned which will also cover matters related to TBT and TRIPS. Because of the importance of this work, VSQ is discussing the detailed requirements for a staff member to cover the subject.

Dr Broome asked whether any of the documents providing information for countries on WTO would be available on the Internet. It was explained that, as a rule, documents available through the GPV Document Centre, such as the ones mentioned, were posted on the Internet.

Dr Nossal asked whether a lack of respect for intellectual property and patents was expected to be a continuing problem. Dr Milstien replied that the importance of these matters was now understood in most countries.
3. Disease control

3.1 Poliomyelitis eradication

Presentation summary
There were two presentations on polio eradication. The first presentation discussed critical issues for achieving polio eradication by the year 2000. With a 90% reduction in reported cases and the limitation of wild poliovirus transmission to sub-Saharan Africa and southern Asia it is still possible that polio will be eradicated globally by the end of 2000. However, the most difficult problems lie ahead. The disease remains endemic in 52 countries, of which 15 present particularly difficult challenges. In seven countries affected by conflict, the health infrastructure is minimal, access to children is limited and programme costs are, as a consequence, high. Eight countries are considered to be major reservoirs where large populations, large birth cohorts, low immunization coverage, crowding, poor sanitation and high migration rates combine to make poliovirus transmission particularly intense. The difficulty of achieving eradication in these countries is demonstrated by the recent isolation of wild type 2 poliovirus in Afghanistan, Benin, India, Nigeria, and Pakistan.

If the target date is to be met and the costs of global eradication are to be held to a minimum it is necessary to accelerate and intensify eradication activities. This will require additional sub-national/national immunization days in major reservoirs, the establishment of polio eradication teams in conflict countries, and the deployment of personnel specifically for surveillance in all countries where polio is still endemic. To achieve this, additional financial support must be secured. For 1998 the total estimated cost is US$ 217 million, and at mid-year the shortfall was US$ 65 million. Mobilizing additional funds will require the full support of the Director-General of WHO and other international leaders.

As eradication approaches, increasing attention is being paid to the issues that will be prominent in the post-eradication era. These are the maintenance of AFP surveillance until global eradication can be certified, the containment of laboratory strains of wild polioviruses, and the cessation of immunization against polio. Since the last meeting of SAGE, consultations have been held on containment and the stopping of immunization. A draft manual for containment has been produced and is being circulated for comment in the scientific community. It was agreed that immunization against polio could eventually be stopped. The available evidence suggests that vaccine-derived polio strains will not circulate indefinitely. The principal concern is that an immunodeficient person with persistent vaccine virus infection could excrete a mutated virus many years in the future. A research agenda was defined to provide additional data so that a decision on the strategy for stopping immunization could be made in 2000 or thereafter.
The second presentation discussed the current status of the development of new methods for quality control of oral poliomyelitis vaccines and polio diagnosis. The monkey neurovirulence test for OPV is a stringent test of the manufacturing consistency of batches of the vaccine. Because large numbers of primates are used in the safety testing of OPV, however, efforts to replace this test with another are of considerable importance. Preliminary experience suggested the feasibility of using a molecular biological assay and a transgenic mouse model for licensing OPV. A WHO collaborative study is in progress to develop and introduce transgenic mice for neurovirulence testing of OPV. The results obtained so far show that this test is no less sensitive that the monkey test for type 3 OPV.

Another WHO collaborative study is under way to develop a molecular biological test (MAPREC) for directly quantifying genomic changes in vaccine batches. The MAPREC assay is now widely use for screening seed virus monovalent bulks to establish the consistency of vaccine production. The proposals to introduce the transgenic mouse model and the MAPREC assay for quality control of OPV by manufacturers and national control authorities will be considered by WHO’s Expert Committee on Biological Standardization in October 1998.

Following EPI’s recommendations, VRD is conducting four research projects aimed at the development of new, rapid and accurate methods for detecting polioviruses in clinical and environmental samples. The differentiation of polioviruses using L20B mouse cells expressing the human receptor for poliovirus was developed and evaluated in field trials. L20B cells are highly selective for polioviruses, since most other human enteroviruses do not grow in mouse cells. The results of the field trials showed a very clear advantage for transgenic cells in terms of sensitivity, specificity and the time needed to identify polioviruses in samples. The available data indicate that L20B cells are suitable for the diagnosis of polioviruses from clinical and environmental samples, and they will therefore be introduced for routine use by laboratories in the WHO global poliovirus network. Implementation of this recommendation is now in progress. With regard to molecular biological tests, studies on technology relating to RNA probe hybridization analysis and restriction fragment length polymorphism are being conducted in regional and national laboratories dealing with the surveillance of polioviruses.

Discussion

The major part of the discussion was directed towards the concern of SAGE members that the polio eradication target might not be achieved because of insufficient resources. This is reflected in the strong recommendation that the new Director-General give full support to the initiative. The question was raised as to whether the 2000 goal should be changed, but it was concluded that this would not be appropriate until after that date. Additional discussion reflected concerns of SAGE members that vital scientific research using polioviruses might have to be stopped. It was established that containment would limit the number of laboratories where poliovirus research could be done, but no plans have yet been made for the destruction of polioviruses.

Sir Gustav Nossal noted that the results of the studies with transgenic mice and transgenic cells expressing the human receptor for polioviruses were an excellent illustration of the translation of basic research into the solution of programme requirements. Dr Schild mentioned that the availability of transgenic mice susceptible to polioviruses could be extremely useful for further research on the eradication of poliomyelitis.
Recommendations

The SAGE notes the dramatic progress made towards global polio eradication by the year 2000, recognizing that in the decade since the initiative was launched there has been a 90% decline in reported cases world-wide, with the virus now being restricted to sub-Saharan Africa and south Asia. This achievement is especially remarkable given that there has been a chronic shortfall in the human and financial resources needed for this task.

Notwithstanding this remarkable progress, SAGE is concerned that unless sufficient resources are mobilized on a timely basis, the eradication goal will not be met.

Because of the extraordinary benefits that the successful conclusion of this eradication initiative holds for the global community, the SAGE strongly urges that WHO markedly accelerate polio eradication activities to meet the year 2000 goal. A failure of this eradication initiative, due solely to insufficient leadership or resources, would have profound implications for other disease control initiatives and public health programmes in general.

The SAGE recommends that:

- As a matter of urgency, the Director-General of WHO call upon the appropriate international leadership to define specific mechanisms for ensuring that the commitment which has already been declared for the goal of polio eradication by the year 2000 is translated into reality. As this goal is only feasible if the necessary funding is rapidly secured, the Director-General should ensure that the immediate and long-term resources are identified by late 1998 and that those funds are made available to the programme in a timely manner.

- GPV should rapidly expand the intensity of eradication activities in the priority areas, while continuing national immunization days (NIDs) in all endemic countries. Particular emphasis should be given to implementing adequate NID rounds, catch-up campaigns, widespread mopping-up in areas of focal transmission in the global reservoirs, posting additional country level staff to accelerate the surveillance of acute flaccid paralysis, and fully implementing the strategies in areas affected by conflict.

- An annual report on progress towards global polio eradication be made to the World Health Assembly, beginning in the year 1999, because of the need for open discussion of the successes and constraints facing the initiative in its final stages.

3.2 Measles control and elimination

Presentation summary

There were two presentations on measles control. The first presentation reviewed a comprehensive strategy for the phased implementation of polio eradication and measles control/elimination and vitamin A activities, and discussed the advantages and disadvantages of this approach.
A careful review and evaluation of potential benefits and difficulties at country and regional level should form the basis for deciding to undertake a phased implementation of new/additional activities, especially in countries representing the highest global priority for the Polio Eradication Programme.

Key factors determining how to introduce measles control/elimination and vitamin A strategies, as well as the most appropriate activities include:

1) the status of the Polio Eradication Programme at national and regional level,
2) the status of the measles control programme, and
3) national and regional capabilities for concurrently implementing the recommended strategies.

The phased implementation of measles control/elimination activities must facilitate and not hinder polio eradication and must enhance the benefits of the overall polio eradication initiative. A framework detailing the most appropriate measles control/elimination activities for each phase of polio eradication is presented.

In countries where polio is endemic or where there is focal poliovirus transmission the acceleration of measles control and the reduction of measles mortality should be the priority, rather than the fixing of a goal for national measles elimination. Where there is a high measles disease burden and a poor health infrastructure, polio eradication activities may offer a unique opportunity to deliver priority interventions such as vitamin A supplementation and measles vaccine. As measles is usually endemic, outbreak prevention activities may not be appropriate for countries where polio is endemic.

Measles elimination should only be considered in countries or epidemiological blocks where adequateAFP surveillance provides evidence that wild poliovirus circulation has been interrupted. A global measles eradication goal will only be endorsed once the major polio reservoirs have disappeared.

The main reason for caution about setting a measles elimination goal is that if a decision were taken prematurely it might result in inappropriate or incomplete implementation of the recommended strategies. In general, experience shows that countries obtain political and financial support for mass campaigns without much consideration being given to the funding of less "attractive" components of the strategy, such as surveillance and the need to maintain immunization activities in the long term. All proposals to conduct supplementary measles immunization activities aiming at measles control/elimination should include a well-defined surveillance component, with identification of the required resources for at least two years and indicators for impact evaluation.

The second presentation by Dr Nigel Gay discussed whether modelling measles epidemiology helps to define optimal immunization strategies. He described how measles outbreaks occur when the number of susceptible individuals in a population is enough to sustain measles transmission. To prevent a measles epidemic or achieve elimination it is necessary to maintain the number of susceptible individuals below the epidemic threshold, i.e., the average age at infection before vaccine introduction. Designing measles elimination strategies includes the determination of the current
population susceptibility profile, the establishment of a susceptibility target (below the epidemic threshold) and the assessment of different vaccination strategies. The susceptibility profile can be estimated using serological surveys, mathematical models and simpler methods including the auditing of coverage and case data.

Serological surveys require time and resources to collect and test samples. Furthermore, the presence of detectable levels of antibodies does not imply immunity, and this approach is not recommended for every country. Mathematical modelling requires data of good quality on vaccination coverage and age-specific case data, and the realization of some simulations can be complex. Fine and Clarkson originally developed simpler audit methods to estimate the measles susceptibility profile in England and Wales.

Audit methods have the advantage of being conceptually simpler and using available data on disease incidence and vaccine coverage. As with mathematical models the results are dependent on the quality of the data.

The purpose of the work presented is to develop a simpler version of the audit methods. Data from Chile, Poland, Romania, Sri Lanka, Thailand, and Tunisia are being used to estimate measles susceptibility profiles by different methods, the sensitivities of which can thereby be compared.

For example, the number of measles cases and the age-specific proportion of individuals susceptible to measles in Poland in 1997 was estimated using a dynamic age-structured mathematical model and a homogeneous model, and the predictions of both methods were compared with the results of a serological survey. Data on age-stratified measles reports between 1960 and 1977 and data on vaccine coverage in Poland were used for the predictions. The model accurately predicted an outbreak of measles. As part of the analysis of a measles epidemic in Romania, age-specific predicted proportions of individuals susceptible to measles were compared with the susceptibility targets for measles elimination in Europe and were used to propose a vaccination strategy.

The preliminary results of this work indicate that modelling can be an additional tool to assist in the design of measles outbreak prevention and elimination strategies. There is a need to continue developing simpler, more accessible methods for estimating susceptibility profiles and to target populations for measles supplementary vaccination activities. Further development should include the optimization of strategies to account for differences in measles transmission between urban and rural areas and to evaluate the potential for measles transmission in adults.

Discussion

Regional achievements in measles elimination cannot be sustained indefinitely and a global eradication end point is necessary. The eradication of measles will require special efforts to co-ordinate regional initiatives and sustain the necessary support in regions where interruption of transmission of the measles virus is achieved earlier. This has become evident in the light of the continuous importation of measles virus into the Americas Region in recent years.

The continued transmission of measles in some industrialized countries has led SAGE to draw attention to the need to encourage European countries and Japan to accelerate
their efforts to interrupt measles virus transmission. A measles elimination plan for
the European Region has been prepared and it is important that a high level of
commitment is achieved among all Member countries. The importation of measles
virus from Africa, Asia and Europe has resulted in outbreaks in parts of South America
and the USA.

The implementation of nation-wide measles campaigns has raised the possibility of
combined measles-rubella elimination efforts as a cost-benefit strategy. However,

to determine the most appropriate strategies and the age

group to target during rubella immunization activities and, more importantly, the
potential changes in the age distribution of susceptible individuals in countries where
routine immunization services are unable to achieve or sustain high immunization
coverage. This is especially relevant because the risk of congenital rubella syndrome
could increase due to a shift in the age at infection with rubella. WHO/GPV and
CVI are currently co-ordinating studies to assess rubella disease burden and evaluate
the impact of different rubella vaccination strategies by means of mathematical models.

Dr Steinglass and Dr Olivé pointed out that failure to achieve high levels of routine
coverage with measles vaccine among infants remains one of the major problems in
many countries in the measles control phase. Dr Steinglass requested SAGE to
draw the attention of countries to the need to evaluate the reasons for poor measles
coverage and to identify actions for improving routine immunization services, since
these remain a cornerstone of measles control programmes.

Dr Sakai mentioned that a strategy to accelerate measles control was proposed in
1994 by the Informal Consultation of WHO/GPV and CVI on Strategies to
Accelerate Global Measles Control and he requested SAGE to endorse it. Dr Olivé
reported that this strategy had been implemented in some African and Asian countries
but that no provision had been made for its evaluation. Dr Steinglass and Dr Olivé
emphasized that the adequate identification of high-risk areas was a key element in
the success of the strategy. There are data indicating that poor urban and peri-urban
areas and major settlements along main roads have the conditions that facilitate measles
transmission. The selection of high-risk areas should be based on available information
on measles transmission in each country and should respond to country realities and
the feasibility of appropriately implementing the strategy and ensuring the safety of
injections. Dr Olivé commented that although political support was generally
provided for the implementation of campaigns, support was often not offered for the
establishment of surveillance systems and the necessary maintenance of high levels
of routine coverage.

The Chairperson noted that regional achievements in measles elimination could not
be sustained indefinitely and that a global eradication end point was necessary. The
eradication of measles would require special efforts to co-ordinate regional initiatives
and sustain support in regions where the interruption of transmission was achieved
earlier. This had become evident in the light of the continuous importation of the
measles virus into the Americas Region in recent years.

Dr Steefener, Dr Levine, Dr de Quadros, Dr Roure and Dr Olivé noted that continued
measles transmission in some industrialized countries demonstrated that there was a
need to encourage European countries and Japan to intensify their efforts to interrupt
the transmission of the measles virus. Dr Olivé reported that a measles elimination
plan for the European Region had been prepared and Dr de Quadros referred to the importance of obtaining a high level of political commitment for measles elimination in all developed countries. The importation of measles virus from Africa, Asia and Europe had resulted in outbreaks in parts of South America and the USA.

Surveillance is a key element of the elimination strategy and resources should be identified to implement adequate measles surveillance before embarking on any measles elimination initiative.

Dr La Montagne commented that because of an increasing number of countries with sustained measles vaccine coverage at high or moderate levels there was a shift in the distribution of susceptible individuals. He emphasized the need to assess the potential influence of adult populations on measles transmission.

Dr de Quadros recognized that there was a continuing need to develop simpler methods to estimate susceptibility to measles and that countries should continue to be helped with the selection of the most appropriate strategy and the determination of the appropriate age groups for and intervals between campaigns. Dr de Quadros and Mr Gay acknowledged that measles elimination strategies were evolving on the basis of experience in the Americas Region and that they might need to be tailored according to regional and country differences in measles epidemiology. The Chairperson recommended that sensitivity analyses be conducted by different methods in order to estimate susceptibility to measles and provide information on the accuracy of the results.

Dr Mochny and Mr Gay pointed out that, whenever possible, methods should allow for differences in transmission dynamics due to different contact rates between age groups and between urban and rural areas.

The development of a rapid field test is a matter of priority. Dr Yamazaki reported that a new assay for measles diagnosis, developed in Japan, correlated well with the neutralization tests. SAGE members agreed that this and other new field diagnosis tests should be assessed with a view to their use in measles control/elimination programmes.

Dr Steefener pointed out that the implementation of nationwide measles campaigns has raised the possibility of combined measles-rubella elimination efforts as a cost-benefit strategy and asked about current WHO/GPV recommendations on the inclusion of rubella vaccine during measles campaigns. Dr Olivé reported that GPV was assessing this matter and remarked that rubella vaccine should not be introduced into national programmes until resources for long-term implementation were available. He also noted that where mass campaigns were planned for measles elimination the substitution of MR or MMR could be an efficient way to protect the child population. However, he emphasized that MR or MMR vaccine campaigns should not be planned unless there was already a CRS control strategy ensuring that women of childbearing age were protected with rubella vaccine and also routine immunization of children with MR or MMR. This is especially important since the risk of congenital rubella syndrome could increase due to a vaccine-induced shift in the age at infection with rubella in countries where routine immunization services are unable to achieve or sustain high population immunity. Dr Figueroa reported that the English-speaking Caribbean countries had set a goal of rubella elimination by 2000. Dr Olivé noted
that, in many developed and developing countries, rubella vaccine was increasingly being administered by the private sector. It will be necessary to evaluate the effect of this on rubella transmission.

**Recommendations**

While high routine coverage among infants continues to be a cornerstone of measles control programmes, many countries have failed to achieve this. Continued measles transmission in some industrialised countries has called the attention of the SAGE to the need to encourage Japan and some countries in Europe to accelerate efforts to interrupt measles virus transmission. A measles elimination plan for the European Region has been prepared and it is important that high level political support is obtained from the Regional Office and all member countries to ensure its proper implementation. In recent measles epidemics, nearly half of the cases reported occurred among young adults. In light of this, WHO/GPV should co-ordinate research studies to evaluate the potential role in measles transmission of an increasing proportion of susceptible adults.

The SAGE recommends that:

- All countries in a measles control phase evaluate the reasons for low coverage and to identify effective actions to improve measles routine immunization coverage at district level.

- In polio endemic countries or countries with focal poliovirus transmission, acceleration of measles control aiming at measles mortality reduction should be the priority. Campaigns should be implemented to reach all children aged nine months to three to five years in urban and peri-urban areas and other high-risk areas. In addition, these countries should provide Vitamin A during any supplemental immunization activity and ensure adequate case management, as effective ways to obtain further reduction in mortality. Following UNICEF/WHO recommendations, provisions to ensure injection safety should be part of the planning process.

- Proposals to conduct supplemental measles immunization activities aiming at measles control or elimination should have a well-defined surveillance component with identification of the required resources for at least two years and indicators for impact evaluation.

- A simpler, more accessible method should be developed for estimating the proportion of individuals who are susceptible to measles infection. This will assist countries in identifying the appropriate target age groups and the required frequency of the supplemental immunization activities for measles elimination.

- WHO/GPV should co-ordinate the evaluation of a recently developed test for measles diagnosis and establish its potential for introduction in the field as an additional tool to monitor susceptibility and measles virus transmission.
3.3 Neonatal tetanus elimination

Presentation summary

The presentation discussed the proposal to replace tetanus toxoid (TT) with tetanus-diphtheria toxoid (Td), bearing in mind requirements for safety and effectiveness. The implications for global supply, production and cost were considered, and recommendations were made for global policy and for implementation at country level.

Periodic administration of booster doses of diphtheria toxoid are needed to ensure long-lasting protection of all individuals. This has become clear in the light of recent diphtheria outbreaks affecting older children and younger adults in developing countries, the resurgence of the disease in industrialized countries, and the loss of the immune boosting effect from natural infection in areas with high DTP3 coverage. Current tetanus vaccination schedules (three doses of DTP in infancy and the use of TT during pregnancy and for women of childbearing age in high-risk areas for neonatal tetanus) leave some individuals at risk: male and female adolescents, male adults and non-pregnant women in low-risk areas. WHO recommends the introduction of a school-based booster programme to increase protection against both tetanus and diphtheria.

It has been clearly demonstrated that it is safe to replace TT with Td for use in older children and adults, and this has already been recommended in the USA and by PAHO. The minor and rare reactions that occur are related to the purity of the toxoid and may be associated with a hyperimmune response to the tetanus component. Studies have failed to demonstrate any difference in the occurrence of systemic reactions between adults who receive TT and those who receive Td. There is no reason to assume that diphtheria toxoid would behave differently from tetanus toxoid in pregnancy. Toxoids are considered safe at any time during pregnancy.

Some studies have shown that all children and young adults who receive a booster dose of Td between 7 and 13 years after three doses of DTP develop protective titres to both diphtheria and tetanus.

Current data show that the replacement of DT with Td provides an adequate level of immunity when the latter is used as a booster dose or if three doses are used for primary treatment. In conclusion, Td can be used in place of TT and DT, it is safe, and it helps to increase protection against diphtheria and to simplify immunization schedules.

Given the short-term potential deficiencies in the global supply of Td for the replacement of TT and DT, a stepwise implementation was recommended on the basis of achievements with DTP3 coverage and the status of school-based booster programmes. Priority for implementation is proposed for countries with DTP3 coverage higher than 70% for at least five years which do not have a school-based booster programme involving the use of diphtheria and tetanus toxoids.

Global capacity is sufficient to meet the demand for Td vaccine. In the short term, however, country or strategy prioritization is necessary. Local manufacturers should be able to change to Td production within 18 months. The projected price increase...
would be about US$ 0.01 per dose. Such a strategy would provide an opportunity to strengthen national control authorities in vaccine production.

Discussion

Dr Martin requested information on the potential impact of a decision to substitute Td for TT on the work to develop a single-dose tetanus toxoid. Dr Milstien replied that this product development activity was using tetanus toxoid as a model for delivery of controlled-release vaccine. If the system worked the use of other antigens could be explored. It was noted that the evidence for replacing DT at school entry by Td might need to be further reviewed.

Recommendations

Elimination of neonatal tetanus remains a priority for GPV. School-based programmes for administering booster doses of tetanus toxoid are required to cover the gaps in immunity against tetanus created by the respective strategies of primary immunization with three doses of DTP during infancy and TT to women of childbearing age.

During recent outbreaks in the former USSR and in some developing countries, cases of diphtheria have been documented in older persons. This reflects a change in the epidemiology of diphtheria. To counter the trend in reduced immunity, new strategies are required.

Replacing TT by Td for both these situations provides a programmatic answer to both problems, especially in light of documented high rates of school attendance in key countries. Additional programmatic advantages include the safety of Td in all age groups including pregnant women.

The SAGE recommends that:

• TT be replaced by Td in a phased manner. As a first priority, TT should be replaced by Td in all countries that have had DTP-3 coverage of 70% or more for at least five years. Where school-based boosters of DT are given, evaluation of the use of Td to replace the first dose of DT should be considered.

• WHO should provide assistance, as needed, to countries as they switch production to, or increase production of Td.

• The need for two DTP boosters (DTP-4 and DTP-5) be reviewed in light of the proposed school-based Td strategy and the local epidemiology of pertussis.

• As with all changes in immunization strategy, there be consultation with vaccine manufacturers and regulatory bodies to ensure supply capacity and vaccine efficacy using the revised strategy.

3.4 Pertussis control

Presentation summary

The presentation discussed what could be done to control the increase in pertussis incidence in adults as a result of the limited duration of vaccine-induced immunity.
Dr LaForce noted there were increasing reports of pertussis in adolescents and adults. Immunity induced by whole-cell pertussis vaccine appeared to wane over time. The lower attack rate in younger persons was consistent with a substantial degree of protection provided by the vaccine, whereas the higher attack rate in vaccinated adolescents and adults reflected waning immunity. Several pertussis epidemics showed higher attack rates with increasing time after completion of the primary DTP immunization series.

Pertussis infections in adults may be mild and are often poorly diagnosed. Epidemiological studies indicate that pertussis is a relatively common cause of persistent cough in adults. Adults may be contagious, and it is of concern that several investigations document adult-to-infant chains of pertussis infection. Further prospective population-based studies are needed to measure the prevalence and clinical characteristics of pertussis in adults so that the disease burden in this age group can be defined. Studies on the disease burden would be facilitated if an unambiguous serological marker of recent infection with *Bordetella pertussis* were available.

Unfortunately, it is not possible to give whole-cell pertussis vaccine after the age of seven years because it is too reactogenic in older persons. Because of lower rates of reactogenicity, acellular pertussis vaccine may prove suitable for enhancing immunity in adults if regular booster doses are administered. However, this vaccine has become available only recently and studies will be needed to determine the duration of protection following immunization.

**Discussion**

Dr Mochny mentioned that Sri Lanka recently reported a pertussis outbreak among adolescents, including many who had been vaccinated. Dr Suleiman indicated that Oman experienced a pertussis outbreak in 1997 involving nearly 700 cases, mostly in immunized older children. It is important for immunization managers to know that vaccine-induced immunity to pertussis wanes five to ten years after the last dose of whole-cell vaccine.

It was agreed that much of the basic epidemiology of pertussis remains to be clarified and that a reliable diagnostic test would greatly facilitate this work. For the purposes of research, WHO defines pertussis as being confirmed if a patient has a paroxysmal cough for more than 21 days and if one of the following indicators is present: (i) positive culture of *B.* pertussis; (ii) serological evidence of *Bordetella*-specific infection by a significant rise in antibody; (iii) household contact with a bacteriologically confirmed case of *B.* pertussis occurring within 28 days before or after the onset of illness in the patient. GPV is working in collaboration with EMC to develop a practical pertussis case definition for routine surveillance.

**Recommendations**

High levels of pertussis control have been achieved in many countries leading to the protection of children during the ages when they are at the highest risk of severe disease. Reports of pertussis cases and deaths have been greatly reduced by immunization. However, immunization has significantly changed the epidemiology of the disease, shifting the reported age at infection to early infancy (before DTP can be given) and later in childhood. Although the age distribution of cases has shifted, it is not clear whether the absolute number of cases in infants and older children has
increased. There has also been a number of studies reporting pertussis in adults who present with several weeks of paroxysmal cough. It is unclear whether pertussis in adults is a phenomenon related to immunization, or whether this has been unrecognized in the past. Establishing the burden of disease in adults is important because the availability of acellular pertussis vaccines makes it possible to give booster doses of pertussis vaccine to older children and adults.

The SAGE recommends that:

- Further prospective population-based studies be undertaken to measure the incidence and clinical characteristics of pertussis in adolescents and adults, in order that the disease burden in this age group can be defined.
- A diagnostic test be developed that can serve as an unambiguous serological marker of recent infection with B. pertussis.
- Further studies be conducted to examine the duration of protection after immunization with acellular pertussis vaccine.
- WHO develop and promote a standard pertussis case definition for routine surveillance.

3.5 Influenza in Hong Kong

Presentation summary

Dr La Montagne and Dr Schild gave a brief presentation on the recent outbreak of avian influenza in Hong Kong. Although limited in scope it was associated with high mortality. Fortunately, the ability of the virus to be transmitted from person to person was limited. In early January the public health authorities undertook the difficult task of eliminating all chickens, ducks and other birds from Hong Kong's marketplaces.

The appearance of the H5N1 virus in Hong Kong was considered to be an extremely important and potentially dangerous epizootic event. An international task force was rapidly established which worked with colleagues in Hong Kong and elsewhere to learn more about this new virus. A number of important problems have arisen which must be resolved in case the H5N1 virus reappears. Two specific issues were identified. In the first place it is necessary to overcome the difficulties associated with the use of the virus in vaccine production. Because of its high virulence for chickens it must be modified if it is to be a valid vaccine strain, and work with the virus must be done under strict laboratory containment conditions – either BioSafety Level 3+ or BioSafety Level 4 (maximum laboratory containment). Recently, intense work in Europe, Japan and the USA has resulted in the identification of promising candidates for use in vaccines, including several that were derived by genetic engineering in order to eliminate the virulent section of the avian haemagglutinin molecule. Continued work on the virus is necessary if the properties of an avian influenza vaccine are to be understood in anticipation of a potential epidemic attributed to this or a related influenza virus. The second major issue is that there is a continuing need to conduct epidemiological surveillance for H5N1 or other avian virus strains in human and animal populations around the world.
Discussion
Agreement was expressed that, in view of the potential for pandemic spread of a new influenza strain, it was important for WHO to continue emphasizing work in the area of influenza virus epidemiology, surveillance and vaccine development. SAGE recognizes the importance of the cases and deaths occurring between May and December 1997 in Hong Kong from influenza (H5N1), a strain previously only found in birds.

Recommendations
The SAGE recommends that:

- Increased surveillance for avian and the variant forms of influenza virus be undertaken.
- GPV, together with the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC), provide a briefing paper of the world status of the virus and the potential for vaccine production at the next SAGE meeting.
- International collaboration to develop a vaccine against this strain be carried out.
4. Self-sufficiency

4.1 The safety of all injections

Presentation summary
A presentation was made on a broad strategy for the safety of injections. Unsafe injection practices are acknowledged within WHO and UNICEF as being a major health problem, leading to the transmission of blood-borne pathogens from patient to patient, from patients to health personnel, and to the community at large. A thorough review of the published literature and unpublished WHO reports indicates that up to 30% of injections are administered in a way that does not guarantee sterility.

Much has been done to improve safety in this area but it should be remembered that immunization injections represent only 10% of all injections. GPV is therefore engaged in a two-pronged approach aiming to make immunization injections safer, and to devise, in collaboration with others in the health sector, a broader strategy to make all injections safer.

Concrete steps have already been taken to improve the safety of injections in mass immunization campaigns through the adoption by WHO and UNICEF of the “bundling strategy”, which calls for donors to finance not only vaccines but also autodestruct syringes and safety boxes for all the mass campaigns they support.

GPV proposes that another step be taken towards phasing out the use of standard disposable syringes from immunization programmes and replacing them with autodestruct syringes as follows:

- Donors should stop procuring standard disposables and switch to autodestruct syringes.
- Donors should support the local production of autodestruct syringes.

Several departments of WHO have met to develop a cross-programme integrated strategy for improving the quality of injection practices worldwide. The overall aims are to develop and implement policies and programmes in collaboration with countries and other partners. This will raise awareness of the gravity of unsafe injection practices, ensure safe and rational use of injections, and reduce the numbers of deaths and the spread of diseases associated with such practices.

GPV therefore proposes that the following steps be taken during the next three years:
• development of the strategy in greater detail;
• identification and collaboration with major partners in order to obtain their endorsement and support for discrete parts of the strategy (international agencies, industry, non-government organizations, medical and nursing associations);
• convening of an international conference to officially launch a plan for safe injections;
• submission of a resolution for endorsement by the World Health Assembly.

A second presentation described a prefilled monodose injection device which may provide a safer, simpler delivery system. As new and more costly vaccines are introduced the opportunity arises for changing to a simpler vaccine delivery system that can increase the safety, performance and efficiency of immunization programmes. Prefilled monodose injection devices, which compete in price with traditional single-dose vials and separate needles and syringes, have demonstrated their value in the field and are now reaching production. Other needle-free monodose devices are being developed.

All monodose devices protect the integrity of the vaccine dose to the point of use, guarantee that devices are not reused, and minimize the problem of disposal. In addition to safer presentation, new drying technologies based on sugar glasses can make the new vaccines heat- and freeze-stable so that they no longer rely on the peripheral cold chain and can be injected rapidly and easily by a prefilled device without manual reconstitution. This new delivery system guarantees that precious multi-antigen combination vaccines are injected safely and successfully in routine immunization sessions, in mass campaigns and in the most remote populations at risk of disease.

While the programmatic and public health benefits of a safer, simpler vaccine delivery system to developing countries are evident, the benefits to markets in industrialized countries, which tend to drive technological change, need to be further explored. It is clear that new financing mechanisms will be needed to provide access to the new vaccines in developing countries and that considerable investment will be required to switch to heat-stable and freeze-stable vaccines in the proposed types of presentation. It is unlikely that vaccines that have already passed through the regulatory process and are in the production pipeline will be re-engineered as new products. Essentially, therefore, a long-term strategy is in play. However, it may be feasible to present existing vaccine formulations in new monodose devices in the relatively near future, and hepatitis B and TT liquid vaccines are the most likely first candidates. WHO will collaborate closely with the vaccine industry to work out the costs and benefits of new delivery systems for consideration by SAGE next year.

Discussion

The discussion focused on the scale of the problem of unsafe injections, on the immediate need to replace disposable syringes with autodestruct syringes for all immunization injections, and on the proposal to move to a monodose, integrated vaccine delivery system.
While commending the progress and the planned expansion of activities relating to injection safety, SAGE members expressed great concern about the scale of estimates of disease transmission made by EPI on the basis of unsafe injection practices witnessed in the field. To ensure that the estimates were fully substantiated, special advisers to SAGE called for a broader peer review of the paper in question before publication and further distribution. A key proposal was discussed to assure the safety of injections for immunization by replacing standard disposable syringes with autodestruct syringes. It was suggested that certain large countries with neither the technology to convert locally made syringe products nor the funds to import them would require assistance with technology transfer if this policy were to succeed.

The proposal to move towards monodose presentation of temperature-stable vaccines was greeted with cautious optimism. Representatives of the United States Food and Drug Administration, USAID, and the vaccine industry agreed that it was necessary to consider changes in the current delivery system to ensure safety and efficiency. However, warnings were issued concerning barriers and the cost consequences of changes in the formulation and presentation of vaccines, with reference to the scale of investment needed, the regulatory hurdles posed by the integration of new plastic injection devices with vaccine products, and the lack of finance for the introduction of new vaccines into developing countries. Notwithstanding these unanswered technical and resource questions, representatives of the vaccine industry expressed a commitment to constructive and strategic forward planning for the introduction of new vaccines and new delivery systems. They proposed mechanisms for collaboration with WHO on clearer definition of priorities and the evaluation of technical options.

The discussions on the monodose injection device focused on the scale of the problem of unsafe injections, on immediate need to replace disposable syringes with autodestruct syringes for all injections for immunization and on the proposal to move to a mono-dose, integrated vaccine delivery system in the future.

While commending the progress and the planned expansion of activities in the field of safety of injections, SAGE members expressed great concern at the scale of the estimates of disease transmission which have been made by EPI on the basis of unsafe injection practices witnessed in the field. To ensure that the estimates are fully substantiated special advisers to SAGE called for a broader peer review of the paper before publication and further distribution. A key proposal was discussed to assure the safety of injections for immunization, by replacing standard disposable syringes with autodestruct syringes. It was suggested that certain, large countries which neither have the technology to convert locally made syringe products, nor have the funds to import them, will require assistance with technology transfer if this policy is to succeed.

The proposal to move towards mono-dose presentation of temperature-stable vaccines in the future was greeted with cautious optimism. Representatives of the US FDA, USAID, and the vaccine industry expressed support for the need to consider changes in the current delivery system to ensure safety and efficiency. However, a number of points were made warning of the barriers and cost consequences of changes in formulation and presentation of vaccines. These points included the scale of the investment needed, the regulatory hurdles posed by the integration of new, plastic injection devices with vaccine products, the lack of finance for the introduction of new vaccines into developing countries. In spite of these un-answered technical and
resource questions, representatives of the vaccine industry expressed their commitment to constructive and strategic forward-planning for the introduction of new vaccines and new delivery systems. They proposed mechanisms for collaboration with WHO to more clearly defined priorities and to evaluate the technical options.

**Recommendations**

SAGE notes with great concern that the reuse of standard disposable syringes and needles, a practice reported and documented in all regions of the world, puts recipients of all types of injections at risk of infection from blood-borne pathogens. SAGE commends the initiatives of the Expanded Programme on Immunization (EPI) towards safer injections. In particular, it notes with great satisfaction the collaboration that has taken place among WHO divisions (GPV, DAP, EMC and HRB) to draft a strategy for the safety of all injections. While commending the successful implementation of the WHO/UNICEF “bundling strategy” in which auto-destruct syringes, safety boxes and good quality vaccines are procured together in the context of mass immunization campaigns, SAGE urges that further efforts be made to move towards the safer administration of vaccines. SAGE endorses the long-term strategy, to be carried out in close collaboration with industry, to plan and promote the development of (a) safer, simpler delivery systems for new vaccines based on mono-dose, pre-filled injection devices and (b) formulations with increased thermo-stability and their corresponding delivery systems.

The SAGE recommends that:

- As a first step, GPV rigorously review as quickly as possible existing data on injection practices, and seek broad scientific review of the report.
- Further efforts be made to finalize the WHO inter-programme plan for safe injections, and broad support gathered from all partners including industry.
- All partners supporting immunization programmes fully enforce the “bundling strategy” and ensure that the funds they provide to support mass immunization campaigns are not used for the purchase of standard disposable syringes.
- The use of standard disposable syringes that are not auto-destruct be gradually discontinued for immunization injections. Additionally, that GPV, together with the vaccine industry, further explores the feasibility of discontinuing the use of standard disposable syringes and the implications that this may bring about for lyophilised vaccines and vaccines combined at the point of use.
- GPV and its partners collaborate to facilitate technology transfer for the local production of auto-destruct syringes when appropriate.
- Studies should be initiated to demonstrate the feasibility of thermostable, dried vaccines and their corresponding methods of delivery.
- The projected costs of the proposed new delivery systems and their anticipated benefits on safety, quality and performance of immunization services should be elaborated and presented to the next SAGE meeting.
4.2 Adverse events following immunization

Presentation summary

No vaccine is completely safe and no system of immunization is free from human error. A shift in public awareness has led to extensive discussion in the press and, more recently, on the World Wide Web, of both real and presumed adverse events following vaccination. If the promise of vaccines is to be fully realized, those used in national immunization programmes must be produced and administered in the safest possible manner and must be effective in disease prevention, and the public must be convinced of their beneficial properties.

Most reactions to vaccines are mild, relatively common and temporary; the more serious reactions occur only very rarely. This reality is used by immunization programmes to promote the use of vaccines and by others to oppose their use. GPV proposes the following actions.

The global community needs to reassess vaccines and their worth. Science and industry must keep abreast of technology to ensure that vaccines of the highest quality are developed and that their production meets the highest possible standards. CVI AND WHO/GPV should exercise an advocacy role with a view to achieving this.

Staff training in general must promote correct care and administration of vaccines so as to minimize human error. The capacity of national control authorities to deal with reports of potential problems relating to vaccines must be strengthened.

GPV should ensure that every country has a surveillance system capable of monitoring the impact of vaccines in the field, including the reporting of adverse events.

Among other matters, research is needed into ways in which the public gains information on immunization, sources of knowledge which command respect, understanding of risk-taking, and triggers for action.

Investment is required into gaining an understanding of methods of communicating with the press and the public. Programme managers need guidance on how to prepare communication material, which communication techniques and strategies to use, and whether to target the press, radio, television or the Internet.

GPV should promote a system of compensation in every country as an integral part of immunization programmes. Compensation should be awarded by a trusted professional body for specific conditions and should be seen as the way society cares for victims rather than as a means of proving causality.

An alliance should be formed with the vaccine manufacturing industry, ministries of health, universities, national vaccine information centres and international organizations to provide trusted information to professionals and the public on adverse events following immunization.

For Discussion and Recommendations see below, under paragraph 4.3.
4.3 Assessing the scientific basis of alleged vaccination-associated diseases

Presentation summary

There is a rising tide of allegations regarding the potential occurrence of immunologically mediated diseases after vaccination: e.g., multiple sclerosis, inflammatory bowel diseases, Guillain-Barre syndrome, and type I diabetes. This situation requires rapid responses from the scientific community at the global level. WHO/GPV is ready to play a co-ordinating role in the scientific assessment of the validity of the allegations.

Since vaccines are often accused of inducing a variety of autoimmune diseases it is essential to differentiate theoretical from real risks and to understand the mechanisms that are responsible for downregulating the development of such syndromes after exposure to infections: the relative importance of molecular mimicry for both B and T cell epitopes, the limitations of autoimmune responses in the context of self-tolerance or of MHC restriction, and the requirement for associated non-specific stimulation of the immune system. It is also important to keep in mind that autoimmune responses do not lead automatically to autoimmune diseases, which require an access of generated T cells or antibodies to autologous antigens or peptides in a potentially sensitive host tissue site.

It is therefore proposed that, in order to deal with these issues, the following strategy should be followed whenever there is a suspicion or an allegation of a potential vaccination-associated abnormal syndrome that is immunologically mediated:

1) Identification and “intelligent” assessment of potential risk at the pre-clinical stage (if feasible!).
2) Monitoring of late side effects during clinical trials.
3) Rapid assessment of allegations: evaluation of presented data and, if needed, epidemiological and immunological studies.
4) Establishment of a WHO network of collaborating scientists/laboratories and development of an international consensus on relative risk of vaccination.
5) Rapid diffusion of relevant information.

Discussion

Dr Schild pointed out that it is not yet known what would be the full effect of a recent article in the Lancet suggesting MMR vaccine caused autism and Crohn’s disease. Currently there has been a 5% drop in coverage, but it may eventually be higher. Dr Streefland described the research carried out on immunization by his team of social scientists in various countries. Although he agreed it was a global problem, developing countries tended to focus on adverse events related to poor care and delivery, while industrialized countries focused on a change or lack of trust in health care providers, and were influenced by competing technologies such as “new age”. Robert Steinglass mentioned the perception in the former USSR that children were “getting weaker” and unable to cope with vaccines. Accordingly there are currently many contra-indications invoked by paediatricians. This can be overcome by arranging conferences between paediatricians and public health physicians. Dr Broome supported the idea of having an international network of communication on the subject.
Recommendations

The SAGE recommends that:

- In view of the increasing reported numbers of adverse events following immunization (AEFIs) which are disrupting coverage and undermining confidence in vaccines and services, WHO/GPV and the CVI work towards the following objectives:
  - the enormous benefit of immunization be strongly advocated to public health;
  - training for health care staff be ensured so that programme-related AEFIs can be minimized and responded to appropriately;
  - surveillance systems be established capable of monitoring and providing up-to-date information in all countries;
  - where feasible, potential risks of delayed immunological or oncogenic effects at pre-clinical stages should be identified and assessed, late side effects during clinical trials monitored and rigorous post-licensure (phase 4 trials) surveillance established;
  - international consensus be developed of relative risks involving all the major players;
  - a network of collaborating scientists and laboratories be established which is able to provide appropriate and rapid scientific responses.

- Social science investigation be used to provide understanding of behaviour and triggers for action by parents and practitioners on immunization.

4.4 The role of WHO in vaccine procurement

Presentation summary

The presentation discussed how to strengthen and implement a changed role for WHO in vaccine procurement. Most countries have become self-sufficient in vaccine supply either through increased production or through the procurement of vaccines internationally. How a country buys vaccines should depend on the skills and knowledge within the country.

To acquire vaccines a country must have funds, the ability to purchase vaccines and the ability to specify and control what the programme needs. The international community can help if any of these factors are missing. Each entity procuring vaccines must involve the EPI manager in defining what the programme needs and the national control authority in determining what is acceptable for the country.

The EPI manager defines how the country programme is set up. If specifications relating to such matters as vial size, markings and label text are incorrect at the time of purchase the programme may be brought to a halt. WHO has standardized many specifications in order that training materials and handling procedures can be predetermined.
The national control authority should prequalify suitable vaccines and at the time of delivery should assess whether products meet the country’s requirements. Countries without an effective national control authority should continue to rely on WHO or UNICEF to purchase vaccines and perform these functions.

Countries choosing to obtain vaccines through WHO/PAHO are entitled to expect more than just vaccines of good quality which meet programme requirements. They should also benefit from good service and low cost. PAHO provides many services but there is room for improvement. WHO provides a routine service that could be improved in many respects. The procurement entity should work closely with the programme, reviewing plans, adjusting forecasts, building buffer stocks and advising the programme when delays are expected.

WHO has a system in place to ensure that all EPI vaccines supplied through UN agencies meet WHO requirements, are produced in compliance with GMP and meet specific programme needs as reflected by compliance with tender specifications. This evaluation process allows WHO/VSQ to publish a regularly updated list of vaccines considered acceptable for supply through UN agencies. The process makes it possible to give advice on the acceptability of candidate vaccines for purchase and monitors the continuing acceptability of vaccines currently supplied. The system is restricted to EPI vaccines and should be expanded to include the evaluation of:

- vaccines used in emergencies;
- traditional vaccines that are only now being introduced in routine immunization programmes;
- new vaccines;
- combinations, for which it is necessary to increase funding through both the regular WHO budget and payments from the purchasing agencies.

Discussion

Questions were raised concerning the WHO position on the targeting of resources. It was confirmed that WHO would continue to request the focusing of resources on the countries in greatest need.

As to whether the suggested improvements in procurement systems would follow a price-tiering strategy, it was explained that they were operational and did not represent changes in policy. A number of old unused vaccines had been available from several competitors for a long time. They should be purchased on the basis of current public procurement principles.

Concern was expressed by the World Bank that WHO should focus on the introduction of vaccines rather than on receiving low prices.

In response to a question as to whether WHO intended to expand procurement in competition with UNICEF, the hope was expressed that UNICEF would remain pre-eminent in vaccine supply. The intention was to improve the existing practices of all other procurement entities to ensure that only vaccines of known good quality would be purchased. For instance, the PAHO system had many excellent elements, particularly its close working relationship with programmes. WHO could improve its global operation by adopting the best practices and creating a common system.
Regarding the proposed expansion of the WHO system to prequalify potential suppliers of new vaccines, concerns were raised about the need to avoid duplicating the activities of national control authorities in manufacturing countries. It was pointed out that the system in place at WHO/VSQ was basically a service to UN agencies involved in purchasing vaccines. These agencies had set specifications for vaccines, and compliance with the specifications needed to be monitored by WHO. In many cases the national control authorities in manufacturing countries were not required to monitor compliance of vaccines for export, and consequently it was desirable for this to be ensured through agreement with these authorities and through direct evaluation by WHO. Most countries receiving the vaccines did not have fully functional national control authorities capable of adequately dealing with these matters.

Recommendations

Encouraged that many countries are becoming self-sufficient in vaccine supply through procurement, SAGE commends the work being done in helping countries purchase vaccines. However, it was acknowledged that there are risks to national programmes if countries purchase vaccines without due regard to their special nature. This purchasing should have the full involvement of the EPI to define programme needs and the involvement of a National Control Authority with vaccine regulatory skills to determine national acceptability. Furthermore, there is a need to increase the availability of procurement training and procurement assistance for countries and agents purchasing vaccines directly.

In addition to offering extra technical support to countries and agents purchasing vaccines, it was recognised that there are areas in which WHO could provide increased support. Changes should be made within WHO to improve the services offered to UNICEF, other agencies and countries. Of particular concern was the need of Vaccine Supply and Quality (VSQ) to assess new companies and new vaccines in preparation for the expanding use of additional vaccines.

It was observed that the separation of Biologicals (BLG) and its Expert Committees from the operational aspects of assessments by VSQ was appropriate. Ways to cooperate more closely with competent National Control Authorities on the assessment process should be strengthened.

SAGE notes with satisfaction the strong re-commitment from UNICEF to purchase and introduce new vaccines.

The SAGE recommends that:

- The National Control Authority and National Immunization Programme in all cases be involved in standard setting for the procurement of vaccines. Countries without a National Control Authority at the present time, should be encouraged to seek assistance from WHO or UNICEF. WHO or UNICEF will offer to support all developing countries in accordance with their needs.

- WHO establish a common system for vaccine procurement. All vaccines supplied through UN agencies should be subject to the same quality assurance assessment, including traditional vaccines, like
MMR and yellow fever, which are only now being introduced into the routine immunization programmes, and new vaccines. All these need to be assessed for pre-qualification. For this purpose extra funding is required. The additional funding should be obtained from regular budget and from all the purchasing agencies that make use of the system.

- The procedure in place at WHO for evaluation of newly licensed vaccines for purchase by UN agencies be reviewed. The SAGE recommends that GPV convene a working group for this purpose.

4.5 Forecasting demand for vaccine production

Presentation summary

The presentation discussed what model might be used to forecast aggregated demand for vaccine production. The purpose of demand forecasting is to ensure the supply of vaccines of high quality in adequate quantities and in good time. This requires the co-ordination of global demand and production capacity, especially in respect of accelerated activities, outbreak response, the introduction of new vaccines, and comparable situations.

If it is desired to increase production capacity beyond a certain level, manufacturers should be given the lead time necessary to make investment decisions and renovate or construct facilities. This process may take many years, and forecasts are needed of the numbers of doses of vaccines to be administered and when they will be required.

To answer these questions the following approaches are proposed:

- For outbreak response a stockpile and a financial mechanism should be established to ensure the immediate supply of vaccines to countries even if they lack financial resources that can be mobilized immediately. This has proved useful with, for instance, the ICG meningitis stockpile.
- For accelerated activities, maximum demand should be calculated in order to determine whether global production capacity needs to be increased in the foreseeable future.
- For the introduction of new vaccines it is critical to determine when production capacity should be increased.

To answer the latter question an attempt to quantify the likelihood of introduction of yellow fever vaccine into national immunization programmes is being made on the assumption that self-sufficiency, coverage rate and disease burden are equally influential. The factors that affect the introduction of new vaccines are being analysed, and the weight of each factor is being taken into account. Calculations will be partly based on quantifiable variables but qualitative factors may also have to be reflected, such as political will and a negative perception of vaccines.

Besides assuring adequate supply, demand forecasting is important for the policy-making process. To support this function, VSQ will work closely with key partners such as governments of countries, donors, manufacturers and other units and divisions of WHO.
VSQ would asked SAGE to consider whether the current model for predicting demand for new vaccines was useful and appropriate in terms of both quantity and time, and how VSQ might highlight the role of demand forecasting in the policy-making process.

**Recommendations**

Demand forecasting for vaccines is needed in four situations: for routine use, for outbreak response immunization, for accelerated immunization activities, and for new vaccine introduction. National capacity to plan for vaccine supply is especially important. The development of methods to respond to the needs of countries experiencing economic crises should also be considered. For the latter three situations, global co-ordination of demand with manufacturing capacity is critical. The SAGE notes the activities of GPV to strengthen demand forecasting capacity in countries, and the models proposed to estimate demand. The SAGE endorsed the activities of GPV in relation to disease burden studies, given the importance of disease burden estimates in demand forecasting, particularly for new vaccines.

The SAGE recommends that:

- GPV strengthen the co-ordination of global demand with global production capacity for accelerated immunization activities, outbreak response, and the introduction of new vaccines.
- Given the importance of the time dimension in demand forecasting for the introduction of new vaccines, efforts continue to develop explicit modelling techniques and the verification of such models against actual data.

**4.6 Maintaining WHO quality standards in vaccine production**

**Presentation summary**

The presentation discussed how WHO quality standards are being maintained for vaccine production, with the increase of developing country research groups and manufacturers.

With regard to vaccines for which the market in industrialized countries may be limited, often called “orphan” vaccines, the standard vaccine development process may not always work. The public sector has sought to find alternative locales in which to stimulate research and development. Much of this work has been done in laboratories in developing countries. Moreover, in order to stimulate demand for products, manufacturers and the public sector have encouraged clinical studies in developing country settings. While this has been logical, on occasions the country chosen has not had sufficient infrastructure to ensure consistency of the product or availability of all the documentation that might be required for regulatory action.

Countries assume that a certain standard of quality and consistency exists if WHO’s name is associated with a product, and it is important to ensure that the assumption is well-founded.
VSQ has considered two possible approaches to this problem. The first involves the development of guidelines that will fill gaps in the present guidelines on good clinical practice for trials on pharmaceutical products related to the special needs for trials on vaccines. For example, the need to ensure that a product for phase III trials has been produced on the scale to be used for actual production rather than on that appropriate for research purposes. Aware of these gaps, VSQ, in collaboration with expert staff from other units, has begun to assess the need for more comprehensive clinical trial guidelines for vaccines.

A document dealing with this matter could be useful in providing clinical trial guidance so that vaccines would be suitable for international use, by serving as a manual in training courses of the Global Training Network and in guiding expert consultants on reviewing clinical trial data.

The second approach is that of accreditation of national control authorities so as to indicate potential sites for consideration of the promotion of research and development activities.

At its 1997 meeting, SAGE suggested that efforts be made to assess how well countries were performing. The assessment process, to be initiated only at the request of countries, would include: assembling an expert review panel to advise WHO on the process; proficiency testing of national control laboratories on a global basis; assessment of national control authorities in accordance with defined indicators; a visit by an assessment team composed of members of the expert review panel to make a final decision on accreditation; the development of an institutional training plan, and training in the Global Training Network to fill gaps detected during the assessment process.

**Discussion**

The discussion was opened with a statement on the important division of labour between VSQ and the Biologicals Unit: guidelines were drafted by the Biologicals Unit and adopted through the Expert Committee on Biological Standardization; VSQ is responsible for implementation. VSQ could not function unless the Biologicals Unit had the resources to do its work and ensure that the guidelines were kept up to date.

There was general support for the idea that guidelines would be welcomed for investigators, manufacturers and regulatory authorities, highlighting the special areas where vaccines differ from pharmaceuticals in development for clinical trials. The need to involve the appropriate experts and to keep the guidelines generic and non-restrictive was emphasized. Although there were precedents for such activities in WHO, the task would be extremely difficult.

SAGE considered that a move towards accreditation of national control authorities would have far-reaching implications and that further discussion in WHO should be initiated. If the approach were agreed the issue should be brought before the World Health Assembly.
Concern was expressed regarding rabies vaccine and other brain-derived vaccines. It was suggested that the history of rabies vaccine production might provide a good model for examination of the issues raised by the paper.

**Recommendations**

The SAGE notes the need for an intensification of WHO activities in relation to the quality control, standardization, and clinical evaluation of new vaccines, particularly in relation to countries lacking regulatory expertise. However, the SAGE feels that accreditation of national regulatory authorities is a subject of such importance that it merits internal discussions within WHO which may lead to a decision to bring it before the World Health Assembly. Furthermore, the SAGE is aware that the work of GPV on improvement of vaccine quality could not continue without the close collaboration of the Biologicals Unit and the Expert Committee on Biological Standardization, which develops guidelines and advice for National Control Authorities, and of the need for these guidelines to reflect current scientific advances.

The SAGE recommends:

- **The provision of guidance to investigators, manufacturers and international agencies in the development of products for WHO-sponsored clinical trials.** Also, the development of guidelines on criteria for manufacture, quality control, and standardization of novel vaccines appropriate to their enrolment for clinical evaluation. These guidelines would supplement already existing guidelines covering other aspects of the vaccine development process. This activity should proceed with input from all appropriate groups within WHO, including VSQ and the Biologicals Unit, using a consultative process which seeks input from knowledgeable experts. The guidelines, which should be advisory rather than restrictive, should then be submitted to the Expert Committee on Biological Standardization for review.

- **The SAGE recognizes the need for an approach to identify those countries whose national regulatory authorities have the capacity to oversee the vaccine development process, and recommends that GPV consider steps to implement such an approach.**

- **Because the current situation with the production of brain-derived vaccines, especially rabies vaccine, in many countries highlights some of the problems of vaccine development, the SAGE recommends that GPV, in collaboration with appropriate units within WHO, prepare for the next meeting a briefing paper on the global situation with respect to brain-derived rabies vaccines.**

**4.7 The quality of EPI data**

**Presentation summary**

The presentation discussed the quality of EPI surveillance data. Vaccine coverage (percentage of target population vaccinated) is the major indicator for immunization programme performance at the local, national, regional and global levels. It is used to target resources and identify areas requiring special attention, and is the core
indicator for access to basic health services. Oral polio vaccine coverage is used as part of GPV/EPI’s evaluation of progress in polio eradication, tetanus toxoid coverage is used in the neonatal tetanus elimination high-risk approach, and all antigens are used as part of the framework for introducing new vaccines. WHO has proposed that diphtheria, tetanus toxoid and pertussis vaccine (DTP-3) coverage should be used as one of the criteria for allocating funds to countries.

We reviewed immunization coverage data officially reported to WHO/EPI by 217 countries and territories for 1991-1996. Coverage data for BCG, DTP3, hepatitis B virus vaccine, measles vaccine, OPV3, TT2+ and yellow fever vaccine where examined for internal consistency and agreement with data from other sources.

In 20.3% of cases there was an increase or decrease in reported coverage of more than 10% from one year to the next. In around 15% of cases there was more than a 5% difference in DTP3 coverage, and OPV3 and BCG coverage was higher than DTP3 coverage in almost 20% of cases. There was more than a 10% difference in 17% of officially reported data and data points when compared with other sources (e.g., UNICEF, DHS, national surveys). The advice of SAGE was sought on whether current levels of completeness, consistency and reliability were inadequate in relation to the purposes for which information on coverage was used. Should the reporting of coverage data be stopped? Should additional resources be invested in order to improve the completeness, consistency and precision of coverage estimates?

Discussion

SAGE recognizes the need to improve the quality of reported immunization data, since it is being used increasingly for major decision-making, including national and international resource allocation.

SAGE also discussed the increasing importance of monitoring reliable immunization data at the district level in countries undergoing health reform.

Recommendation

The SAGE recommends that

- GPV increase the efforts and resources for improving the quality of national immunization data (and validating these data) in the context of strengthening national health information systems.
5. New vaccines

5.1 Typhoid vaccines

Presentation summary

The presentation discussed when typhoid vaccines should be used. Diarrhoeal diseases are still responsible for about three million deaths annually, of which 600 000 are estimated to be caused by typhoid fever (TF). Thus TF remains an important public health problem in many developing countries, particularly in South-East Asia, where multidrug-resistant strains have emerged. Two effective vaccines are available and licensed: Vi polysaccharide is injectable and is given in one dose, and live Ty21a is administered orally in three doses at intervals of two days.

In most of the affected countries a high incidence of TF is seen in people aged 5-19 years, whereas infants show much lower incidence rates. The target population for the use of the vaccines includes children of school age and infants being routinely immunized under the Expanded Programme on Immunization. Other important target groups are travellers and clinical microbiology technicians.

Discussion

Sir Gus Nossal enquired whether the vaccines against typhoid fever should be used now or whether vaccination packages against diarrhoeal and enteric diseases should first be developed. Dr Ivanoff emphasized the value of currently available vaccines in school-age children in high-risk areas. Both the oral Ty21a and the parenteral Vi polysaccharide vaccines are very well tolerated and confer a good level of protection in school-age children which lasts several years. In a large effectiveness trial involving more than 200 000 schoolchildren in Santiago, Chile, Ty21a was found to be useful in school-based immunization programmes. Dr Steinglass further emphasized the need to seek opportunities to vaccinate schoolchildren in areas of acute endemicity, given the high enrolment rates in Africa and Asia. Opportunities should also be sought to evaluate the administration of typhoid fever vaccine together with Td in children of school age.

Dr Ali Jaffar asked if food handlers should be considered as a target population for vaccination. Dr Levine replied that they should be screened for the Vi antigen. Vaccination for chronic carriers is not useful and treatment is the preferred choice. However, if vaccination is performed, the Ty21a oral vaccine, which does not contain the Vi antigen, should be employed.

Dr Taky Gaafar stressed the importance of vaccination in view of the growing antimicrobial resistance that was presenting a real public health crisis. Dr Levine
agreed and summarized the emergence and evolution of strains of S. typhi with multidrug resistance. Before 1948, when oral chloramphenicol was shown to be effective in treating acute typhoid fever, case fatality rates were around 50%. However, a large epidemic of chloramphenicol-resistant strains of S. typhi occurred in Mexico in 1972; after two years the antibiotic-resistant strain disappeared and S. typhi strains in Mexico once again became chloramphenicol-sensitive. A similar set of epidemiological events occurred in Lima, Peru, in 1979-1980. Since 1990 the incidence of multidrug-resistant S. typhi has increased rapidly, particularly in the Indian subcontinent and elsewhere in South-East Asia. Although alternative antibiotics (quinolones and cephalosporins) are now being used, there were reports of S. typhi isolates resistant to ciprofloxacin during the 1997 epidemic in Tajikistan.

Dr Mulholland emphasized that vaccines against typhoid fever may have a double function in reducing antimicrobial resistance: elimination of the need for treatment and indirect reduction of the probability of antibiotic use against a general syndrome whose bacterial origin is unconfirmed.

**Recommendations**

The control of typhoid fever requires the provision of potable water and basic sanitation and the promotion of personal hygiene. The global burden of typhoid fever (estimated 30 million cases and 600,000 deaths annually) is largely borne by school-aged children, 5-19 years of age who, in most developing countries, account for approximately two-thirds of all cases. The epidemiological situation has steadily worsened since the emergence in 1989, and the continuing spread thereafter, of Salmonella typhi strains resistant to multiple antibiotics. Two typhoid vaccines (injectable Vi capsular polysaccharide and attenuated live oral strain Ty21a) are now available and are known to be well tolerated and effective in preventing typhoid fever in this age group.

The SAGE recommends that:

- Immunization of school-aged children be undertaken wherever a priority. Such school-based typhoid immunization programmes should be limited to geographical areas where typhoid fever is a recognized public health problem and areas where antibiotic-resistant S. typhi strains are particularly prevalent. The use of typhoid vaccines in school children should be harmonized with the school-based administration of Td.

**5.2 Financing new vaccines**

**Presentation summary**

The presentation discussed the options for financing new vaccines. Advances in science and technology have led to the development of several new vaccines and there is now increased scope for saving lives. Mainly for economic reasons, however, some two million children die annually from vaccine-preventable diseases.

The rapid introduction of new vaccines into national immunization programmes is one of WHO’s most important missions. Approaches devised by GPV are in the process of being re-evaluated.
Globally, there has been a general lack of consolidated knowledge and viable approaches made available to countries. Sufficient emphasis and effort have not been given to the mobilization of new resources. At the country level there have been difficulties in allocating additional resources because of competing priorities and restricted health budgets, and general management skills have not improved.

It is therefore necessary to adopt a more country-based approach and to develop innovative financing mechanisms in order to introduce vaccines rapidly and effectively.

Countries should develop national vaccine supply plans that include explicit financing components. WHO global and regional offices should give the highest level of technical support to countries and develop an information repository to which they can readily refer.

With regard to financing, development loans offer one option. They should be employed with caution but can be useful transition instruments for some countries endeavouring to become self-reliant and introduce new vaccines.

Thus a new look at financing is required in order to meet the demands for new vaccines. Several approaches are possible and should be explored. Two in particular are worthy of note. Countries should develop their own vaccine supply plans with the support of WHO and other parties as necessary. New financing models should be investigated, including the use of loans from development banks.

Discussion

Attention was drawn to the gravity of the situation associated with the limited financing available for new and established vaccines in developing countries. The cost-effectiveness of vaccines made them particularly beneficial, yet there was growing global inequity because of finance-limited access to them in developing countries. Dr Cochi declared that this situation was unacceptable. SAGE strongly urged that an immense effort should be made to deal with the matter.

SAGE felt that the elaboration of country-based strategies was important and that WHO/VSQ should provide support as necessary to national vaccine supply plans. Furthermore, maximum attention should be given to financing issues in countries of greatest need (Bands A and B).

The need to adopt new financing mechanisms was underlined. SAGE felt that development banks, distributing large financial resources, should play a key role in working with countries to ensure that adequate priority was given to vaccines. Dr Cochi called on WHO to continue and strengthen its relationship with development banks and to provide all necessary technical assistance and co-ordination.

Dr Mochny argued that other novel financing mechanisms, such as the use of trust funds and revolving funds, should be considered and developed. Cost recovery for vaccines and the use of revolving funds and other mechanisms were discussed. Dr Stoeckel and Dr Sakai considered that cost recovery was useful for enhancing community participation. However, Dr Sakai said that in most cases it was preferable to use charges from curative services to cross-subsidize the costs of immunization and other preventive services.
Dr Arita and Dr Broome commented that because many health systems were undergoing reforms involving changes in financing mechanisms there was an opportunity for countries to re-examine not only the amount of domestic funding dedicated to immunization but also the sources and cross-subsidization features of vaccine financing. In order to ensure adequate and sustainable financing it was therefore important for immunization to be explicitly considered in these reform processes and for every opportunity to be taken to stress the cost-effectiveness and increasing financial needs in this area.

Recommendations
Financing for new vaccines and the sustainability of financing for existing vaccines are among the most critical issues facing immunization programmes. Despite the fact that immunization is the most cost-effective health intervention available today, the SAGE notes substantial weaknesses in the global infrastructure to finance both the supply of existing vaccines and the introduction of new vaccines, particularly in low income countries. These shortcomings represent a threat to further progress towards bringing the benefits of vaccines to the world’s children.

The SAGE recommends that:

- **Country-specific approaches be developed.** These include:
  - the development of national vaccine supply plans. WHO should support these by collecting, analyzing, disseminating information and proposing financing options and guidelines, and
  - the focusing of resources to the countries of greatest need (bands A and B).

- **WHO** examine and address the financing needs for new vaccines for the present and the future in collaboration with UNICEF and other partners.

- **WHO** provide the development banks, other partners, and countries with technical assistance. This should ensure the development and implementation of vaccine financing mechanisms at the country level.

- **Other mechanisms**, such as trust funds and revolving funds, also be considered. One approach, which may be facilitated by health care reform, is the diversion of curative care financing to preventive approaches such as vaccines.

5.3 Accelerating the introduction of new vaccines

Presentation summary
The presentation discussed how to reduce the long intervals between the licensing and the use of vaccines in industrialized countries, and their introduction into developing countries, especially the poorest, which often greatly needed them to avert deaths and suffering. The introduction of hepatitis B and Hib vaccines would be examined to elucidate the lessons learnt; the possible contribution of quantitative policy analysis and introduction decisions would be outlined, and a model of country decisions There followed four presentations on the theme.
(i) Introduction of hepatitis B vaccine: important factors in national decisions to introduce the vaccine

Dr Kane, summarizing the lessons learnt from the introduction of this vaccine, suggested they indicated that “In order to get something you must want it and be able to make it, afford it or get someone to give it to you”.

Hepatitis B vaccine was introduced into industrial countries in 1982 as an expensive (approximately US$ 100.00 per series) vaccine indicated for “high-risk groups” defined by lifestyle and occupation. This strategy failed to control the disease in all groups except health care workers (who received 80% of the vaccine but represented less than 10% of clinical cases) and infants of carrier mothers. The major high-risk groups who acquired hepatitis B through sexual activity or drug use or because they belonged to an ethnic category of high endemicity did not receive significant amounts of the vaccine. These groups proved difficult to reach and the delivery infrastructure for the vaccination of adults was, in general, ineffective. Because of the large market among health care workers, however, the hepatitis B vaccine became the most profitable product in the vaccine industry.

Because of the failure of the high-risk strategy, all industrialized countries except Ireland, the Netherlands, the Scandinavian countries and the United Kingdom now routinely immunize infants and/or adolescents as part of their national immunization programmes. This has proved economically attractive in most countries, where the price per paediatric dose in large public sector programmes has fallen to about US$ 10.00.

Most developing countries, with the highest burden of hepatitis B disease, were unable to afford the vaccine until the price fell to about US$ 1.00 per paediatric dose with the entry of South Korean manufacturers into the market. Western producers had switched to DNA recombinant vaccine and a marketing battle between the newer vaccine and the older, less expensive plasma-derived vaccine ensued. Western producers reduced prices dramatically. Meanwhile, the ability to produce the vaccine was developed, or is being developed, by Brazil, China, Cuba, India, Indonesia, Myanmar, Viet Nam, and other countries.

Unfortunately, the poorest developing countries have not been able to obtain hepatitis B vaccine because, with some exceptions, the partners in development have not supplied it. The poorest countries often depend on them for their vaccine supply. UNICEF, the World Bank and other partners have recently made positive statements about supporting hepatitis B immunization.

Important factors to be taken into account when decisions are being made by developing countries include:

- the strength of the immunization programme
- the perceived priority of the disease
- the stability of the ministry of health
- the ability to make or buy vaccine (GNP and size)
- the importance of outside input into the setting of national priorities
- the attitudes of important partners in development
• the behaviour of neighbouring countries
• competing priorities within and beyond the immunization field

WHO played an important role in the many countries that accepted its 1991 recommendation to include the vaccine in national immunization programmes. The clustering of countries that adopted hepatitis B vaccine in regions where the WHO Regional Office was supportive demonstrated the significance of WHO’s contribution.

The role of the vaccine industry, the awareness of the medical community and the role of partners in development are also important factors in the introduction of the vaccine.

The basic problem is that the financial infrastructure underlying the provision of vaccines to the poorest countries cannot support the introduction of new vaccines, each of which would double or triple the total cost of vaccines in these countries. Our most important challenge is to develop new financing mechanisms to solve this problem.

(ii) Lessons from the introduction of Hib vaccine

As of June 1998, 34 of the 212 states reporting immunization data to EPI routinely used Hib vaccine in their infant immunization programmes. A number of other countries, primarily in the African, Americas, and Eastern Mediterranean Regions, will be introducing the vaccine in the next two years. The decision to introduce Hib vaccine and subsequent experience in introducing it have been reviewed through visits to four countries that were among the first in their regions to adopt this new prevention tool (Chile, Kuwait, Qatar, and Uruguay).

All the countries considered country-specific data on the Hib disease burden during the decision-making process. For two countries, the perception of disease severity was as important as, or more important than, the actual number of cases. Previous in-country experience with the vaccine was a positive factor in its adoption in three countries. This experience ranged from a large randomized trial to widespread use in the private market. In all countries, the paediatric community had a major influence on the decision taken. The major obstacle that had to be overcome in the decision-making process in three countries was that of price.

In all countries, introduction proceeded without major problems, and no country provided any specific additional resources for transport or the cold chain, although most organized some preliminary formal training. No major adverse effects were noticed, there was a marked impact on disease in countries where evaluation was carried out, and public acceptance was good. It proved difficult to decide on follow-up tenders because of the numerous formulations and combinations of Hib vaccine which are now available. Additional information on wastage will be critical in designing the most cost-effective ways of using these relatively expensive vaccines.

The information gained from this evaluation will be used to develop introduction guidelines and training material for introduction. Furthermore, it provides a basis for additional work on the decision-making process and on how this may be influenced.
The major factors that have influenced the adoption of Hib vaccine, either positively or negatively, thus appear to be:

- the desire to prevent the burden of Hib disease
- the availability of data on disease incidence
- information on disease severity
- interest of local paediatrician groups
- public concern about meningitis and/or pneumonia in children
- the compatibility of the vaccine with the immunization schedule and programme
- the ease of introduction with DTP
- experience with the vaccine through studies or private market exposure
- the multiplicity of formulations and combinations
- the success of the vaccine in other countries
- the price

(iii) Possible contributions of quantitative policy analysis to decisions on the introduction of new vaccines

Dr Miller, CVI Secretariat, summarized the major elements and potential contributions of a systematic, quantitative approach to decisions at country level on the introduction of new vaccines.

The methods developed by the CVI Secretariat called for the calculation of:

- the disease burden
- the costs of implementing vaccination programmes, including actual costs or estimates of delivery, or e.g., of tiered vaccine prices
- the health benefits that would accrue from vaccination programmes with assured vaccine efficacy, coverage, etc.
- the cost savings that would arise because of a reduced need to treat disease

These calculations could be refined by using the latest country-specific estimates, and the results could be expressed as:

- deaths, hospitalizations or cases averted
- cost savings
- cost per unit of health benefit, e.g., cost per death averted or cost per disability-adjusted life year saved
- cost expressed as a function of gross national product (GNP) or per capita GNP

In the future the methods could be modified to take indirect costs into account, such as those of travel to clinics and time lost from work.
Such quantitative analysis promoted the full utilization of all available country information. Unlike subjective systems of comparison it also permitted assessment of the relative importance of uncertain variables (such as vaccine efficacy), disease estimates, and assumptions (such as discounting over time).

The methods, which could be improved if better country-level data were obtained, already offered considerable benefits for the policy-making process.

Dr Miller reported the results of analyses conducted on the basis of a range of plausible assumptions. The cost-effectiveness of hepatitis B, Hib and rotavirus vaccines in the poorer developing countries was of the same order as for traditional vaccines (<US$ 100 per disability-adjusted life year saved). Thus, even though priced higher than traditional vaccines, the new vaccination efforts were of excellent value according to the World Bank criterion of less than the per capita GNP per disability-adjusted life year saved.

(iv) Using a conceptual model to anticipate information needs for new vaccine introduction

Dr Widdus summarized a conceptual model, developed by the CVI Secretariat, of the process by which various players in countries reached conclusions about the introduction of new vaccines (see GPV/CVI/SAGE 98.WP.14).

The model incorporated the observations on the introduction of the hepatitis B and Hib vaccines, outlined above. It postulated that the decision-making process on new vaccine introduction took into account:

- recognition of the disease
- social norms among both public and providers, and other health and social
- problems competing
- the perceived benefits and risks of the vaccine
- possible barriers, such as perception of costs
- cues for action, such as activities that raised awareness, epidemics, ‘champions’, or WHO recommendations.

Dr Widdus suggested that the length of the country decision-making process and, consequently, the delay in introduction in many developing countries, could be shortened by anticipatory actions, such as early definition of country disease burdens, for vaccines in late development. He invited SAGE members to identify the elements in the model which they felt would most accelerate the introduction of new vaccines. This was an urgent task because of the many new vaccines in development and because of the delays of 10-20 years previously experienced in the use of new products in developing countries.

Discussion

SAGE members in general agreed that all the issues identified in the Secretariat presentations influenced decisions on new vaccine introduction. It was also agreed that each country process and each new vaccine probably had its own characteristics, although there were elements in common.
Dr Steinglass remarked that factors beyond the public health realm sometimes led to inappropriate decisions on adoption or priorities. There was general agreement that every effort should be made to protect the decision-making process from inappropriate influences, e.g., personal awards of procurement commissions, while seeking political support for rational choices through early sharing of information.

There was unanimous agreement that the process of introducing new vaccines into developing countries had been far too slow. Dr Maynard of PATH emphasized that closing the gap was an ethical imperative for children's welfare in developing countries, as well as an issue of anticipating technical information needs.

Dr Salisbury identified the need to consider carefully the case to be made regarding resource allocation for new vaccine introduction. Treasuries often assumed that new vaccination efforts could be financed by reallocation of existing projects (by cancellation or extra efficiencies). A strong case had to be made for the provision of money that was really new. Other SAGE members emphasized the need to press for additional spending, since, especially in the poorer countries, the use of vaccines was generally more cost-effective than hospital-building and other health interventions.

Dr La Montagne pointed out that the total amount needed for new vaccines in the next decade was, in comparison to the global economy, relatively small. Dr Martin agreed and advocated fresh efforts to mobilize new resources. Dr Widdus announced that CVI would be organizing a meeting on Sustainable financing for vaccination programmes towards the end of 1998 or early 1999.

Dr Msambichaka raised the matter of incentives for new vaccination efforts in funding mechanisms such as the UNICEF Vaccine Independence Initiative. At present, countries were judged to have met their self-sufficiency goals if they reached the target percentage of funding for traditional vaccines (priced much lower than new vaccines). If a new vaccine were introduced with some external assistance, countries might be regarded as moving away from self-sufficiency on the basis of the percentage of total vaccine costs covered, as the price of the new vaccine would raise the total bill substantially.

The Chair, with the agreement of SAGE members, requested the Secretariat to draft a recommendation proposing a review of the Vaccine Independence Initiative and other funding mechanisms to ensure that incentives were created for the introduction of new vaccines.

Referring to the points raised by Dr La Montagne and Dr Martin, the Chair drew attention to the need for development by the CVI Secretariat and collaborators of a comprehensive picture of the financial requirement for polio eradication, reaching under-served populations, and new vaccine introductions, as envisaged in the CVI Strategic Plan. This suggestion was endorsed by a number of SAGE members. Dr Melgaard noted that the '0-10-20' plan of WHO and UNICEF would be a contribution to this big picture of financial needs. Dr Martin said that this financial requirement should be presented as an investment in the economic development of countries.

Among the areas that needed strengthening in many countries to facilitate the introduction of new vaccines, Dr Steinglass identified surveillance systems as being
of the highest priority. It was agreed that there was a need for good diagnostic tools to identify diseases and assess disease burdens.

Dr de Quadros highlighted the role that advocacy had played in the Americas Region in creating fertile ground and political support for new vaccine introduction. The PAHO/Regional Director, who was regularly briefed, raised the subject of immunization when he met Heads of State. A topic connected with immunization was considered each year at a meeting of health ministers. Work had been co-ordinated at political summits and with parliaments on immunization budget lines. A consolidated purchase revolving fund operated for most countries in the Region and ‘First Ladies’ had been involved in immunization issues.

Dr Streefland was supported by several other SAGE members when he said that social and behavioural research and tools could play a major role in helping to build public understanding of and demand for vaccination. Without public support, programmes were not sustainable. The quality of the services greatly affected demand. Dr Broome agreed and stressed the need to understand the political issues and the potential influence of providing vaccination through the public sector on public sector uptake.

SAGE members broadly agreed that major new efforts were required in order to reduce delays in the utilization of new vaccines, and that new approaches were needed. Current delays could be reduced but not eliminated entirely for reasons of capacity and pricing. As a way of closing the gap, Dr Martin proposed examination of a joint public-private strategy that focused on getting new vaccines into selected Band A and B countries as soon as feasible.

Recommendations

In light of the historically observed lag between the development of a new vaccine and its introduction and widespread use, SAGE made the following recommendations to ensure wide and equitable access to the benefits of vaccination, including early access in the poorest countries.

It was agreed that there was a need to strengthen delivery infrastructure in some countries, to reach badly ‘under-served’ population. Such a focused effort might raise new resources and break the impasse that seemed to exist. CVI should promote such an effort, as an ethical cause. The desirability of engaging the new WHO Director General as a supporter of immunization was emphasized by a number of members.

The SAGE recommends that:

- The CVI Secretariat, WHO/GPV, UNICEF, the World Bank and other partners should make their best endeavours to reduce the delay in the adoption of new vaccines and new combinations, inter alia through the following:
  - Preparation of a comprehensive plan for accelerating new vaccine introduction, where appropriate, to complement expansion of coverage, where needed, and polio eradication efforts.
− Encouragement that countries establish a clear and transparent process, based on their national priorities, for decisions on new vaccine introduction, as part of their national immunization planning, and guidance on suitable processes for this, including anticipation of national information needs.

− Collection of information from countries and regions on new vaccine introduction.

− Anticipation of and support from the global level for generating information related to decisions on new vaccine introduction, including: disease burden and cost recognition; demonstration of vaccine efficacy and safety in different geographic locations; vaccine cost-effectiveness and demonstration of the economic benefits of investments in vaccination (as outlined in GPV/C VI/ SAGE 98.WP.14).

− Development of a comprehensive assessment of financing needs and financing options for introduction of new vaccines and for strengthening national programmes, wherever necessary.

− Modification of the mechanisms used in the Vaccine Independence Initiative for assessing a country’s progress towards vaccine self-financing such that they provide incentives for new vaccine introduction.

Recognition that purchase of vaccines from national budgets should not compromise the funding necessary for delivery infrastructure.
6. Immunization and health reform

Presentation summary

The presentation discussed the implications of decentralization on immunization and health reform. Major change is under way in many countries in the way health services are delivered. Concerns have been raised over the effects of health reforms on immunization, with particular reference to the implications of decentralization, the major strategy for the alternative delivery of services. A consultancy (undertaken by BASICS and WHO) studied health reforms in two countries and to draw general lessons from the reform process. The objectives were to review the EPI in Uganda and Zambia in relation to the health reform process, and to develop a reference guide for national immunization programmes during health reforms.

No single model encapsulates health reform, which sometimes involves radical constitutional and structural changes not only in health services but also in other sectors. These reforms do not occur in linear stages; in most cases there are multiple streams of change moving at different rates.

Health reform is an occasion and opportunity for reanalysing immunization priorities and policies. When this happens, due consideration has to be given to financial and operational parameters.

One of the key lessons learnt from the effects of decentralization on family planning programmes is that some functions should not be decentralized.

The lessons learnt should provide opportunities that will enable those concerned with immunization to operate more effectively within a changing environment:

- Keep abreast of technical developments and international initiatives.
- Introduce policy updates and new epidemiological strategies.
- New approaches to procurement may need to be developed, reconciling the new responsibilities for planning and budget allocation at the subnational level with the desire of donors to direct resources into immunization.
- The new structures, processes and resources that are put in place may imply that more suitable programme strategies should be developed.
- Are the necessary staff in place?
- Do health workers have adequate qualifications and skills for providing immunization services?
- Do managers and supervisors of health services at each level have the capacity to function as expected in the plans?
• Make adequate preparation before presenting subnational staff with the "wide horizon" initiatives originating in national and international agendas, and be prepared to build consensus.

• Be aware of the country’s planning cycle and of how much advance notice is required at the national and subnational levels when proposing new or additional activities.

Immunization programmes have well-established indicators for tracking both the quantity and quality of services. Where reforms have emphasized increasing access to care the health system needs to compare uptake with potential demand. EPI's long use of immunization coverage in monitoring performance provides a well-tested example of this type of indicator.

Discussion
Following Dr Melgaard's presentation, discussion focused on the impact of health sector reform on immunization services.

Several participants re-emphasized the need to ensure that key essential functions be maintained at the central level: policy setting, procurement of vaccines and equipment, quality control and international coordination were clearly identified by representatives from the newly independent states, South America, and the United Kingdom. In addition, some functions such as surveillance clearly require close co-ordination between the central and peripheral levels: indeed, PAHO's experience with health sector reform has revealed a deterioration in the quality of polio surveillance indicators.

It was also pointed out that immunization coverage and surveillance indicators need to be maintained as core health outcome indicators throughout the reform process and that GPV should work closely with agencies driving the reforms in order to ensure that these indicators are considered.

The need to identify new health/immunization financing mechanisms was pointed out as one of the main areas needing attention, since it was often intrinsically related to the drive for health sector reforms. The representative of the World Bank announced that the Bank would soon be launching pilot projects in six countries to study in more detail and in close collaboration with technical agencies which new financing mechanisms could be implemented and how they would impact on the sustainability of programmes.

Recommendations
Health reform has implications for immunization programmes in many countries. SAGE discussed the need to ensure that key essential functions of immunization systems be maintained at the central level, such as policy setting, programme management, procurement of vaccine and equipment, quality control and international co-ordination. In addition, surveillance needs close co-ordination between the central and peripheral levels. Immunization coverage and surveillance indicators provide valuable core health sector indicators throughout the Health Sector Reform (HSR) process. GPV should work closely with agencies and governments implementing such reforms to ensure that these indicators are considered.
There are a number of ways in which immunization could be jeopardized by the HSR process. It has been shown that decentralization leads to a deterioration of the quality of polio surveillance indicators. Hence, when services are decentralized, attention should be paid to the preservation of immunization data that could be lost in integrating information systems.

The search for new mechanisms for financing health and immunization often becomes the drive for health sector reforms, and may result in devolving finances to peripheral levels in ways which make them vulnerable to competing demands. SAGE recognizes the importance to immunization programmes of the current move towards health reform in many countries. As countries undertake such reforms, the risk from decentralization of immunization services takes on a special importance. SAGE notes with concern that immunization services may not receive adequate funding from local authorities in cases where there are competing demands for the same resources. SAGE urges countries to consider carefully aspects of immunization programmes that can be decentralized and will strengthen local services, as well as those elements that should be retained at central level.

The SAGE recommends that:

- Certain elements of immunization programmes should remain under central level authorities, especially policy making, programme management, quality control, regulatory activities, surveillance and national monitoring.
- Coverage and surveillance indicators be used to monitor the impact of decentralization and health reform on the delivery of immunization services.
## Functions of immunization services that are responsibilities at national level

<table>
<thead>
<tr>
<th>Function</th>
<th>National level only</th>
<th>National and/or other levels</th>
</tr>
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<tbody>
<tr>
<td>Formulating national policies, standards and guidelines</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Planning international coordination (e.g., for national immunization days)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Planning service delivery strategies</td>
<td></td>
<td>National level co-ordinates with other levels and disseminates news of creative and successful local solutions</td>
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<tr>
<td>Advocacy for allocation of funds from central government; coordinating donor support</td>
<td>Preferable to ensure equitable distribution</td>
<td></td>
</tr>
<tr>
<td>Procurement: preparation of tender documents, monitoring quality of products bought under tender (vaccines, equipment, supplies)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Purchase, customs clearances, storage, stock management, distribution</td>
<td></td>
<td>These functions may be delegated (as in South Africa)</td>
</tr>
<tr>
<td>Forecasting, quantification</td>
<td>Monitor the quantities forecast</td>
<td>With bottom-up forecasting, the national level can aggregate totals from lower levels, but total quantity ordered may be others' responsibility (as in South Africa)</td>
</tr>
<tr>
<td>Monitoring, surveillance and reporting; design of formats for nationwide use</td>
<td>Aggregate data from lower levels; key role for AFP surveillance. Forward data to WHO Regional Office.</td>
<td>Local staff, close to point of service delivery, can act promptly, before data reaches the national level.</td>
</tr>
<tr>
<td>Focal point for research pertaining to immunization</td>
<td>Yes; choice of topics, priority-setting and coordination are needed for best use of resources</td>
<td></td>
</tr>
<tr>
<td>Organizing reviews</td>
<td>Yes</td>
<td>Lower levels participate</td>
</tr>
<tr>
<td>In-service training; updating skills</td>
<td>Skill requirements defined according to policies, standards and guidelines</td>
<td>National level participates in curriculum development; training itself can be delegated and decentralized</td>
</tr>
<tr>
<td>Supervision</td>
<td>(See monitoring and reviews)</td>
<td>May be delegated</td>
</tr>
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</table>
7. The Children’s Vaccine Initiative (CVI) — organizational issues

7.1 The CVI strategic plan and collaboration between the public and private sectors

Presentation summary
Dr Widdus, Coordinator, Children’s Vaccine Initiative, reviewed the four main elements of the CVI Strategic Plan, released early in 1998:

1) Facilitating development of new and improved vaccines
2) Promoting the wide availability of quality vaccines
3) Promoting the introduction and use of needed vaccines
4) Fostering a culture of prevention through advocacy of vaccines

The strategies and activities related to these four key elements laid out in the CVI Strategic Plan could also be viewed as a series of tasks:

- reducing impediments to vaccine research and development
- the physical development of vaccines and simple vaccination methods
- enhancement of vaccine delivery and financing
- advocacy
- enhancing communication and information exchange
- monitoring the vaccine continuum and developing consensus on how best to deal with gaps in desirable activities

Viewing implementation of the CVI Strategic Plan as a series of tasks led to the identification of instances where collaborative action was most crucial on the vaccine development and utilization continuum.

The Proposed CVI Secretariat Plan of Activities and Budget for 1998 (CVI/GEN/98.07) outlined areas where the CVI Secretariat proposed to be active. In particular, the areas of consensus development and advocacy were to be increased in 1998 and beyond. Fostering collaboration between the public and private sectors began at the CVI/Rockefeller Foundation Meeting on Strengthening Collaboration, reported in “The Global Supply of New Vaccines” (CVI/GEN/98.01), and this was to be a major component of activities in 1998 and subsequently.
Dr Widdus requested comments from SAGE on the implementation of the CVI Strategic Plan and the CVI Secretariat Activity Plan. Critical topics for further discussion between the public and private sectors could be identified and would be taken up with industry over the next 12 months. A report would be presented to SAGE on this matter at its next meeting.

Discussion

Dr La Montagne, Chair of the CVI Task Force on Strategic Planning, emphasized the importance the Task Force and its advisors had placed on expanding advocacy. He believed that the message of vaccine benefits had been underplayed, and that the benefits to society should be communicated beyond health policy-makers to the highest levels of government.

Dr de Quadros noted that a range of activities conducted by the Pan American Health Organization had contributed to the success of polio eradication, immunization in general, and the introduction of new vaccines. The activities included the provision of regular updates to Heads of State (when the Regional Director visited countries) and to Ministers of Health at PAHO Regional Committee meetings. The assumption of national responsibility (e.g., for schedules and budget lines) was encouraged, inter alia by the involvement of ‘First Ladies’ and placing immunization on the agenda of regional summit meetings. Regional solidarity and peer encouragement were promoted by collective actions, as exemplified by the PAHO Vaccine Procurement Revolving Fund, which also provided an opportunity for discussion with vaccine companies on future needs.

Dr Streefland emphasized the need, identified in the CVI Strategic Plan, to consider the impact of the quality of immunization services on the social demand for vaccination. The social sciences had made and could continue to make contributions to a better understanding of this aspect of demand and could contribute to the design and organization of vaccine delivery strategies.

To better manage infectious disease control, Dr Msambishacka identified the need for easy-to-use tools to facilitate the diagnosis of infectious diseases in rural health facilities.

A number of participants stressed the need for advocacy directed towards organizations capable of providing resources to support programmes in countries in the greatest financial need, as well as towards the governments of these countries.

Dr Martin commented on the useful role a body such as the CVI could play in providing long-term advocacy to overcome the financial resource constraint that operational entities like GPV and certain national immunization programmes were facing. Because considerably greater resources would be needed in the future, radical new collaborative measures would have to be devised in order to provide the poorest countries (Bands A and B) with the benefits of vaccines in a timely and equitable fashion. The case for this was strong from both the health and economic standpoints.

Recommendations

The SAGE noted and endorsed the proposed expansion of activities on advocacy within the proposed CVI Secretariat Plan of Activities for 1998 (CVI/GEN/98.07)
as part of implementing the overall CVI Strategic Plan. It further recommended that the CVI Secretariat identify and address with industry, critical issues for public-private dialogue, at all stages of the vaccine development and utilization continuum.

7.2 International Vaccine Institute

Presentation summary
Dr Mahoney, Chief Development and Administrative Officer, International Vaccine Institute (IVI), presented a brief update on the progress of this body.

In the last year, a number of additional countries had signed the agreement for the creation of the Institute, bringing the total to over thirty. As of June 1998, legal responsibility for IVI had been transferred from UNDP to the IVI Board of Trustees; in October 1997 a headquarters agreement was near completion with the Government of the Republic of Korea; plans for the IVI/headquarters building were completed and construction was expected to take place within a year; international and Korean IVI support councils were established and three candidates for the post of Director had been short-listed.

Important clarifications of the IVI constitution were made by the Board of Trustees, indicating that the Institute would not produce vaccines for commercial sale and that it would respect and promote the protection of intellectual property.

The first activities of the Institute were already taking place, on economic and policy analysis for vaccine introduction and on the burden of Haemophilus influenzae type b disease and other causes of meningitis (e.g., S. pneumoniae and N. meningitidis) in selected countries of South-East Asia and the Western Pacific. Both of these were being conducted with input from CVI. Close collaboration with WHO and CVI was contemplated, two members of the Board of Trustees being nominated by WHO and the Executive Secretary of CVI serving ex officio.

Recommendations
SAGE noted with satisfaction the excellent progress being made in the establishment and scientific activities of the International Vaccine Institute, Seoul, Republic of Korea. It welcomed the proposed collaboration, commended the research plan developed by the Board of Trustees, and requested to be informed at future meetings of the Institute's progress.

7.3 The future role of the Children's Vaccine Initiative

Presentation summary
Dr Lee, Executive Secretary of CVI and Director of WHO's Global Programme on Vaccines and Immunization, outlined recent events. Following publication of the CVI Strategic Plan a meeting was convened in March 1998 in Washington DC by the President of the World Bank, Mr James Wolfenson, at which questions were raised on the prospects for working more collectively in immunization.

Dr Lee remarked that during the last three years GPV’s resources had grown, predominantly for polio eradication, and integration across units had improved. CVI had established a useful role as a think-tank convener and advocate for vaccination.
There was less overlap and duplication. In order to do more, three possibilities existed: to continue as before; to redesign CVI on a basis of informal collaboration; or to create a new organization. Dr Lee's personal preference was for a redesigned CVI; this might be housed outside WHO and might be headed by a person who did not come from WHO or another cosponsor. The timing was auspicious for discussions on how to strengthen collaboration. Consultations would go on over the next few months and further discussions would be held around the time of the CVI Consultative Group Meeting on 9-10 November 1998.

Discussion
A number of SAGE members expressed appreciation of the work of Dr Lee on harmonizing GPV and CVI activities and roles. Members also expressed thanks for being invited to comment and appreciated the openness of the proposed consultation process. In particular the Chair noted the useful role of the CVI Secretariat in the areas of cost-effectiveness assessment, new vaccine introduction and advocacy. With the agreement of other SAGE members, the Chair emphasized the need to fully involve industry in the discussion of future CVI structures and activities so as to achieve its full integration into the partnership.

Dr Broome noted that it was desirable to appraise with care the benefits accruing from close cooperation between the CVI Secretariat and GPV so that they would not be inadvertently lost. Dr Jaffar commented that a clearer definition of roles would lead to a greater appreciation of CVI's work.

Recommendations
SAGE endorsed the proposals for a wide consultation to take place on the options for evolution of the role and activities of the CVI and the CVI Secretariat. It emphasized the crucial importance for this process to engage industry and to consider the need for increased advocacy, in addition to those functions that CVI already undertook. SAGE also expressed the wish to continue its advisory role for CVI, as well as for GPV.
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Ms Fabienne Adam, Administrative Assistant, GPV
Ms Paula Bevin, Secretary, GPV
Ms Alison Delo, Secretary, GPV

* Unable to attend.
Annex 2: Annotated agenda

Tuesday, 9 June

09.00-09.30 Opening of the meeting
   Introduction of the Chair and the Members
   Overview by Dr J.W. Lee, Director, GPV

09.30-10.15 Reports on progress in implementing 1997 SAGE recommendations.
   Presentations from EPI, VRD, VSQ. (45 minutes)

10.15-10.30 Discussion on foregoing reports.
   (15 minutes + 30 minutes after the coffee break)

10.30-11.00 Coffee break

11.00-11.30 Discussion on foregoing reports. (30 minutes)

11.30-11.45 Immunization and health systems: which way forward for EPI? Dr B. Melgaard. (15 minutes)

11.45-12.20 Discussion and recommendations. (35 minutes)

12.20-12.30 What is the quality of EPI data? Mr Anthony Burton (10 minutes)

12.30-14.00 Lunch

14.00-14.15 What are the critical issues for achieving the polio eradication goal for the year 2000? Dr H. Hull (15 minutes)

14.15-14.30 Current WHO studies in the development of new methods for quality control of oral poliomyelitis vaccine and polio diagnosis. Dr Peter Wright (15 minutes)

14.30-14.45 What research is needed for polio eradication and the post-eradication strategies? Dr Stephen Cochi (15 minutes)
14.45-15.15 Discussion and recommendations (30 minutes)

15.15-15.30 Phasing measles control and eliminating activities in the context of the polio eradication initiative. Dr J.-M. Olivé (15 minutes)

15.30-16.00 Coffee break

16.00-16.15 Can modelling of measles epidemiology help to define optimal immunization strategies? Dr Nigel Gay (15 minutes)

16.15-16.45 Discussion and recommendations (30 minutes)

16.45-17.00 Can Td replace TT globally? Dr F. Gasse (15 minutes)

17.00-17.15 Increasing incidence of pertussis in adults as a result of the limited duration of vaccine-induced immunity: what can we do about it? Dr Marc LaForce (15 minutes)

17.15-17.45 Discussion and recommendations (30 minutes)

18.00 Reception on the terrace of the WHO cafetaria

Wednesday, 10 June

09.00-10.00 Review and adoption of previous day’s recommendations

10.00-10.15 When should we use typhoid vaccines?
Dr B. Ivanoff and Dr D. Heymann (15 minutes)

10.15-10.30 Prefilled monodose injection devices: a safety standard for new vaccines? Dr J. Lloyd and Dr T. Aguado (15 minutes)

10.30-11.00 Coffee break

11.00-11.30 Discussion and recommendations (30 minutes)

11.30-11.45 A broad strategy for the safety of all injections. Mr M. Zaffran (15 minutes)

11.45-12.00 To what extent are vaccine adverse events a deterrent to immunization? Dr C.J. Clements (15 minutes)

12.00-12.15 How can GPV assess the scientific basis for alleged adverse effects of vaccination? Dr P.-H. Lambert (15 minutes)

12.15 -12.45 Discussion and recommendations (30 minutes)
12.45-14.00  Lunch

14.00-14.15  Procurement: how can we strengthen and implement a changed role for WHO in vaccine procurement? Mr P. Evans (15 minutes)

14.15-14.30  Financing: what are our options? Dr H. J. Choi (15 minutes)

14.30-15.00  Discussion and recommendations (30 minutes)

15.00-15.15  Demand forecasting: what are the models we can use to forecast aggregate demand for vaccine manufacturing? Dr M. Kawano (15 minutes)

15.15-15.30  New vaccines: with the increase of developing country research groups and manufacturers, how can we be sure that WHO quality standards are reached? Dr J. Milstien (15 minutes)

15.30-16.00  Coffee break

16.00-16.30  Discussion and recommendations (30 minutes)

Thursday, 11 June

What actions will accelerate the introduction of new vaccines?

09.00-09.20  Accelerating the intro of ew vaccines. Brief presentations on:

- Lessons learnt from H B, Hib, yellow fever and other ‘new’ vaccines, including combinations
- Models for considering new vaccine introduction
- How can quantitative assessments help policy choices?
- In what countries should we consider ‘new’ vaccine introduction?

09.20-10.30  Discussion: what actions will accelerate ‘new’ vaccine introduction most effectively? (70 minutes)

10.30-10.50  Coffee break

10.50-11.45  Continuation of above discussion (55 minutes)

11.45-12.45  What actions are most needed to implement the CVI Strategic Plan? (60 minutes)
12.45-14.00  Lunch

Public-private sector collaboration

14.00-15.00  In what areas is public-private sector collaboration most needed from the public sector perspective — research, orphan vaccines, industrial development, licensing, policy formulation, marketing, tendering, pricing or advocacy? (60 minutes)

15.00-15.20  Coffee break

15.20-16.20  Review and adoption of previous day’s recommendations (60 minutes)

16.20-17.00  Review of current day’s recommendations and summing-up (40 minutes)

17.00  Closure of meeting
Annex 3:
List of documents

GPV-CVI/SAGE.98/01 Annotated agenda
GPV-CVI/SAGE.98/02 List of participants
GPV-CVI/SAGE.98/03 List of documents
GPV-CVI/SAGE.98/04 Documents relevant to agenda items

Working papers

GPV-CVI/SAGE.98 Reports on progress in implementing the 1997 SAGE recommendations: EPI, VRD, VSQ
GPV-CVI/SAGE.98/WP.02 Current WHO studies on the development of new methods for quality control of oral poliomyelitis vaccine and polio diagnosis
GPV-CVI/SAGE.98/WP.03 Polio eradication and measles control/elimination: Paving the way towards a comprehensive EPI strategy
GPV-CVI/SAGE.98/WP.04 Replacing tetanus toxoid (TT) and diphtheria-tetanus toxoid (DT) with tetanus-diphtheria toxoid (Td) (draft)
GPV-CVI/SAGE.98/WP.05 When should we use typhoid fever vaccines?
GPV-CVI/SAGE.98/WP.06 Prefilled monodose injection devices: a safety standard for new vaccines or a revolution in the delivery of immunization?
GPV-CVI/SAGE.98/WP.07 A broad strategy to promote the safety of all injections
GPV-CVI/SAGE.98/WP.08 To what extent are vaccine adverse events a deterrent to immunization?
GPV-CVI/SAGE.98/WP.09 Procurement of vaccines: roles and responsibility
GPV-CVI/SAGE.98/WP.10 Financing of new vaccines: what are our options?
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<th>Document Reference</th>
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<tr>
<td>GPV-CVI/SAGE.98/WP.11</td>
<td>Demand forecasting: what are the models we can use to forecast aggregate demand for vaccine manufacturing?</td>
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<td>New vaccines: with the increase of developing country research groups and manufacturers, how can we be sure that WHO quality standards are reached?</td>
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<tr>
<td>GPV-CVI/SAGE.98/WP.13</td>
<td>Immunization and health reform: the implications of decentralization</td>
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<tr>
<td>GPV-CVI/SAGE.98/WP.14</td>
<td>What actions will accelerate the introduction of new vaccines?</td>
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**Background documents for presentations**

| Presentation by Dr Harry Hull | Polio eradication — Status report 1998 and issues for achieving the year 2000 target |
| Presentation by Dr Stephen L. Cochi | Draft conclusions of the working group of the meeting on the scientific basis for stopping immunization against poliomyelitis |
| Presentation by Professor F. Marc LaForce | Increasing incidence of pertussis in adults: what are the issues and what could be done about it? |

**Reports and programme documents**

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<tr>
<td>WHO/GPV/97.05</td>
<td>Report of the meeting of the Scientific Advisory Group of Experts (SAGE) 11-13 June 1997</td>
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<tr>
<td>CVI/GEN/97.04</td>
<td>The CVI Strategic Plan: “Managing opportunity and change: a vision of vaccination for the 21st century”</td>
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<tr>
<td>CVI/GEN/98.01</td>
<td>Children’s Vaccine Initiative/Rockefeller Foundation, Conference on the Global Supply of New Vaccines, Bellagio, February 1997</td>
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<tr>
<td>CVI/GEN/98.06</td>
<td>Progress Report of the CVI Secretariat</td>
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<tr>
<td>CVI/GEN/98.07</td>
<td>Proposed CVI Secretariat Plan of Activities and Budget for 1998</td>
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<tr>
<td>WHO/GPV/98.01</td>
<td>Programme Report 1997</td>
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<tr>
<td>WHO/GPV/98.03</td>
<td>Brochure of the Global Programme for Vaccines and Immunization, 1998</td>
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Annex 4:
Terms of reference for the Joint CVI and GPV Scientific Advisory Group of Experts (SAGE)

Functions

The joint CVI and GPV Scientific Advisory Group of Experts (SAGE) shall have the following functions:

To review, from a scientific and technical standpoint, the content, scope, policies and operations of both CVI and GPV.

To provide for the Director of GPV, the Executive Secretary of CVI, and all organizations collaborating with CVI and GPV, a continuous and independent evaluation of the scientific and technical aspects of the activities.

To advise on priorities for action by GPV or other CVI collaborators.

To review the CVI strategic plan and the plan of action of GPV prepared by the CVI Secretariat and WHO respectively, and to make comments and give advice to the Meeting of Interested Parties through the Executive Secretary, CVI and the Director, GPV.

Composition

SAGE shall have no more than 16 members, who shall serve in their personal capacities to represent the broad range of disciplines required for both CVI and GPV activities.

Members of SAGE, including the Chairperson, shall be proposed by the Executive Secretary, CVI and the Director, GPV, on the basis of scientific and technical criteria in consultation with the Meeting of Interested Parties. The need to ensure proper representation of the different WHO Regions and of developing countries shall be taken into consideration.

Members of SAGE shall not be investigators in studies funded by CVI or GPV.

Members of SAGE, including the Chairperson, shall be appointed to serve for a period of three years, and shall be eligible for immediate reappointment only once.

Operation

SAGE shall meet not more than once a year.

WHO and the CVI Secretariat shall provide secretariat support for SAGE.
SAGE shall elect a Vice-Chairperson and a Rapporteur for each meeting from among its members.

SAGE may establish subcommittees to facilitate the performance of its functions. Subject to subsequent decisions of SAGE concerning subcommittees, three subcommittees shall be established initially to provide advisory services related to (1) policy and strategic planning, (2) research and development and (3) vaccine production, quality assurance and immunization delivery, including surveillance and disease control.

SAGE shall prepare an annual report on the basis of its review of the scientific and technical aspects of CVI and GPV operations. This report, containing its findings and recommendations, shall be submitted to the respective Meetings of Interested Parties through the Executive Secretary, CVI and the Director, GPV.

The Meeting of Interested Parties for the Children's Vaccine Initiative

This meeting is the twin of a similar Meeting of Interested Parties for the Global Programme for Vaccines and Immunization. Logistics permitting, the two meetings will be held back-to-back.

The Meeting of Interested Parties provides a forum for dialogue on, and coordination of, activities for the Children's Vaccine Initiative with donor agencies, industry, recipient countries, nongovernmental organizations and other interested parties. SAGE and the Meeting of Interested Parties for the Children's Vaccine Initiative shall be coordinated: one or more representatives of each meeting shall attend the other meeting and the reports of each shall be exchanged.