

# Report of the Strategic Advisory Group of Experts (SAGE)

Geneva, 14-15 June 2001



**DEPARTMENT OF VACCINES  
AND BIOLOGICALS**



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# Abbreviations

AD	auto-disable (syringe)
ADC	accelerated disease control
AFP	acute flaccid paralysis
AFRO	WHO Regional Office for Africa
AVI	accelerated vaccine introduction (priority project)
BCG	bacillus Calmette-Guérin (vaccine)
BSE	bovine spongiform encephalopathy
CDC	Centers for Disease Control and Prevention (USA)
CJD	Creutzfeldt-Jakob disease
DFID	Department for International Development (UK)
DTP	diphtheria–tetanus–pertussis (vaccine)
ECBS	Expert Committee on Biological Standardization (WHO)
EMRO	WHO Regional Office for the Eastern Mediterranean
EPI	Expanded Programme on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
HBV	hepatitis B virus
HepB	hepatitis B (vaccine)
Hib	<i>Haemophilus influenzae</i> type B
ICC	interagency coordinating committee
ICG	International Coordinating Group
IEC	information, education and communication (materials)
IMCI	integrated management of childhood illnesses
IPV	inactivated polio vaccine
IUATLD	International Union against Tuberculosis and Lung Disease
IVR	Initiative for Vaccine Research
MMF	macrophagic myofascitis
MNT	maternal and neonatal tetanus
MVP	Meningitis Vaccine Programme

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NID	national immunization day
NRA	national regulatory authority
NT	neonatal tetanus
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
SAGE	Strategic Advisory Group of Experts
TCG	Global Technical Consultative Group for Poliomyelitis Eradication
TSE	transmissible spongiform encephalopathy
TT	tetanus toxoid
UNF	United Nations Foundation
UNFPA	United Nations Population Fund
UNGASS	Special Session of the United Nations General Assembly
UNICEF	United Nations Children's Fund
V&B	Department of Vaccines and Biologicals (WHO)
VVM	vaccine vial monitor
WHA	World Health Assembly

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# Executive summary

## Introduction

The Strategic Advisory Group of Experts (SAGE), established by the Director-General of WHO in 1999 to provide guidance on vaccines and biologicals, held its third annual meeting on 14 and 15 June 2001 in Geneva, Switzerland.

Progress was reviewed in relation to various objectives and targets set by the Department of Vaccines and Biologicals (V&B). In his opening address, Dr Yasuhiro Suzuki, Executive Director of WHO's Health Technology and Pharmaceuticals cluster, pointed out that guidance from SAGE would be critical as WHO began reviewing and revising the strategic plan covering vaccines, immunization and biologicals for 2002–2005. The Director of V&B, Dr Bjørn Melgaard, outlined the dramatic changes that had transformed the global immunization scene in the preceding year and the issues that SAGE would address. Important among these were:

- how the Global Alliance for Vaccines and Immunization (GAVI) would come to terms with a possible new mandate as an alliance for the whole global immunization agenda;
- how to close the polio funding gap;
- how to align the objectives of GAVI with polio eradication and other disease control objectives;
- how to strive towards equity in immunization by achieving access and high coverage throughout the world;
- how the infusion of huge additional resources was leading to the introduction of new tools and technologies and creating a need for more partnership in vaccine research. Professor Sir Gustav Nossal, SAGE Chair, referred to the hope and dynamism that GAVI had created and to the roles of WHO, SAGE, GAVI and the Vaccine Fund.<sup>1</sup> He remarked that whereas GAVI was financed for five years, WHO would exist until the world was healthy enough not to need it. Furthermore, whereas the Vaccine Fund was narrowly focused, GAVI had to have a broad vision. Sir Gustav considered that the objectives of GAVI and V&B should be identical.

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<sup>1</sup> Formerly the Global Fund for Children's Vaccines.

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## The deliberations

On the first day there were three parallel sessions, covering innovation, the strengthening of immunization systems, and accelerated disease control. WHO's work, including projects conducted with UNICEF and other partners, was presented and questions were put to SAGE. For each topic of discussion a list of endorsements and recommendations was agreed by a subgroup. On the second day, summaries of the previous day's deliberations were presented to a plenary session and recommendations based on them were adopted. Additional matters, including GAVI, were discussed, and recommendations concerning them were also made. A summary of the main topics of discussion is given below, followed by the recommendations.

## Main topics of discussion

### *Innovation*

The considerable achievements of V&B in the area of innovation were noted. These included internal advocacy in many countries for the introduction of new vaccines. Some of the issues discussed are listed below. Fuller summaries are given in Section 2.

- **Disease burden activities:** the feasibility of estimating the *Haemophilus influenzae* type b (Hib) pneumonia burden in Asia using vaccine intervention trials.
- **Vaccine introduction:** the collection of information in order to develop a position on infantile hepatitis B (HepB) immunization for presentation to SAGE.
- **Combination vaccines:** a paper presented to SAGE on demand and supply issues was an excellent example of WHO's role in making critical information available to countries and decision-makers on the introduction of new vaccines.
- **Initiative for Vaccine Research (IVR):** a discussion of IVR's role in integrating WHO's vaccine development activities.
- **Meningococcal A/C vaccine:** exploring public-private partnerships, as reflected in the V&B initiative relating to the meningococcal vaccine project for Africa.
- **Pneumococcal conjugate vaccines:** the importance of additional efficacy studies in developing countries to determine the impact of vaccine on pneumonia and mortality.
- **Rotavirus:** the need to develop rotavirus vaccines and test new candidates in both industrialized and developing countries.

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### ***Immunization systems***

Dr Mohammed Suleiman Ali Jaffer congratulated V&B on the new format of SAGE. The following were among the issues discussed. (See also Section 3.)

- **Strengthening immunization systems.** There were still problems in many countries and innovative solutions and approaches were needed in order to improve coverage, attain better outreach services, decrease dropout rates, and involve communities in immunization. It was necessary to apply lessons learnt from the polio programme.
- **Coverage.** Collaboration between UNICEF and WHO in order to obtain improved estimates of immunization coverage.
- **Immunization safety.** Use of auto-disable (AD) syringes by all countries by 2003 and the provision of technical assistance to countries on environmentally friendly solutions to waste disposal problems.
- **BCG vaccine.** Continued use of BCG immunization in routine immunization services and the need to collaborate with industry in order to ensure an adequate supply of high-quality vaccine.
- **Thiomersal.** Theoretical concerns about the presence of thiomersal in some vaccines and the need to examine options to eliminate or reduce its use in monodose vials and to study alternative preservatives.
- *Transmissible spongiform encephalopathies (TSEs)/bovine spongiform encephalopathy (BSE) and vaccines. **The availability of International Reference Materials for diagnostic purposes, and the need to secure the safety of the materials used for vaccine production.***

### ***Accelerated disease control***

- **Polio eradication.** SAGE noted the tremendous progress that had been made in polio eradication and the discussions of the Global Technical Consultative Group for Poliomyelitis Eradication (TCG). Angola and other countries undergoing complex emergencies were of particular concern, and surveillance would be particularly difficult in these countries. Laboratory support would be important, especially with respect to information on circulating strains. There was a need to build on the established immunization infrastructure for polio eradication. The subgroup noted that the policy options for stopping immunization were limited, that countries should not make premature decisions on this matter, and that WHO and UNICEF should work closely with manufacturers on it. (See Section 4.)
- **Measles elimination and control.** SAGE endorsed the idea of providing a second opportunity to give measles vaccine and noted that the goals of measles control strategy had to be carefully stated because the economic implications of a time-limited goal were different from those of one that continued into the future. It was important to link measles control strategies, including surveillance, with the polio eradication initiative.
- **Elimination of maternal and neonatal tetanus.** SAGE endorsed the WHO/UNICEF strategic plan for maternal and neonatal tetanus (MNT) elimination by 2005 and noted the need for strong advocacy for the MNT initiative.

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- **Vitamin A supplementation.** SAGE agreed that the particular advantages of administering vitamin A through immunization contacts should be recognized. This practice enabled deep outreach into communities. It was also desirable to encourage vitamin A delivery through programmes other than EPI and to define areas of responsibility for implementation and monitoring.

SAGE endorsed the recommendations put forward by the subgroup.

### ***Plenary session***

The subgroup Chairs presented summaries of the previous day's proceedings and agreement was reached on recommendations. Further topics were presented and recommendations were endorsed in connection with these also. (See section 5.) Among the issues discussed during this session were the following.

- **The Global Alliance for Vaccines and Immunization.** SAGE recognized the importance of GAVI, which had been evident in all sessions. A major part of the discussion centred on the sustainability of financing. Also considered was the question of how GAVI funds might meet the unfinished measles and polio agenda, i.e. beyond the present limitations. SAGE agreed that WHO should continue to play an active role in the development of GAVI policy and in the implementation of objectives.
- **GAVI and accelerated disease control.** There was approval for current efforts to align GAVI with accelerated disease control initiatives, including polio eradication, measles control, MNT elimination and vitamin A supplementation. It was important that GAVI should not lose focus while using the guiding principles of equity and access.
- **Vaccine supply.** The implications of the divergence of vaccine products used in developing and industrialized countries was discussed. Concern was expressed about potential threats to vaccine security and the predictability of demand. SAGE agreed that steps should be taken to keep key manufacturers in the market, communicate strong positions on product selection, and attend to quality.
- **Yellow fever.** A resurgence of the disease had occurred and the vaccine supply was inadequate. Furthermore, immunization coverage was low, surveillance was poor and adverse events were occurring. SAGE recommended measures for improving the vaccine supply, immunization coverage, outbreak response and vaccine quality.
- **Report of the Global Advisory Committee on Vaccine Safety (GACVS).** This Committee had been unable to support the conclusions of a survey in Guinea-Bissau which had found increased mortality associated with diphtheria–tetanus–pertussis (DTP) vaccine. Discussion centred on faults in the Guinea-Bissau study design, which would be rectified in new studies, and on the importance of understanding public concern. SAGE endorsed a proposal for the development by V&B of a communications strategy that would take account of public concern about adverse effects of vaccines.

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## Recommendations

### *Innovation session*

#### Accelerated vaccine introduction project

1. Sage endorses V&B priorities and activities intended to accelerate the introduction and evaluate the impact of new and underutilized vaccines. Three major components of this effort are:
  - support for countries in connection with the introduction of new vaccines and coordination of GAVI-related activities by enhancing regional expertise and capacity, developing an expanded pool of consultants for assistance to countries, and preparing guidelines and materials for advocacy, information, education and communication;
  - development and use of disease burden tools in order to obtain data for advocacy and prioritization of new vaccines at the country level;
  - assistance in the coordination of GAVI agendas for Hib, pneumococcal and meningococcal vaccines.
2. SAGE recognizes the efforts being made to define disease burden and the cost-effectiveness of vaccines, including the development of tools for local advocacy and surveillance protocols. Recent efforts have focused on HepB and Hib vaccines, and in 2002 attention will turn to rotavirus and pneumococcal disease. Questions that remain about the burden of vaccine-preventable Hib pneumonia can only be answered through well-planned, controlled vaccine intervention trials. SAGE recommends that WHO evaluate the feasibility of estimating the Hib pneumonia burden in Asia on the basis of such trials. The technical design of studies of this kind must ensure that they have adequate power to measure the burden of disease so that decisions on vaccine introduction can be taken.
3. Under existing EPI policy, routine infant HepB immunization is recommended as the most effective strategy in countries with chronic hepatitis B virus (HBV) infection in 2% or more of the population. In countries with a lower prevalence, the immunization of adolescents may be considered as an addition or alternative to infant immunization. SAGE recognizes that new information is available that may support a recommendation for routine infant vaccination as the preferred strategy in all countries. SAGE recommends that WHO collect the information necessary for developing a position on universal infant immunization, to be considered by SAGE in 2002.
4. Combination vaccines have become a part of many national immunization services. Their use has a significant impact on supply and programme flexibility. SAGE makes the following recommendations.
  - WHO should review the possible combination vaccines and the implications on supply, regulation, presentation and price, and assist countries to assess the appropriateness of each combination for their national immunization services. Consideration of the role of production in developing countries and of the implications of obtaining supplies from a single source should be part of this process.

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- WHO, in collaboration with partners, especially vaccine manufacturers, should provide accurate forecasts of demand for the various combination vaccines (determined by national immunization service managers to be beneficial, programmatically feasible, financially sustainable and worth introducing if funding is available). This information should be given to United Nations agency purchasers and directly to manufacturers well in advance so as to avoid a crisis in global supply. WHO and UNICEF should coordinate their activities and speak with one voice to the manufacturing community, and should make joint recommendations and requests. WHO should also continue to collect information on factors influencing the supply of different components in order to assist countries in decision-making.
  - WHO should place priority on continuing action to monitor progress in the licensing of vaccines in industrialized countries for use in developing countries.
5. SAGE endorses the strategy of the meningitis vaccine project and commends the broad alliance that has made it possible. SAGE commends the early involvement of African countries in the project and emphasizes the value of public-private partnership in accelerating the development and introduction of vaccines specifically targeted at developing countries. This may serve as a model for other vaccine development projects.
  6. SAGE applauds the current initiative on bacterial meningitis surveillance undertaken by the WHO Regional Office for Africa (AFRO), and recommends expansion to all countries in the region and consideration of similar approaches for other regions, e.g. the WHO Regional Office for the Eastern Mediterranean (EMRO). This should include the collection of epidemiological data, the establishment of regional laboratory capacity for typing/subtyping bacterial meningitis pathogens (specifically, meningococcus and pneumococcus), and the use of international reference laboratories for the additional characterization of appropriate strains.
  7. SAGE recognizes the promise of pneumococcal conjugate vaccines as evidenced by the efficacy of the 7-valent vaccine in industrialized countries. V&B is urged to continue playing a leading role in the evaluation of pneumococcal conjugate vaccines in developing countries. This work includes efficacy studies providing critical data concerning the impact on pneumonia and mortality, correlates of protection, and possible replacement disease. In a parallel effort, V&B should work with partners on the proof of concept of candidate common protein vaccines.
  8. SAGE underlines the importance of the early testing of new candidate rotavirus vaccines in industrialized and developing countries simultaneously so as to accelerate their introduction.

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### **Initiative for Vaccine Research**

1. SAGE emphasizes the pivotal position of IVR vis-à-vis developing countries, which makes it unique in comparison to other organizations involved in vaccine research and development. This special role includes a continuing obligation to focus on orphan/under-addressed vaccines and to promote approaches that may be particularly appropriate for use in developing countries. Furthermore, IVR can have a broader focus and a longer time perspective than the GAVI Research and Development Task Force.
2. SAGE endorses the IVR concept and, in particular, the increased emphasis on exploring public-private partnerships as a means of accelerating the development of vaccines, as in the meningitis vaccine project for Africa.

### ***Immunization systems session***

#### **Strengthening immunization services**

1. SAGE draws attention to the need to find appropriate and innovative solutions for improving immunization coverage, with special reference to outreach activities and dropout rates.
2. SAGE emphasizes the need to capitalize on the polio eradication experience for strengthening immunization services.

#### **Coverage**

SAGE notes with appreciation the methods that have been developed and the results obtained in the WHO/UNICEF review.

1. SAGE recommends that further development be encouraged of these and other appropriate measures for determining immunization coverage at the local, national, regional and global levels.
2. Critical points raised during the discussion at the SAGE meeting of this programme have been recorded.

#### **Steering Committee on Immunization Safety**

1. SAGE endorses the recommendations made by the Steering Committee on Immunization Safety at its second meeting, held on 26 and 27 October 2000.
2. SAGE recommends that, in order to reach the target that all countries use AD syringes by 2003, appropriate support be given to countries for the transition to these syringes, with particular focus on sterilizables, and that wider endorsement of the joint statement by WHO, UNICEF and UNFPA be attained.
3. SAGE recommends that waste disposal be given sufficient attention and encourages WHO to work with UNICEF on this matter, with special reference to environmentally friendly options.

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## **BCG vaccine**

SAGE strongly endorses the continued routine use of BCG vaccine as a means of minimizing the harmful effects of tuberculosis infection in the first year of life. SAGE recommends that the vaccine be used until an alternative improved anti-tuberculosis vaccine becomes available. It is likely that this will not be achieved for at least 10 years. In the meantime, national immunization services are encouraged to maintain the highest possible coverage of infants.

1. SAGE endorses the need to maintain an adequate supply of high-quality BCG vaccine. This will entail working closely with industrial partners.
2. As more industrialized countries can be expected to consider shifting from routine to selective use of BCG during the next decade, the recommendations of the International Union against Tuberculosis and Lung Disease (IUATLD) are supported as the appropriate guidelines for countries thinking of discontinuing BCG vaccination.
3. SAGE reinforces WHO's recommendation that no booster dose of BCG be given, as there is no evidence for the efficacy of such a dose.

## **Thiomersal and vaccines**

SAGE considers that the benefits of vaccination with thiomersal-containing vaccines far outweigh the risks, if any, of exposure to thiomersal. However, as the consumption of mercury of any sort is considered less than optimal, it is considered wise to promote efforts to reduce the thiomersal content of vaccines whenever feasible. WHO is also encouraged to undertake activities related to assessing the risk associated with thiomersal-containing vaccines and the safety of using vaccines with reduced amounts of thiomersal. SAGE makes the following recommendations.

1. WHO should examine the options for redefining its criteria for maximum safe intake levels of mercury in the context of thiomersal in vaccines.
2. V&B should work with manufacturers with a view to reducing the amount of thiomersal in monodose containers and in monodose prefilled devices.
3. V&B should determine whether vaccines with reduced amounts of thiomersal, or vaccines containing alternative preservatives, can be used safely in the context of the current multidose vial policy.
4. V&B should review programmatic strategies relating to the use of multidose presentations in high-use settings.
5. V&B should convene a meeting with national regulatory authorities (NRAs) in order to develop criteria for reviewing products with changes in preservative content.

## **BSE/TSEs and vaccines**

1. SAGE endorses the activities of WHO in the area of TSE/BSE vaccines.
2. The planned review on medicinal and other products in relation to human and animal TSEs should focus, in particular, on the use of bovine serum, other ruminant-derived materials, and human plasma-derived products in vaccine production. WHO is encouraged to keep this issue under constant review.

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3. SAGE recommends that adequate resources be made available in order that the development and evaluation of international reference materials for the diagnosis and study of human TSEs be completed as soon as possible.

### ***Accelerated disease control***

#### **Polio eradication initiative**

SAGE notes the tremendous progress made towards the eradication of poliomyelitis, demonstrated by the reduction in the number of confirmed cases by 60% between 1999 and 2000. SAGE endorses the recommendations of TCG concerning the continued acceleration of polio eradication activities, recognizing that especially intensified efforts are required in the six countries currently at highest risk of ongoing transmission after the end of 2002: Angola, the Democratic Republic of Congo, Egypt, Ethiopia, Nigeria, and Pakistan.

1. Immunization against polio should ultimately be stopped in order to derive the greatest possible benefit from the eradication of the disease. SAGE endorses the programme of work developed by the polio research steering committee under the direction of TCG and reaffirms that adequate resources must be made available so that it can be rapidly carried out.
2. The urgent need to mobilize resources in order to close the estimated funding gap of US\$ 400 million for activities between 2002 and 2005 requires extraordinary efforts on the part of WHO at the highest level. Closing the funding gap must be an institutional priority, not just a priority of V&B. To this end SAGE suggests the following approaches.
  - Although national interagency coordinating committees (ICCs) must address the entire spectrum of immunization, in the countries where the disease is still endemic the ICCs should give priority to closing the polio funding gaps.
  - WHO should host a special donor event in late 2001/early 2002 to launch the revised resource requirements for the period until 2005.
  - GAVI should encourage the remaining countries where polio is endemic to use the Vaccine Fund to cover those elements of the national polio funding gaps which represent costs of the routine immunization infrastructure.
3. SAGE recognizes that the immediate priority in areas affected by conflict must be to improve the quality of activities in those areas that are accessible. WHO and partner agencies should give increased attention to overcoming the problems occurring in areas affected by conflict. In particular:
  - political advocacy should be directed at increasing access to currently unreached children;
  - it is necessary to recognize that, compared with stable countries, these areas require increased per capita funding for the effective implementation of strategy;
  - contingency plans should be developed to cover the possibility that access to children may be further compromised by new conflicts.

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4. With the recent expansion of V&B's polio eradication infrastructure, particularly as regards human resources, SAGE believes that the management and administration of these resources may need to be strengthened in some countries. SAGE recommends that WHO regularly review the performance of its management and administrative support for polio eradication and take corrective action as needed.
  5. Because of the importance of the broad engagement of the scientific community in the polio end-game, WHO should review the mechanisms that the influenza network has put in place for rapidly sharing new virological data as they become available.
  6. In the course of revising the resource requirements for polio eradication in the period up to 2005, WHO should ensure that the figures include the funding needed for completion of the research agenda for guiding decisions on the cessation of immunization.
  7. Vaccine-derived polioviruses that have circulated in the population should be subjected to laboratory containment procedures similar to those used for wild polioviruses. Further work should be undertaken to ensure the collaboration of the research community in all parts of the world in the containment plan, which should include better definition of the risks associated with potentially infectious laboratory materials.
  8. Substantial international consensus-building will be necessary in order to ensure that the end-game strategies obtain broad support in the scientific and political communities. SAGE therefore recommends that the end-game issues be placed on the agenda of the WHO Executive Board in January 2002 and on that of the subsequent World Health Assembly (WHA).
  9. SAGE should be responsible for recommending specific policy options for stopping polio immunization to the WHA. It is further recommended that these policy options be defined by TCG for consideration by SAGE. Using the best available information, WHO should develop a tentative timeline for the cessation of polio immunization. This timeline should commence when no cases have been reported globally for 12 months.
  10. Recognizing that the remit of TCG will increasingly focus on matters relating to the polio end-game, SAGE should adopt the principal responsibility for overseeing expansion of the polio infrastructure with a view to dealing with the broader immunization agenda. WHO is requested to work with partner agencies on the development of an appropriate strategy for ensuring that these resources are sustained and to present a detailed report to SAGE on this issue in 2002.

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## **Measles**

1. SAGE recommends that WHO take the necessary steps to draft a resolution supporting the WHO/UNICEF Measles Mortality Reduction and Regional Elimination Strategic Plan 2001–2005<sup>2</sup> for presentation at the WHA in 2002. This arises because the targets depart significantly from previous targets and should therefore reflect the perspectives of countries and align with the agenda of the Special Session of the United Nations General Assembly (UNGASS).
2. SAGE strongly advocates the use of measles immunization as the most cost-effective intervention to reduce childhood mortality and deaths caused by vaccine-preventable disease.
3. SAGE endorses the targets and strategies outlined in the WHO/UNICEF Measles Mortality Reduction and Regional Elimination Strategic Plan 2001–2005, including the intention that all children should have a second opportunity for measles vaccination. SAGE notes that the cornerstone of measles control is access to the vaccine through the routine system.

## **Maternal and neonatal tetanus**

1. SAGE endorses the WHO/UNICEF strategic plan for the elimination of maternal and neonatal tetanus (MNT) by 2005, and stresses the importance of implementing the high-risk approach by increasing routine immunization coverage with at least three doses of vaccine containing tetanus toxoid (TT) to at least 80% of women of childbearing age in high-risk areas.
2. SAGE recommends that the proposed approach to monitoring and validating MNT elimination be adopted.
3. SAGE recommends that a progress report on MNT elimination should be presented at its meeting every year until 2005. For 2002, SAGE recommends that WHO and UNICEF should document and report significant achievements, including progress in strengthening the monitoring/surveillance of MNT elimination and in the alignment of this initiative with other disease control activities.

## **Vitamin A**

1. SAGE recommends that WHO support better coordination between national focal points for nutrition and immunization, including plans defining areas of responsibility for implementation and monitoring.
2. SAGE supports the continued use of opportunities to include vitamin A supplementation in routine and supplementary immunization services, including the contact with measles immunization at 9 months of age and treatment of childhood illnesses, in accordance with the guidelines for integrated management of childhood illnesses (IMCI).
3. SAGE favours the inclusion of other interventions with immunization contacts if and when there is evidence to support them.

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<sup>2</sup> *Measles Mortality Reduction and Regional Elimination Strategic Plan 2001–2005* (WHO/V&B/01.13)

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4. SAGE requests that at its 2002 session a report be submitted on progress in improving the monitoring of vitamin A delivery with routine immunization services.

### ***Plenary session***

#### **GAVI**

1. SAGE recommends that WHO continue to play an active role in all aspects of GAVI policy development and implementation, and affirms the importance of dedicating significant V&B staff time to accomplishing the objectives of the GAVI Working Group and GAVI task forces.
2. SAGE endorses WHO's role as the leading technical agency of GAVI and urges V&B to continue contributing its expertise in the areas of product supply and quality, logistics, financing, and service delivery and surveillance, including immunization safety.
3. SAGE acknowledges WHO's responsibility for providing technical assistance to countries and encourages the further development of GAVI regional working groups that aim to strengthen coordination mechanisms at the country level and build national capacity in programme management and priority-setting.
4. SAGE affirms WHO's responsibilities in coordinating research and development on vaccines and strongly endorses the role of the leader of IVR as Secretary of the GAVI Task Force on Research and Development. Whereas this task force focuses chiefly on research and development goals that are achievable within five to seven years, WHO's research and development agenda should encompass a longer period.
5. SAGE notes with satisfaction the considerable progress achieved by GAVI since its inception and urges WHO and V&B to capitalize on opportunities offered by GAVI to strengthen national immunization services in a manner that generates sustainability.
6. SAGE recognizes that it is essential to strengthen national ICCs in order to ensure local mobilization of resources from national governments as well as from multilateral agencies, bilateral donors and private organizations.
7. SAGE recognizes that vaccine manufacturers from both industrialized and developing countries play a critical role in meeting global immunization needs. Support should be given for initiatives intended to ensure that new vaccines and immunization-related technologies are available to enhance access to affordable products of high quality.

#### **GAVI and initiatives in accelerated disease control**

1. SAGE reaffirms its conviction that the principles of accelerated disease control are fundamental to the reduction of vaccine-preventable morbidity and mortality. These principles include surveillance-based outcome monitoring, epidemiologically driven supplementary immunization activities, and innovative strategies and technologies for accessing unreached children. The sustainability of the gains obtained depends on countries ability to achieve and maintain high routine immunization coverage.

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2. SAGE recommends that WHO advocate that GAVI:
- a) approve the immediate establishment of a new accelerated disease control objective, a new milestone, and new indicators.
    - ***new objective:*** support the *national* accelerated disease control targets for vaccine-preventable diseases;
    - ***new milestone:*** by 2005, the world to be certified polio-free;
    - ***new indicators:*** addition of disease outcome indicators; selection of the most appropriate indicators (polio, measles, MNT, vitamin A) to be proposed by the working group after consultation with partners;
  - b) place renewed emphasis on GAVI's first objective, i.e. "*improve access to sustainable immunization services*". This would serve to unify all immunization initiatives by making their primary aim "*access to all children and target populations*";
  - c) immediately revise the second objective as follows: "Expand the use of all existing safe and cost-effective vaccines, *and promote the delivery of other appropriate interventions at immunization contacts*";
  - d) request that GAVI partners provide financial support for a human resources infrastructure for immunization. As a first step, UN agencies should develop for consideration by the GAVI partners an immunization human resources plan (i.e. minimum staff for each country) and costing based on the current human resources, including those that are funded under the terms of accelerated disease control. GAVI partners should have a funding mechanism in place for supporting this plan by 2002 (e.g. by designating GAVI funding for this purpose at source).

**Vaccine selection: divergence of products for public sector immunization services**

SAGE advises WHO and its partners to:

1. Develop and communicate strong positions on product selection in order to minimize issues related to perceived safety and quality of developing market products.
2. Keep key manufacturers in the market through clear communication, improved demand forecasting, and advocacy for the intrinsic value of vaccines. Consideration should be given to examining the possibility of multiyear contracts and commitments to purchase.
3. Ensure that appropriate systems exist for the licensing and regulatory oversight of these products.

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## **Yellow fever**

1. SAGE recognizes the short-term crisis in yellow fever vaccine supply and endorses the policy adopted by WHO, UNICEF and the International Coordinating Group (ICG) for prioritizing the use of limited supplies. For the longer term, SAGE recommends that WHO urgently work closely with countries in order to determine real demand by time period, including desired vial sizes. Once these demand estimates are completed, WHO should explore the available supply, the potential capacity, and the need for expanding capacity with manufacturers, UNICEF Supply Division and the PAHO Revolving Fund.
2. SAGE strongly endorses the AFRO Regional strategy and milestones for yellow fever control.
3. The policy of vaccinating travellers to areas where yellow fever is endemic should be continued.
4. All countries at risk should strive for a rapid response to outbreaks. This is particularly significant during the current vaccine shortage as it ensures a more efficient use of vaccine.
5. SAGE requests that the Global Advisory Committee on Vaccine Safety (GACVS) review the safety of yellow fever vaccination.

## **Global Advisory Committee on Vaccine Safety**

1. SAGE commends the work of GACVS in examining the evidence relating to the non-specific effects of vaccines on mortality, and endorses GACVS's conclusion that, on the basis of the evidence currently available, no association between diphtheria-tetanus-pertussis (DTP) vaccine and increased mortality has been demonstrated.
2. SAGE commends the efforts of GACVS to commission additional studies aimed at determining whether the findings reported from Guinea-Bissau (British Medical Journal, 9 December 2000) are reproducible in Guinea-Bissau and elsewhere in developing countries, and awaits the outcome of these studies.
3. SAGE endorses the proposal for the development by V&B of a communications strategy that would deal with public concern regarding the adverse effects of vaccines in general.

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# 1. Opening remarks

## 1.1 Dr Yasuhiro Suzuki, Executive Director of the Health Technology and Pharmaceuticals cluster

Dr Suzuki welcomed the participants and recalled that SAGE's function was to advise WHO on: (i) the global mission and objectives for vaccines and immunization; (ii) the V&B strategic plan and progress towards the main objectives; and (iii) organizational capacity and roles in vaccines and immunization.

At its first meeting in 1999, SAGE had reviewed and endorsed the strategic plan for the period up to 2003. The second meeting in June 2000 had covered priority projects, the departmental budget and the establishment of GAVI.

During the current meeting, WHO expected SAGE to review progress in relation to various objectives and targets set by V&B and SAGE. Input from SAGE would be critical at this juncture, as WHO was starting to implement a process for reviewing and possibly revising the strategic plan for 2002–2005.

Dr Suzuki explained that the meeting would start with three parallel sessions. There would then be a plenary session during which broader issues, including GAVI, would be discussed. GAVI was undoubtedly reshaping the vaccines and immunization agenda. WHO and GAVI shared many objectives, including the strengthening of immunization systems, safe immunization and the introduction of new vaccines. WHO continued to be responsible for global policies and strategic direction. SAGE was WHO's principal adviser on shaping the agenda for vaccines and immunization.

Dr Suzuki expressed confidence that SAGE would ask questions, demand explanations, and continue to provide WHO with the best possible strategic advice.

## 1.2 Dr Bjørn Melgaard, Director, Department of Vaccines and Biologicals

Dr Melgaard outlined the dramatic changes that had transformed the global immunization scene in the preceding year and indicated the issues that SAGE would address.

1. **GAVI.** GAVI had moved forward rapidly with the disbursement of funds. It had enabled partners to come together and had quickly consolidated procedures and mechanisms, particularly at the global level. However, GAVI still had to come to terms with its mandate.

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GAVI was initially created to speed the introduction of new vaccines and to strengthen immunization systems, but the important question now was whether GAVI should become the alliance for the *whole* global immunization agenda. Other questions arose with regard to GAVI's role at country level and the role that WHO and UNICEF should play in supporting country operations.

2. **Polio.** Despite outstanding progress towards polio eradication, the funding gap of US\$ 400 million remained a critical risk. SAGE would discuss how lessons learnt from polio could be translated into a broader immunization agenda, and would hear about discussions on aligning the objectives of GAVI with polio eradication and other disease control objectives.
3. **Growth.** As a result of growth in both departmental and regional offices, V&B's ability to support countries had greatly increased, as had the burden of work performed by staff in response to needs arising from GAVI.

V&B and the regions had moved forward in relations with UNICEF. It was important for WHO and UNICEF to work closely together in supporting countries and shaping global policies. Many meetings had been held in the preceding year in order to consolidate the joint approach within GAVI.

Research capacity in WHO had been strengthened with the creation of the IVR.

4. **New directions.** Dr Melgaard expected that access would become the key matter in the coming years and that the world health community would need new strategies to reach all children with all vaccines in the schedule. Major rethinking might be required. It might be necessary to do away with the term *routine* in relation to immunization.

Progress was hindered by the preoccupation with five contacts with children in a fixed period based on the optimal immunogenic age. The fundamental requirement was that the highest possible number of children should immunized.

Redefining the access concept and creating new service delivery concepts were major challenges for the future. At the Special Summit for Children in September 2001 a number of new targets would be set.<sup>3</sup> These would consolidate the notion that an effort should be made to attain equity by achieving access and high coverage throughout the world.

5. **Infusion of huge additional resources.** The extremely generous contributions of the Gates Foundation could be expected to allow more rapid progress with the help of new tools and technologies. Dr Melgaard emphasized that more partnership in vaccine research was needed as so many new players had been created.

### 1.3 Sir Gustav Nossal, Chair of SAGE

Professor Sir Gustav Nossal referred to the new hope that had accompanied the extra dynamism created by GAVI. This was not exclusively a matter of money. GAVI had been a catalyst. A new spirit had been engendered and was inducing many elements to work together in a way that had not been achieved before.

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<sup>3</sup> The Summit was postponed to May 2002 due to events taking place in September in the USA.

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Some people were confused about what GAVI was and how it related to WHO. GAVI was a very loose, unincorporated, minimally staffed alliance of partners. It was simply a group of people who had said they would work together in order to achieve aims that they could not achieve separately.

Whereas GAVI was financed for five years, WHO could be expected to exist until the world was healthy enough not to need it. Sir Gustav considered that the longer-term goals of GAVI and WHO should be identical. Measles control and polio eradication were undoubtedly GAVI objectives. However, the Vaccine Fund, or at least that component given by the Gates Foundation, had more restricted goals, primarily dedicated to the strengthening of immunization services and the introduction of new vaccines, with a small amount going to research and development. Whereas GAVI had to have a wide vision, the Vaccine Fund was necessarily limited, targeted and focused.

Sir Gustav considered the relationship of WHO and SAGE to GAVI. GAVI had many partners, including UNICEF, industry and the World Bank. WHO had the heavy responsibility of technical, scientific and policy guidance, in collaboration with partners. SAGE had to bear in mind that it was WHO's key advisory structure in the field of vaccines and biologicals.

While WHO had to work in harmony with the GAVI Research and Development Task Force, it was important to appreciate that GAVI was more time-constrained. GAVI would look at three groups of vaccines and three technologies that would enter into a five-year framework. SAGE was interested in that framework but also had a wider one and a longer vision.

The greatest single thing to emerge from GAVI had been an enormously vibrant interaction between the public sector and industry. It was vital for industry from both the industrialized world and the developing world to be a full and equal partner in deliberations.

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## 2. Innovation

*Chair: Dr Claire Broome*

*Rapporteur: Dr M. Greco*

Dr Broome welcomed the participants, remarked that the new format would allow more discussion in individual areas, and encouraged free and open discussion. Research and development issues beyond those identified by GAVI could be discussed during this session.

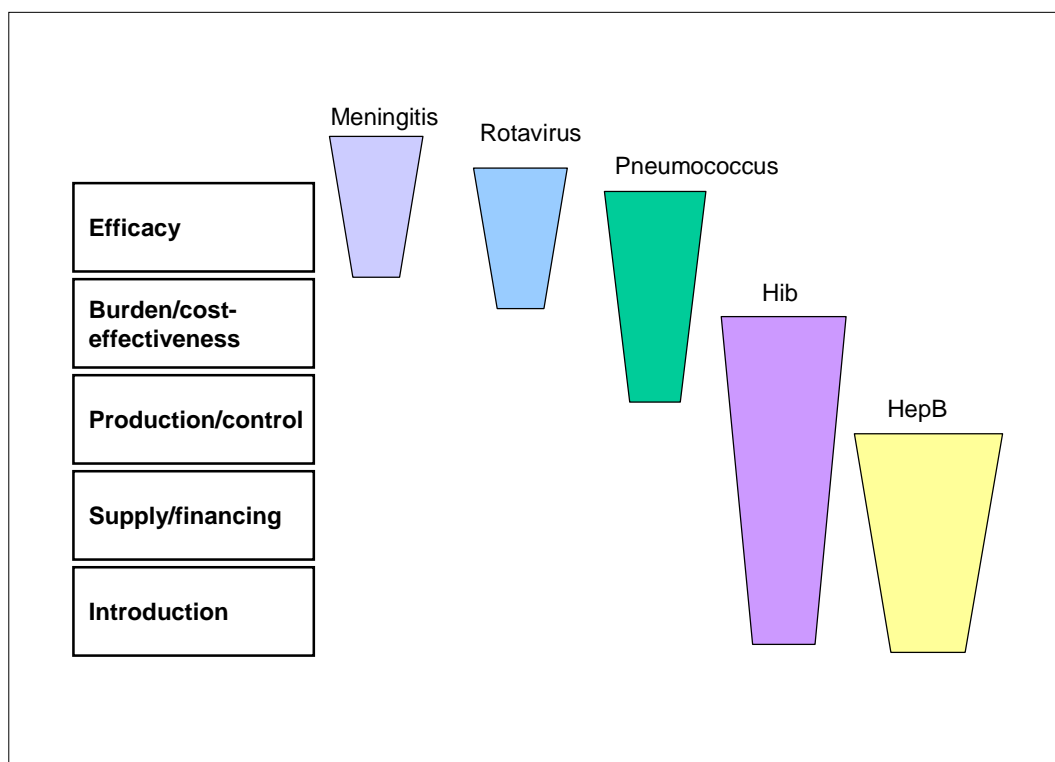
### 2.1 An overview of the priority project

#### *Presentation (J. Wenger)*

The priority project for accelerated vaccine introduction (AVI) priority project was an effort to facilitate the introduction of new and underutilized vaccines in the developing world. It predated GAVI and was separately funded. The project included the activities of teams within V&B aimed at developing the infrastructure required in order to facilitate new vaccine introduction. It encompassed tools that measured disease burden and cost-effectiveness, the evaluation of vaccine efficacy, guidelines for the production and control of vaccines, efforts to establish reliable supply and funding sources for new vaccines, and technical help with the introduction of new vaccines.

Different vaccines were at different stages of development: hepatitis B (HepB) vaccine and *Haemophilus influenzae* type b (Hib) vaccine were already available and required efforts in the areas of supply, financing and introduction; pneumococcal vaccine required studies on efficacy and disease burden; meningococcal vaccine was even newer (figure 1). Work was needed in the following areas in accordance with the stage of development: efficacy versus safety issues for rotavirus vaccine; unclear burden for pneumococcus and Hib; lack of correlates of immunity for Hib and pneumococcal conjugates; in connection with supply and financing, a monopoly situation and short supply for certain combination vaccines; and a need for programmatic changes in order to reduce wastage associated with the introduction of costly new vaccines.

**Figure 1: Stages in the introduction of new vaccines**



Increases in the number of countries using HepB and Hib vaccines had been recorded in the preceding year (table 1) and further increases were expected with the approval of applications to the Vaccine Fund; 29 additional countries would be incorporating HepB and/or Hib vaccine during the next year.

**Table 1: Proportions of countries that have introduced HepB and Hib vaccine**

HepB		Hib	
March 2000	116/216 (54%)	March 2000	63/216 (29%)
June 2001	129/216 (60%)	June 2001	71/216 (33%)

Within the next year there would be a large increase in the uptake of HepB. Hib would also show an increase, although at a lower rate.

### ***Discussion and issues***

#### **Cost versus cost-effectiveness**

SAGE recognized the problems related to the sustainability of vaccination programmes after Vaccine Fund support was no longer available. For GAVI recipients the switchover to self-financing after five years presented a challenge, and the Vaccine Fund might have to support certain countries for longer. Although it was hoped that prices would fall during the next five years it was not advisable to rely on there being large decreases.

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It was noted that additional antigens were substantially more expensive than the traditional EPI antigens. The cost of pentavalent vaccines was 10 times higher than that of EPI vaccines, not so much because of production costs but because of additional antigens. Dr Broome pointed out that vaccines were priced very low in comparison with therapeutic medicines. The cost of the new combination vaccines could be considered acceptable, given the value of the new antigens and the public health savings obtained by administering all in one.

## **MMR**

Mumps and rubella vaccines were relatively inexpensive, and a question was raised about WHO's plans for introducing measles-mumps-rubella (MMR) vaccine in the interest of equity between developing and developed countries. It was explained that a meeting had been held a month previously and that a report would be issued on the mumps component. Concerns regarding complications associated with the use of the vaccine and low disease morbidity meant that a different approach was needed for introducing this particular combination. Work was in progress with this in view.

## **Disease burden**

It was pointed out that one of the things hindering Hib vaccine uptake by countries in comparison with HepB was a lack of recognition of the disease burden.

## ***Recommendations***

Sage endorses V&B priorities and activities aimed at accelerating the introduction of new and underutilized vaccines and evaluating their impact. Three major components of this effort are:

- support to countries for the introduction of new vaccines and coordination of GAVI-related activities through enhancing regional expertise and capacity, the development of an expanded pool of consultants for assistance to countries, and the preparation of guidelines and of materials for advocacy, information, education and communication;
- development and use of disease burden tools in order to obtain data for advocacy and prioritization of new vaccines at the country level;
- assistance in the coordination of GAVI agendas for Hib, pneumococcal and meningococcal vaccines.

## **2.2 Decision-making tools and information for the introduction of new and underused vaccines**

### ***Presentation (C. Nelson)***

When considering the introduction of a new vaccine, decision-makers required to know the magnitude of the local problem and the potential impact of a vaccine on it. Data on the cost-effectiveness of the vaccine and evidence of its impact in comparable settings in the same region were also important.

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V&B was tackling these matters by focusing on the following activities: the estimation of disease burden using existing data; the development of protocols for population-based surveillance of disease; the development of disease burden rapid assessment tools; and the development of surveillance protocols that could be used to demonstrate the impact of a vaccine after introduction. In addition, protocols had been developed for assessing the economic impact of disease. For example, V&B was building a network of economists who were working with the pneumococcal vaccine trials in order to collect standardized data that could be used to estimate the vaccine's cost-effectiveness.

In the preceding year the main focus of work had been on HepB and Hib vaccines. It was estimated that hepatitis B infection led to between 500 000 and 750 000 deaths globally each year and that the corresponding figure for *H. influenzae* type b was approximately 450 000 deaths. In the coming year, special attention would also be given to pneumococcus and rotavirus, which were estimated to account for 1 million and 600 000 deaths each year respectively. Table 2 shows the activities that have been initiated.

**HepB.** Disease burden estimates had been developed in collaboration with technical partners in the United Kingdom's Public Health Laboratory Service, and tools for rapidly assessing disease burden and the potential impact of alternative vaccination schedules had been developed in collaboration with the Hepatitis Branch of the United States Centers for Disease Control and Prevention (CDC). An overview of strategies for assessing the impact of HepB vaccination programmes and a protocol for conducting coverage and serosurveys had been developed with technical assistance from the University of British Columbia and the British Columbia Disease Control Center.

**Hib.** Disease burden estimates were being drafted and at several sites the population-based surveillance of Hib meningitis, involving the use of a WHO protocol, was nearing completion. These activities were supported by WHO or through separate funds. An Hib disease burden rapid assessment tool had been developed and field-tested. For impact assessment a protocol for laboratory-based paediatric bacterial meningitis surveillance had been developed and, in collaboration with CDC, a network had been launched in AFRO and would soon be introduced in EMRO and other regions. This activity was particularly important for establishing local disease burden before the introduction of a vaccine and for documenting its impact subsequently.

**Pneumococcus.** Work with pneumococcal vaccine had just begun. A protocol for the study of disease burden had been developed and would be field-tested. A working group was developing tools for standardizing radiographic interpretations. A costing protocol developed for the rapid assessment of local disease burden was being used in pneumococcal vaccine trials.

**Rotavirus.** Dr Nelson stated that attention would be turning to rotavirus in the coming year. Plans were being made to develop disease burden estimates and a disease burden assessment tool and to finalize a protocol for the population-based surveillance of rotavirus disease.

**Table 2: Outline of activities**

	Disease burden estimates	Disease burden studies	Local disease burden tools	Impact assessment
HepB	X	—	X	X
Hib	X	X	X	X
Pneumococcus	X		X	
Rotavirus		X		

X = activities in progress. For HepB a large number of disease burden studies were conducted in the 1980s and 1990s in all regions of the world.

### ***Discussion and issues***

#### **Invasive Hib disease in Asia: study difficulties**

SAGE questioned the low reported incidence of invasive Hib disease in Asia. Several factors associated with these studies possibly accounted for this. They included low lumbar puncture rates, poor laboratory performance and a tendency to use antibiotics extensively before lumbar punctures were performed. For example, a survey in Viet Nam showed that lumbar punctures were not being used as frequently as necessary, and in the Philippines it was found that parents usually refused to grant permission for lumbar puncture. Both situations resulted in only a small number of specimens of cerebrospinal fluid being collected and in potentially misleading results. Given the limitations of many studies, it was difficult to determine the true magnitude of the problem.

#### **Possibility of lower Hib burden**

It was pointed out, however, that a few well-conducted studies, notably in China (Province of Hong Kong) and Japan, had indicated low rates of Hib meningitis. It was suggested that if certain diseases had a lower incidence in some subgroups than in others because of genetic or epidemiological factors there was no reason why the populations concerned should not also show a low incidence of Hib disease. Given the limitations of the available studies, results from the vaccine intervention studies in Lombok, Indonesia, where a trial was in process, and at other sites, e.g. China and India, were eagerly awaited.

The use was questioned of the Hib disease burden rapid assessment tool in the context of Asian countries with reportedly low incidence. Dr Wenger explained that the results given were sensitive to the implementation of clinical and laboratory practices of high quality as well as to the use of antibiotics before a lumbar puncture was performed. For this reason the tool was more useful for local advocacy purposes where robust regional data had already suggested that Hib was a problem.

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## **Measuring vaccine impact on Hib pneumonia burden**

It was agreed that current studies did not fully deal with the burden of Hib pneumonia for all regions. It was felt that this could only be measured by studying the impact of vaccine on the Hib pneumonia burden and comparing pneumonia incidence between vaccinated and unvaccinated individuals. SAGE felt that such studies were important and necessary in order to establish the burden of Hib-related pneumonia in the community.

### ***Recommendations***

SAGE recognizes the efforts being made to define the burden of disease and the cost-effectiveness of a vaccine, including tools for local advocacy and surveillance protocols. It is noted that recent efforts have focused on HepB and Hib vaccines, and that in the coming year attention will turn to rotavirus and pneumococcal disease. Questions remain about the burden of vaccine-preventable Hib pneumonia, which can only be answered with well-planned, controlled vaccine intervention trials. SAGE recommends that WHO evaluate the feasibility of estimating the Hib pneumonia burden in Asia by means of such trials. The technical design of such studies must ensure they have adequate power to measure disease burden so that decisions on vaccine introduction can be made.

## **2.3 Second-generation rotavirus vaccines**

### ***Presentation (B. Ivanoff)***

The current activities on rotavirus research within V&B were described. These included studies on the prevalence of intussuption, strain surveillance, phase I and II studies with new vaccine candidates (GSK), and hospital-based studies on disease burden (Vaccine Assessment and Monitoring team) in several developing countries.

The GSK vaccine had only one serotype. G1 was the prevalent serotype worldwide. G1 cross-reacted with G3 and G4 but not with G2. However, G2 was the prevalent serotype in Viet Nam, demonstrating the importance of strain surveillance.

SAGE was asked to consider whether it was important to reinforce the need for parallel testing of other vaccines in developed and developing countries on the basis of experience of problems with Rotashield™.

### ***Discussion and issues***

#### **Further study necessary**

The need to understand the science of intussuption following vaccination was stressed.

It was noted that, in developing countries, intussuption did not appear to be directly associated with human rotavirus infection, suggesting that a vaccine based on a human rotavirus strain might not have the same problem with intussuption as rhesus or bovine strains. However, it was felt that the available evidence was inadequate to permit any recommendations to be made.

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It was felt that the two trials with GSK vaccine should be closely coordinated with other candidates being tested in India. It was reported that these trials were being conducted under the same protocol.

### **Vaccine cost-effectiveness in countries where mortality is high?**

In the USA there were estimated to be 50 deaths annually from rotavirus. In developing countries it was estimated that 60 deaths per *hour* were attributable to the same cause. The opinion was expressed that countries with significant mortality from rotavirus should be empowered to make their own decisions about the cost-effectiveness of vaccine, even if it had side-effects making it unusable in developed countries. However, other participants felt that this was a complex issue that might go beyond what SAGE was able to recommend.

### ***Recommendations***

SAGE underlines the importance of early testing of new candidate rotavirus vaccines in parallel in industrialized and developing countries so as to accelerate their introduction.

## **2.4 Pneumococcal conjugate vaccines**

### ***Presentation (T. Cherian)***

One of the GAVI priority projects was to assure the availability, affordability and use of pneumococcal conjugate vaccines for the developing world within seven years (vaccines against *Streptococcus pneumoniae*). GAVI had urged that gaps and leading partners be identified in order to move the product from its current prelicensed state to being fully developed, manufactured and delivered to children in developing countries.

Dr Cherian described current WHO activities with pneumococcal conjugate vaccines. They included the monitoring of efficacy trials, the development of standard tools for measuring key outcomes of public health interest in developing countries, studies in special populations, and the development of the GAVI agenda for accelerating the introduction of pneumococcal conjugate vaccines in developing countries.

WHO had been closely involved in the first three trials of pneumococcal conjugate vaccine in the Gambia (recently started), the Philippines (begun in 2000), and South Africa (nearing completion). It had been involved in monitoring these trials and in an effort to develop standardized tools for measuring their outcomes. A number of coordinating groups had arisen. One of the key issues would be to measure the impact of the vaccine on pneumonia by means of a radiological end-point.

One group was working with nasopharyngeal carriage, an important method of measuring potential herd effect and potential serotype replacement disease that could occur following the use of a vaccine that contained only a limited number of serotypes. This work included a search for standardized methods to detect serotype replacement and capsular switching.

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Another group had undertaken to create a standardized method for interpreting chest radiographs in order to facilitate X-ray diagnosis for epidemiological purposes.

WHO had become involved in setting up reference laboratories and had supported a few special studies. One of these concerned the immune response to pneumococcal polysaccharide vaccine in HIV-infected people in Uganda. In this case-controlled study there was an increased rate of pneumonia in immunized subjects.

Some efficacy trials in developing countries were in jeopardy because manufacturers were considering changing their policies on conjugate vaccines in response to the requirements of the United States Food and Drug Administration for licensure of their candidates in the USA on the basis of immunogenicity data.

### ***Discussion and issues***

#### **Encouragement for a promising vaccine**

Concern was expressed about the slowdown in the development of conjugate vaccines. It was universally felt that the available data suggested that the pneumococcal conjugate vaccine showed great promise and had the capability to substantially diminish childhood morbidity and mortality in developing countries. It would be very unfortunate if efforts to further evaluate these vaccines in developing countries were abandoned, especially if this happened because of immunogenicity results obtained in the absence of good correlates of protection.

#### **Importance of correlates of protection and serotype monitoring**

It was important to develop a body of evidence based on good laboratory analysis of serological correlates of protection in populations in developing countries. Many opportunities for this had already been missed. One trial in which the opportunity had been lost involved Australian Aboriginals, who had one of the highest incidences of pneumococcal disease in the world. The vaccine would be introduced with effectiveness estimates and no serological correlates of protection. It was felt that there was a dichotomy between the availability of a licensed vaccine and the absence of serological correlates.

SAGE felt that additional efficacy studies in developing countries were of paramount importance. They should be designed to determine the impact of vaccine on pneumonia and mortality, to determine correlates of protection applicable in developing countries, and to support future monitoring for serotype replacement.

#### **Protein vaccine alternatives in parallel**

Sir Gustav Nossal pointed out that problems arising with pneumococcal conjugate vaccine were serious enough to considerably delay introduction. It was necessary to actively pursue the parallel development of alternatives, such as protein vaccines. However, the subgroup agreed that this should not be done at the expense of further development of conjugate vaccines. There was little evidence that protein vaccines would be effective and it was considered important to address the proof of concept of candidate common protein vaccines.

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## ***Recommendations***

SAGE recognizes the promise of pneumococcal conjugate vaccines as evidenced by the efficacy of the 7-valent vaccine in industrialized countries. It encourages V&B to continue playing a leading role in the evaluation of pneumococcal conjugate vaccines in developing countries, including efficacy studies that provide critical data relating to the impact on pneumonia and mortality, correlates of protection, and possible replacement disease. In a parallel effort, V&B should work with partners to address the proof of concept of candidate common protein vaccines.

### **2.5 Case study on new vaccine supply and financing: combination vaccines**

#### ***Presentation (S. McKinney)***

Mrs McKinney presented a case study that had been conducted with Dr Milstien, which dealt with combination vaccines based on diphtheria, tetanus and whole-cell pertussis (DTwP) and measles-based combination vaccines.

There were both positive and negative aspects to the expanding use of combination vaccines. The benefits included fewer injections and syringes, less thiomersal exposure, and the possibility of greater transparency in the introduction of a new antigen. The drawbacks included programmatic instability, regulatory issues, a shortage of suppliers and implications for availability and price, and the need for cold chain expansion.

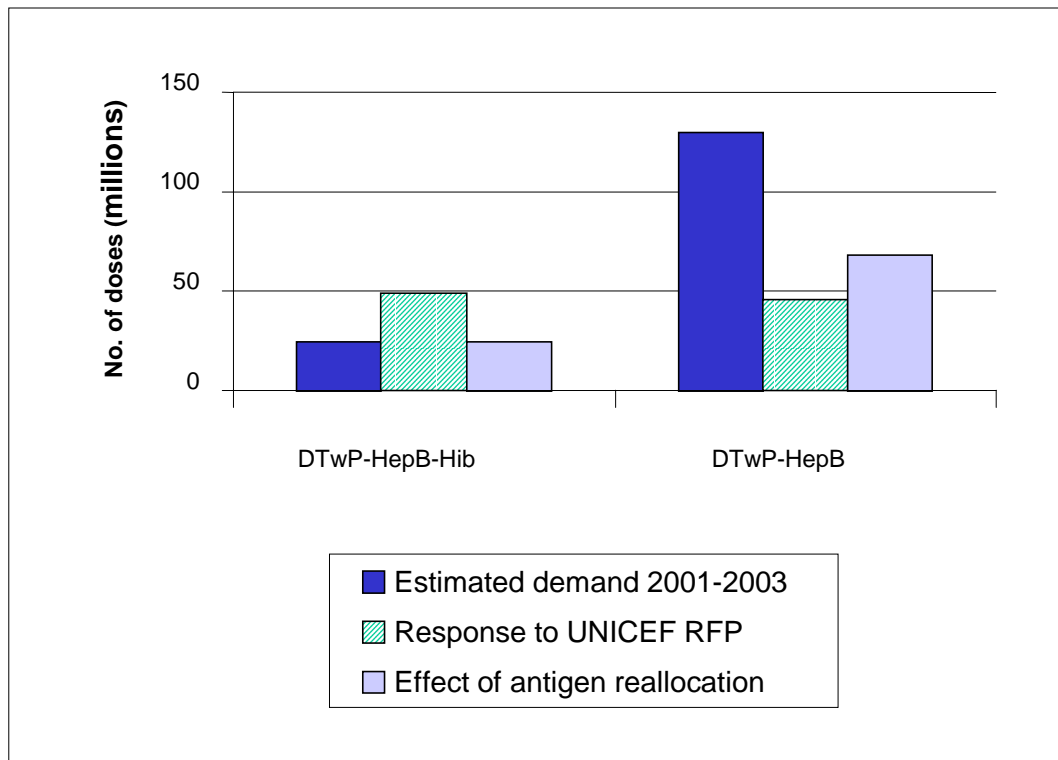
The study tried to assess what the public sector could do in order to facilitate the introduction of these vaccines, bearing in mind that the goal was to ensure that vaccines were produced in adequate quantities and supplied at reasonable prices so as to meet the priority needs of developing countries. It was pointed out that combinations that were developed might not be what the public health community demanded. Furthermore, the production of combinations affected the supply of the individual antigens that might be needed in developing countries.

There had already been a decrease in the number of DTP suppliers. Among other things, this was attributable to a low price that had discouraged prequalified manufacturers and to strict regulatory guidelines discouraging local manufacture. In addition, 77% of UNICEF's DTwP supply came from two developing country sources that were moving aggressively towards DTP-HepB combinations of their own. This could have a significant impact on the traditional DTwP vaccine supply.

In the case of measles vaccine, three-quarters of UNICEF's supply came from a single developing country source. Availability was narrowly meeting demand. Many manufacturers preferred to use measles in a combination that yielded a higher profit. For a given production space and time, 500 million doses of measles could be made as against 60 million of measles-rubella or even fewer of measles, mumps and rubella combinations.

The response by Glaxo Smith Kline to the new demand is shown in figure 2.

**Figure 2: Antigen reallocation: review of one producer's response**



RFP = request for proposals.

The one prequalified supplier's response to UNICEF's request for DTwP-HepB resulted in a substantial undersupply, while the response to the request for pentavalent DTwP-HepB-Hib resulted in a substantial oversupply. The demand for DTwP-HepB was four times greater than that for DTwP-HepB-Hib.

These data demonstrated how essential antigen allocation was in terms of planning. It was important to work with suppliers on estimates of demand and on ways of meeting demand so as to avoid crises in global supply. In this process it was essential to examine different market characteristics. Different markets had varying demands for combination vaccines because of programmatic, financial or political factors. It was critical for WHO to work with manufacturers in order to clarify what quantities of which combination vaccines would meet the demands of developing countries as opposed to middle-income countries.

The process of antigen allocation needed to be very carefully managed in order to ensure that the demands and desires of countries were met adequately and affordably *without jeopardizing the global supply of traditional vaccines*. WHO and its partners would have to review possible combination vaccines and take a firm position on the acceptability of each combination. While the regulatory issues were in hand, WHO should also continue to address and monitor this activity in order to ensure that combination vaccines were available to developing countries.

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## ***Discussion and issues***

The discussion centred mainly on supply problems that might result from demand created by the GAVI initiative. It was stressed that forecasting demand and supply was like aiming at a moving target.

### **Increasing demand for combination vaccines and supply issues**

The fact that the poor countries eligible for support from GAVI were receiving new combination vaccines should create a demand worldwide. However, in the present situation of monopoly supply the new vaccine was expensive and the supply was hardly sufficient for the GAVI recipients.

An aspect of the changing supply scenario was that developing country manufacturers were becoming suppliers of combination vaccines. For many years they would probably be able to supply only their own countries. Meanwhile, as they moved into combinations the traditional vaccine supply would diminish. For example, the issue might be DTP versus DTP–HepB or measles versus MMR. At present, developing country manufacturers were mainstay sources of traditional vaccines.

### **Impact of market decisions**

The trend towards combination vaccines posed related problems. If there was a move to a preference for combination vaccines and if that reduced the number of suppliers of all types of vaccine, how vulnerable would we be in public health to market and business decisions that were really beyond our control? It was stressed that this complication should be borne in mind.

### **Individual preferences for different combinations**

There was a call for clarification of WHO's position on recommending combinations. Mrs McKinney and Dr Milstien felt that WHO should take account of different countries' preferences for different combinations when helping them to evaluate all the factors, including the programmatic and financial factors. It was agreed that WHO should be open to individual solutions and that it was perhaps not necessary to have global ideological views.

### **Realistic planning**

It was suggested that there could be a return to long-term commitments with suppliers in order to assure supplies.

Dr Broome said that the impact of simultaneous developments was evident: new funding, new combinations, and the emergence of new producers in the developing world. When it was known what the issues were it would be possible to devise creative procurement strategies.

However, care should be taken not to impede the market process, and both traditional and emerging suppliers should be encouraged by providing sufficient information. Mrs McKinney agreed and reiterated that it was important to look at market characteristics and to work in conjunction with UNICEF and manufacturers in order to facilitate realistic planning.

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WHO should carry out advocacy through better information on disease burden so as to help countries to decide when more complicated combinations should be adopted. However, it was essential to get things right in terms of demand forecasting, production and supply.

It was agreed that the issue was extremely important and SAGE commended WHO on this study.

### ***Recommendations***

Combination vaccines have become part of many national immunization services. Their use has a significant impact on supply and programme flexibility. SAGE makes the following recommendations:

- WHO should review the possible combination vaccines and the implications for supply, regulation, presentation and price and should assist countries to assess the appropriateness of each combination for national immunization services. Consideration of the role of developing country production and the implications of sole source suppliers should be a part of this process
- WHO, in conjunction with partners, especially vaccine manufacturers, should provide accurate demand forecasting for the various combination vaccines (determined by national immunization service managers to be beneficial, programmatically feasible, financially sustainable and worth introducing if funding is available). This information should be given to UN agency purchasers and directly to manufacturers well in advance so as to avoid a crisis in global supply. WHO and UNICEF should coordinate their activities and speak with one voice to the manufacturing community, should make joint recommendations and requests. WHO should also continue to collect information on factors influencing the supply of different components in order to assist countries in decision-making.
- WHO should give priority to continuing action on addressing and monitoring progress on the licensing of vaccines in industrialized countries for use in developing countries.

## **2.6 Accelerated vaccine introduction – global and regional activities**

### ***Presentation (J. Wenger)***

Recent developments in the global immunization milieu had resulted in increased opportunities for the uptake of new vaccines that could have a substantial impact on the disease burden in developing countries.

Through GAVI the 74 poorest countries were eligible for HepB or Hib vaccine if they had more than 50% DTP coverage, or for yellow fever vaccine in areas where this disease was endemic. In order to obtain the vaccines the national governments had to submit proposals. Evidence had to be provided of a functioning ICC, a recent immunization assessment and a multiyear plan for immunization.

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Since many of these countries lacked one or all of these components, WHO had provided assistance with their development. Consultants could be sent to countries when required and country support was given through the regional offices. Proposals had been received from half of the countries and the AVI team was trying to follow up on proposal response, introduction and experience with new vaccines.

Dr Wenger mentioned that activities in V&B included the development of guidelines on the management of vaccine introduction. Staff in the WHO regions who were knowledgeable about new vaccines played a key role in regional GAVI working groups. In ways that were specific to the regions, groups of partners dealt with the introduction of new vaccines and the improvement of immunization systems. The training of regional consultants was taking place.

The first three reviews of proposals resulted in 25 being funded out of the 47 that were processed. The rest were pending. The process had provided a major boost to the introduction of new vaccines.

### ***Discussion and issues***

#### **Sustainability of finance for new vaccines**

Questions were raised about the financing and sustainability of new vaccines in countries eligible for support for GAVI support. In the guidelines of the Vaccine Fund, each country was required to provide a plan for sustainability with the mid-term review, which would take place about two years into the life of the proposal.

There had been considerable activity within the GAVI Financing Task Force in relation to options for financing, and guidance for countries had been discussed. However, much more needed to be done. It was suggested that these high-level discussions should be shared with developing countries and that their participation in ongoing discussions would be useful. Dr Wenger explained that it was felt that solutions for long-term sustainability should initially be developed in the ICCs with the involvement of partners and ministries.

#### **Universal hepatitis B immunization**

On the subject of universal HepB immunization, Sir Gustav Nossal pointed out that in Cuba, where HepB coverage had exceeded 80%, the seroconversion rate had fallen by over 99%, an amazing herd immunity effect among infants.

The recommendation on universal HepB immunization for infants made in an earlier draft document was not included for discussion. The subgroup felt that the information on which to base a recommendation should be collected for consideration at the next meeting of SAGE.

### ***Recommendations***

It is WHO policy to recommend routine infant HepB immunization as the most effective strategy in countries where the prevalence of chronic HBV infection is 2% or more. In countries with a lower prevalence the immunization of adolescents may be considered as an addition or alternative to infant immunization.

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However, new information is available which may support a recommendation for routine infant vaccination as the preferred strategy in all countries. SAGE recommends that WHO collect the information necessary to develop a position on universal infant immunization for consideration by SAGE in 2002.

## **2.7 Elimination of epidemic meningitis in sub-Saharan Africa: the meningitis vaccine project**

### ***Presentation (L. Jodar)***

Dr Jodar pointed out that all countries suffered from endemic meningococcal disease, primarily in children under the age of five years, at an annual attack rate of around 1 to 3/100 000. In the sub-Saharan African meningitis belt, countries suffered enormously from recurrent meningococcal epidemics, often in irregular cycles of 5–12 years. During epidemics there were high attack rates not only in infants but also in people up to the age of early adulthood, and this caused social and economic chaos.

Current public health interventions were disruptive, expensive and only partially effective. A vaccine was needed which could be administered with other routine vaccinations and provide long-term protection in children and adults, prevent epidemics, and eliminate the need for chaotic emergency interventions. There were good reasons to believe that serogroup A/C meningococcal conjugate vaccines could meet this need.

Successful serogroup A/C conjugate prototypes that had been evaluated in African infants were highly immunogenic, and others against meningococcal C disease had proved effective in the United Kingdom. By 1999, however, vaccine manufacturers had halted the development of serogroup A/C meningococcal conjugate vaccines for several reasons. Firstly, the disease caused by serogroup A was largely limited to sub-Saharan Africa and some areas in the Eastern Mediterranean Region and Asia. Secondly, the market niche shrank when some European countries decided to license a monovalent serogroup C meningococcal conjugate vaccine. Finally, the costs discouraged the development of an Africa-specific conjugate meningococcal vaccine.

The Meningitis Vaccine Programme (MVP), a partnership between WHO and the Program for Appropriate Technology in Health (PATH), was created to help deal with this important public health problem. In collaboration with CDC and other agencies, MVP would work with vaccine manufacturers to develop, evaluate and introduce serogroup A/C meningococcal conjugate vaccines in Africa. It was exploring strategies for a public-private partnership aimed at lowering the costs and risks of product development. Discussions during the preceding year with vaccine manufacturers had resulted in a comprehensive analysis of costs and timelines for the development of a serogroup A or A/C conjugate vaccine. Issues such as manufacturing capacity, process development, clinical and regulatory activities and the cost per dose had been considered. Negotiations with vaccine manufacturers had provided realistic, independent cost estimates of vaccine development, manufacturing and production. In addition, the African community had expressed a clear commitment to using a safe and immunogenic meningococcal vaccine.

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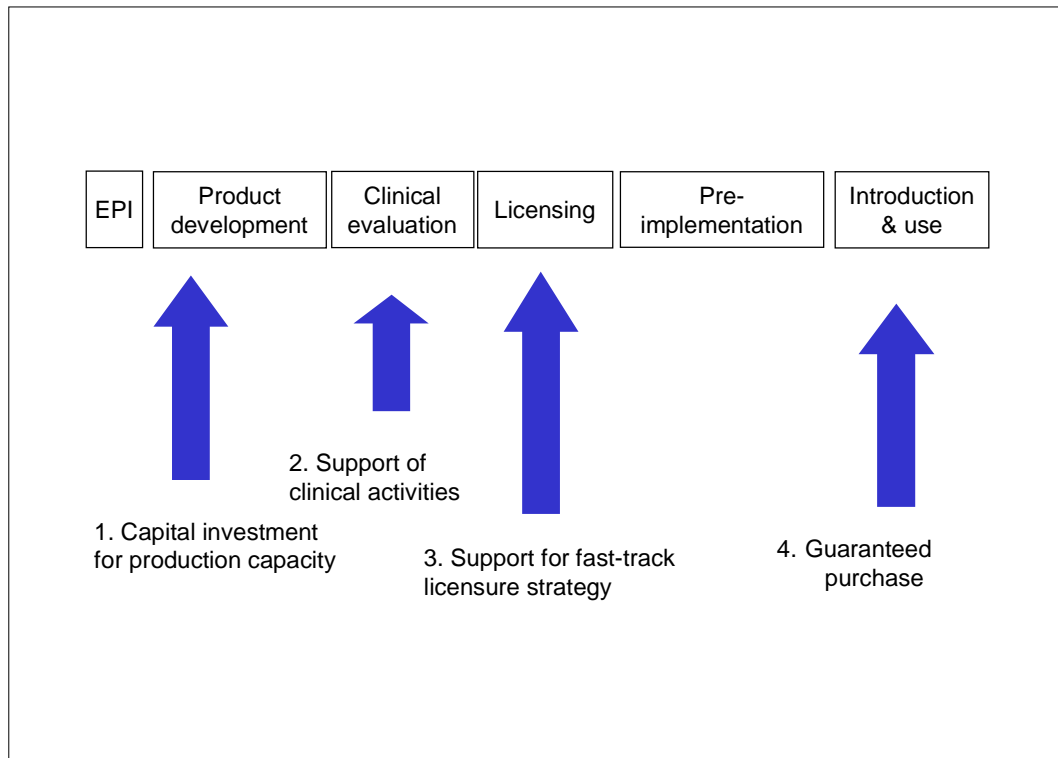
Delegates from Burkina Faso, Ethiopia, Mali, Niger, Nigeria, Saudi Arabia, Sudan, AFRO and EMRO had evaluated a variety of proposed strategies, and, together with multilateral organizations, vaccine companies and the scientific community, had affirmed the goals of this project.

MVP was launched in May 2001 with core funding of US\$ 70 million over the next decade from the Bill and Melinda Gates Foundation with the purposes of:

- developing a meningococcus A/C conjugate vaccine and evaluating it in Africa;
- creating a pathway for the licensure of vaccine which would be used largely in Africa;
- assuring production in sufficient volume to meet projected needs;
- constant monitoring to assure the effectiveness and safety of the intervention;
- financing the procurement of vaccine through existing or global programmes;
- introducing the vaccine through mass and routine immunization in synergy with other public health programmes.

MVP would meet these goals by developing contractual relationships, characterized by realistic milestones and timelines, with vaccine companies. MVP was also developing a comprehensive package of activities for 2002, including the development of a fastest-track licensing clinical development plan, the creation of alternative licensing pathways for products that might not be registered in the country of production, the standardization and validation of serological assays, recommendations for quality control and production of meningococcal conjugate vaccines, the development of a demand-forecasting database, the establishment of surveillance networks and laboratory capacity in the meningitis belt, assessment of the socioeconomic impact of meningitis epidemics and the development of a comprehensive regional plan with AFRO for the introduction of these vaccines. Meanwhile the GAVI Financing Task Force was advising the project on potential mechanisms for ensuring the appropriate supply of vaccine. Finally, the GAVI Research and Development Task Force would hold a meeting in Africa with the objective of enumerating the local research and development activities required to achieve the MVP goals.

**Figure 3: The meningitis vaccine project partnership: approaches to stimulate commercial interest**



### ***Discussion and issues***

#### **Surveillance**

Concern was expressed about the possibility of replacement disease through capsular switching. It was felt that surveillance for defining incidence and serogroup prevalence and ongoing surveillance for replacement were important. Dr Jodar explained that efforts to get a system in place for better surveillance for meningococcus and other bacterial meningitis was being undertaken. Early detection of an epidemic caused by serogroups other than A/C, such as W135 *N. meningitidis*, would require rapid changes in control strategies. Longitudinal surveillance was needed because recent data suggested that, in some settings, meningococcal epidemics caused by different serogroups could overlap. It was also desirable to gather further information on the serogroups causing endemic disease in Africa so as to gain an improved understanding of circulating strains. This information would also help towards an understanding of circulating pathogenic strains and towards ensuring that new serogroup-specific conjugate vaccines were optimally formulated to control first epidemics and then endemic disease in countries of the meningitis belt.

Because correlates of protection for meningococcus were well defined it was hoped that a conjugate vaccine would be licensed on the basis of immunogenicity data without the need for a double-blind randomized efficacy trial. After licensure the first step would be a pilot introduction strategy in one or two countries where assessments would be made of such matters as the duration of immunity, herd immunity or impact on disease incidence. Preparation for these trials would require the surveillance system to be strengthened.

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Surveillance for serotype switching was considered again in the plenary session. Dr David Salisbury explained that although there were concerns about the promiscuity of meningococcus in exchanging genetic material, as yet there was no evidence that the meningococcal serogroup C conjugate vaccine had caused capsular switching. Nevertheless, it was essential to have good follow-up of the molecular epidemiology of the disease in order to ensure that no serotype switching was occurring.

### **Production capacity and guaranteed purchase**

During the session on innovation, Dr Jodar explained that WHO and partners were working hard on the introduction strategy and on developing a credible forecasting model on demand and needs in order to have meaningful negotiations with vaccine companies.

With regard to guaranteed purchase of a certain number of vaccine doses, Dr Jodar explained that nothing had been decided and that several financing options were being analysed through the GAVI Financing Task Force in order to ensure an appropriate supply of vaccine following licensure.

### **Model partnership**

The project had worked so far, in that generous funds to start it had been obtained. However, it was agreed that there were uncertainties ahead. Although the subject had been deeply prestudied by WHO, PATH and partners, certain problems would have to be solved downstream.

SAGE recognized that the project was a model for successful public and private sector partnership. Although not “business as usual”, the project merited strong endorsement.

### ***Recommendations***

1. SAGE endorses the strategy of the meningitis vaccine project and commends the broad alliance that has made it possible. SAGE commends the early involvement of African countries in the project and emphasizes the critical importance of a public-private partnership as a means of accelerating the development and introduction of vaccines specifically targeted at developing countries. SAGE suggests that this may serve as a model for other vaccine development projects.
2. SAGE applauds the current initiative on bacterial meningitis surveillance undertaken by AFRO and recommends expansion to all countries in the Region and consideration of similar approaches for other regions (e.g. EMRO). These should include the collection of well-designed epidemiological data, the establishment of regional laboratory capacity for typing/subtyping bacterial meningitis pathogens (specifically meningococcus and pneumococcus), and the use of international reference laboratories for additional characterization of appropriate strains.

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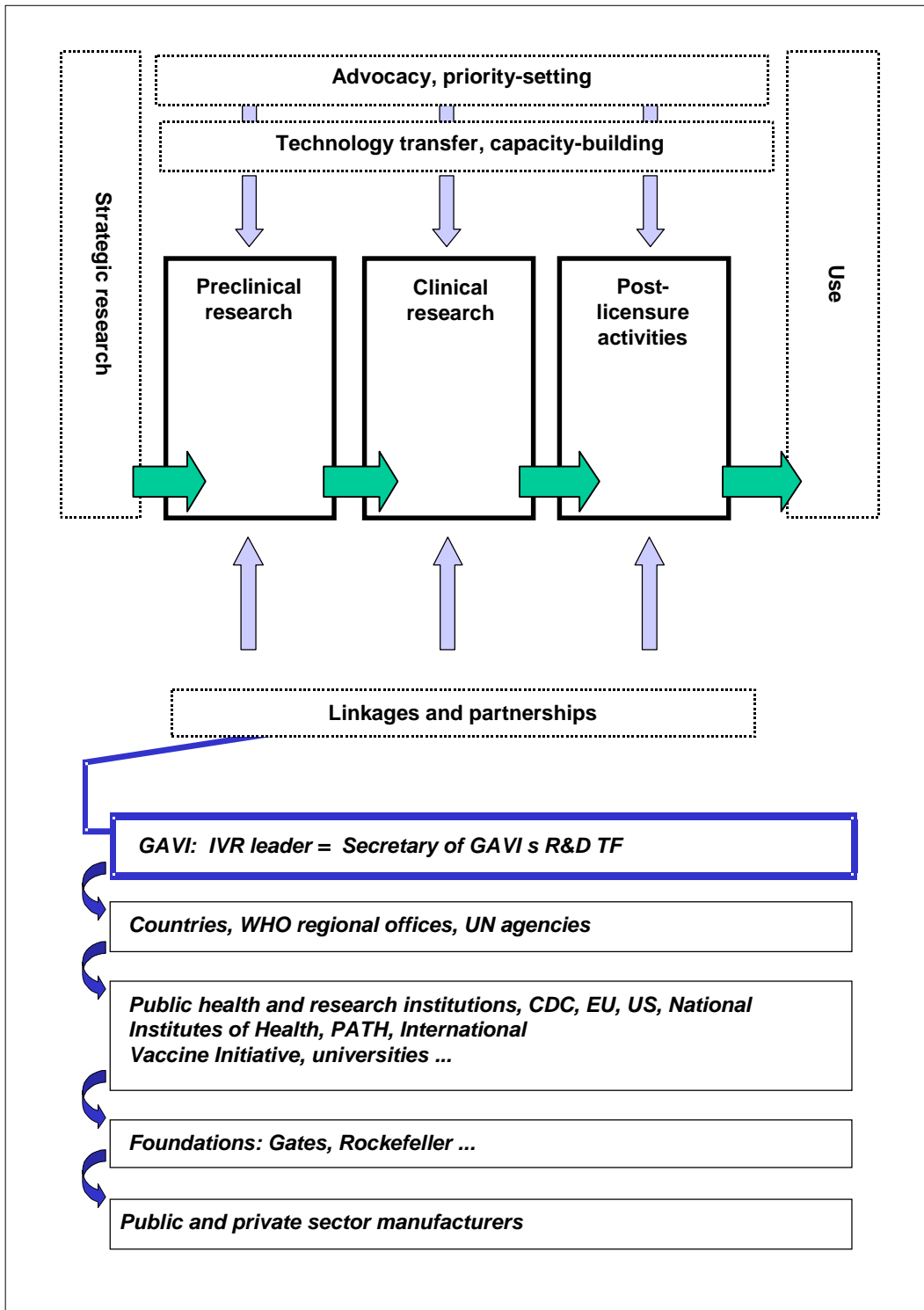
## 2.8 The WHO Initiative for Vaccine Research and its interaction with other vaccine R&D initiatives

### *Presentation (T. Aguado)*

The Initiative for Vaccine Research (IVR) represented a synergy of the vaccine research and development activities of WHO and UNAIDS. IVR provided guidance and facilitates international research on vaccines of public health importance, particular consideration being given to the needs of developing countries. It was the key international body responsible for drawing together the necessary expertise and efforts to address worldwide vaccine priorities and gaps. The research and development activities of IVR were cross-sectional, spanning preclinical, clinical and postlicensing issues (figure 4). The disease focus was also broad, including platform technologies (such as improved delivery systems), global targets (HIV, malaria, tuberculosis, rotavirus, pneumococcal disease), and diseases that usually received low priority (leishmaniasis, dengue, human papillomavirus).

IVR's role was not primary research but prioritization, coordination and guidance. Therefore, IVR did not see itself as being in competition with the various other agencies devoted to specific aspects of vaccine research and development, but rather in a more central overarching role. Such a structure was critically dependent on links and partnership both within and outside of WHO. In-house liaisons included all the teams in V&B, all entities of the WHO Communicable Diseases Cluster, UNAIDS and the AIDS programme of WHO. As a WHO entity, IVR had a particular responsibility for incorporating developing countries into the flow and exchange of information. Links with regional and country offices were therefore indispensable. With regard to external partnerships, IVR provided interested public and private sector agencies and organizations with a single, easily identifiable WHO counterpart. A special liaison existed with GAVI: the IVR coordinator had been designated Secretary to the GAVI Task Force on Research and Development.

Figure 4: IVR organization and links



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## ***Discussion and issues***

SAGE members requested information on how IVR's partnerships were working. Using the example of IVR's partnership with PATH on the meningitis vaccine programme for Africa, Dr Aguado explained that the two organizations were combining their respective strengths in order to bring forward the availability of serotype A meningitis vaccine.

The relationship between IVR and GAVI in the area of research and development was discussed. SAGE noted that GAVI had identified certain vaccine research and development projects that were quite advanced and therefore had a marginal risk of failure. While recognizing that success in these areas would lend GAVI credibility and allow it to tackle more risky projects later, SAGE expressed concern that in the medium term this strategy would lead to the neglect of upstream research of relevance to developing countries. Dr Aguado explained that while IVR was an important partner in GAVI and acted as Secretariat for its Research and Development Task Force, IVR's objectives were broader than those of GAVI and its priority diseases included some not in the GAVI portfolio, including those requiring upstream research.

## ***Recommendations***

1. SAGE emphasizes the pivotal position of IVR vis-à-vis developing countries, which distinguishes it from other organizations involved in vaccine research and development. This special role includes a continuing obligation to focus on orphan/under-addressed vaccines and to promote approaches that may be particularly appropriate for use in developing countries. Furthermore, IVR can have a broader focus and a longer time perspective than the GAVI Research and Development Task Force.
2. SAGE endorses the IVR concept and, in particular, the increased emphasis on exploring public-private partnership approaches to accelerating the development of vaccines, as in the meningitis vaccine project for Africa.

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# 3. Immunization systems

*Chair: Dr M.S. Ali Jaffer*  
*Rapporteur: Dr A. Kraigher*

## 3.1 Strengthening immunization services

### *Presentation (J.-M. Olivé)*

Five key steps for strengthening immunization systems were endorsed by SAGE 2000. The conceptual framework used for any health intervention had been rephrased to suit immunization services: sustainable financing, building institutional and human resources, management, and operations, the latter with five established components.

Problems, strategies and tools had been defined for each of the four areas. In particular, it was considered important to address the remaining gaps in the accessibility of vaccines and outreach services.

Dr Olivé presented the plan of work, which included:

- *sustainable financing*: appointment of immunization advisers, support for ICCs and the multiyear plan of action;
- *advocacy*: a campaign aiming at reducing dropout rates;
- *training*: updating of existing tools, relying much on regional institutions to strengthen capability in the regions;
- *management*: development of a tool for data collection analysis at local level carried out with the GAVI Task Force on Country Coordination;
- *operations*: improving access with the help of an officer dedicated to this purpose; raising coverage; testing a dropout rate tool in a few countries and implementation in selected countries; finalizing the development of a safety assessment tool to be implemented in selected countries.

### *Discussion and issues*

It was felt that there was a need for innovative solutions to improve outreach, reduce dropout rates and develop the necessary human and financial resources for more effective immunization systems. There was also discussion of supply issues and the introduction of AD syringes.

### **Outreach and increased coverage**

New outreach concepts that would change the face of routine immunization were considered. The question was raised as to how this would be observed at regional and country level.

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Poor outreach had been identified as an important problem. Outreach services did not exist at all in many countries. It was desirable for such services to operate as a complement to fixed routine immunization. There was consequently a need to define strategies for outreach services. Scarce resources and funds meant that there was also a major need for advocacy.

Dr Olivé said that V&B could conceivably perform analyses of dropouts in order to pinpoint managerial problems that might be solved without extra financial input.

It was important to involve communities. Discussions on how the more stable vaccines, such as tetanus and HepB, could be left in communities, focused on the need for appropriate simple technologies, e.g. Uniject™, that would allow administration by health workers other than the most highly trained.

### **The impact of polio eradication**

Increased capitalization on the polio eradication initiative was discussed. Such vertical initiatives would be of great benefit to immunization services. The possibility of linking up opportunities and funding to renew cold chain capacity was raised. The establishment of ICCs purely for polio eradication instead of according them a broader mandate represented a missed opportunity.

### **Funding**

The question was raised as to how improved ways of increasing funding for immunization might be identified. It was felt that WHO could be more proactive with advice to health ministries on freeing funds for immunization through debt relief. Tools that helped health ministries to negotiate with their finance counterparts could be important.

### **Management**

Decentralization meant that immunization services managers would have to manage human resources, budgets, projects, communications, advocacy and the cold chain. This implied that a broader approach was necessary to the improvement of human resources through training at the local, regional and national levels. It was suggested that there had been a concentration on the quality of data instead of adopting a wider approach.

### **Supply issues**

It was felt that there should be a closer link between supply forecasting and provision. The question was raised as to how a global capacity could be built up for supplying AD syringes in the quantities that would be needed in 2003.

Dr Milstien gave answers to several questions in a brief outline of activities. A project on training in vaccine management was being piloted in Africa. The issues being examined included demand forecasting, the cold chain, and how vaccines were being managed. The project was contributing significantly towards changes at country level and the identification of major gaps in the planning process.

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Through the GAVI Financing Task Force a series of tools had been developed which would be of value in many countries that lacked the capacity to deal with financing issues.

### ***Recommendations***

1. SAGE would like to draw attention to the need to find appropriate and innovative solutions in order to improve immunization coverage. Special attention should be given to improving outreach activities and reducing dropout rates.
2. SAGE emphasizes the need to capitalize on the polio eradication experience for strengthening immunization services.

### **3.2 Coverage**

#### ***Presentation (A. Burton)***

An accurate historical representation of coverage was important for assessing trends in the performance of immunization systems, determining the relationship between immunization service delivery and disease occurrence, and providing a framework for setting future goals. Three major considerations made the accuracy of immunization coverage important at the global level.

1. *Face validity.* Previous analyses had not only described the extent of missing reports but had also identified a variety of unusual patterns in reported data. Data lacking face value or plausibility, unsupported by reasonable justification, tended to cast doubt on the validity of other reported data.
2. *Accurate trends.* In some countries, recent estimates based on immunization coverage surveys showed markedly lower coverage than previous estimates based on administrative records. Further investigation indicated that coverage had been improving in these countries in recent years and that the previous estimates had probably been too high.
3. *Report on 1990 World Summit for Children goals.* In September 2001 the UN Secretary-General would indicate what progress had been made towards the goals set by the 1990 World Summit for Children. The results of this review would constitute the quantitative basis for the Secretary-General's report (see footnote 3 on page 2 of this report).

In 1998 these considerations led SAGE to request that V&B examine the completeness and quality of immunization coverage data reported to WHO. In 1999 WHO, jointly with UNICEF, began a systematic review of national immunization coverage from 1980 to 1999.

During the review additional data had been identified and a more consistent method for assessing levels of coverage had been used. In some instances, previous reports of levels of coverage had been updated, and this had led to more accurate and consistent estimates not only at the national level but also at the regional and global levels.

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## **Methods and process**

*Updating national reports.* The first step was to review and update data officially reported by Member States through the WHO regional offices in order to ensure that the WHO databases correctly reflected national data. The UNICEF database of immunization coverage was also used.

*Searching in the scientific literature.* Secondly, information on immunization coverage was sought from various other sources, primarily published surveys.

*Making draft estimates.* Draft coverage estimates for each country, year and antigen were made on the basis of the above data. Mr Burton explained that regional offices and, where possible, national experts, had also been consulted in order to obtain more detailed information. These consultations proved invaluable for a fuller understanding of the functioning of specific national systems.

*Reviewing by national authorities.* The draft estimates were sent to each national authority for review, comment and contributions. Communication with the national authorities was considered indispensable.

*Revising draft estimates.* The draft estimates were revised on the basis of the comments received from the national authorities.

*External reviewing.* The methods and findings were reviewed by a group of external experts with broad experience in immunization systems and survey methodology. The group supported the methods and recommended a series of future activities.

*Finalization, publication and dissemination.* The final estimates were communicated to the regional offices and national authorities and published in September 2001.

*Following through.* On the basis of the experience of this review, WHO and UNICEF hoped to work with regional offices and national authorities in order to improve the accuracy, precision, timeliness and usefulness of measures of immunization coverage at the local, national, regional and global levels.

## ***Discussion and issues***

- SAGE commended WHO and UNICEF for undertaking this work. It was pointed out that such activities represented a good example of constructive collaboration between the two agencies.
- It was suggested that although the work presented was a major step forward, additional analysis, stratifying the data further, should be undertaken. Stratified analysis should be undertaken not only between regions and countries but also within countries.
- SAGE agreed that countries with poor reporting should not be stigmatized. Care should be taken to maintain the distinction between the quality of immunization services and the quality of the data describing them.

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- Mr Burton emphasized that various technical issues were involved in accurately estimating coverage. For example, the size of a target population was often estimated on the basis of censuses done as much as 10 years previously and an underestimate could easily result in inaccurate coverage estimates. It was necessary for WHO to develop more sensitive measures of coverage in order to improve estimates not only at the global and regional levels but also at the national and local levels.
  - In some instances, WHO/UNICEF estimates might be at variance with national estimates and the difference might cast doubt on a country's eligibility for GAVI funding. Mr Burton explained that it was hoped to minimize this possibility through prior consultation with countries. To the degree possible, estimates were based on technical considerations, and GAVI requirements had not influenced the decisions. It was pointed out, however, that a small percentage difference was entirely acceptable.

### ***Recommendations***

SAGE notes with appreciation the methods that have been developed and the results obtained in the WHO/UNICEF review.

1. SAGE recommends that further development of these and other appropriate measures for determining immunization coverage at the local, national, regional and global levels be encouraged.
2. Critical points raised during the discussion of this programme have been recorded.

### **3.3 Steering Committee on Immunization Safety**

#### ***Presentation (A. Kraigher)***

In October 2000 the Steering Committee on Immunization Safety reviewed the strategies, targets and priorities of the immunization safety priority project and made a series of recommendations, with particular reference to advocacy and the building of partnerships. It also stressed that safety criteria should be given as much prominence as coverage in the GAVI objectives and that disbursements from the Vaccine Fund should be linked to safety criteria. In this respect the injection safety assessment tool could be used as a quality indicator.

A number of recommendations had been made in response to the UNICEF–WHO–UNFPA joint statement that by the end of 2003 all countries should be using only AD syringes for immunization. V&B had prioritized activities that would facilitate the changeover to these syringes. The joint reporting form would be used for assessment and monitoring.

About 50% of countries planned to introduce AD syringes in 2001 and 90% used them for campaigns.

Another set of recommendations dealt with waste disposal. It was recommended that vaccine donors should be encouraged to supply sufficient funds for this purpose.

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It was recommended that safety issues become an important part of training. A system for quality control of AD syringes and other equipment should be developed, and indicators were necessary for monitoring progress in immunization safety.

### ***Discussion and issues***

#### **AD syringes**

The target that all countries should be using AD syringes by 2003 was discussed. The question arose as to whether there were cost and supply constraints associated with this goal. More problematic, however, was how countries would manage the shift to AD syringes and cope with possible parallel systems. Increased support and guidance for countries was required and plans of action had to be prepared.

Dr Duclos pointed out that the issue of cost should be looked at in terms of cost-effectiveness. The differential cost between AD syringes and standard disposable syringes was becoming minimal compared with the price of the vaccine and other costs. At the same time, because of booming demand, there was an increasing need to broaden production potential, and this would create a downward pressure on prices. There was initial resistance from many countries that manufactured other types of syringe but they were expected to switch to AD syringes.

In some countries using sterilizable syringes, notably Indonesia and Namibia, there was resistance to switching to AD syringes for reasons of cost. A plea was made that the international community should find some way of supporting these countries.

The question arose as to why AD syringes should be used for immunization but not for other medical care. It was suggested that vaccine providers had a moral and legal responsibility to make immunization safe.

#### **Waste management**

The group recognized that waste management was an important issue. Many countries were preparing for the shift to AD syringes. However, disposal had not been planned. Some options existed but they had to be demonstrated and further tested. There was no universal solution for waste management, and existing solutions were limited to certain regions.

Several speakers suggested that the management of injection wastes should be integrated into waste management for the whole health system. Unfortunately, many countries, e.g. in Africa, did not have the funds for this, and a way should be found to support them.

Dr Duclos said that current assessments showed that waste disposal was a common problem associated with immunization. Both WHO and UNICEF, in trying to help countries with immunization, had to consider not only the injection of the vaccine or the product in the vial but a comprehensive process that went right to the disposal stage.

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### **Safety indicators**

An injection safety assessment tool had been developed and used. Dr Duclos said that countries were willingly undergoing assessments by means of this tool as a stepping stone towards improvement. These assessments had shown that a major problem was associated with the reuse of standard disposable syringes. The joint reporting form would also provide appropriate information on safety. In addition, the inclusion of safety in routine data collection had been considered. Dr Duclos said that awareness of safety should become important at every level, including the district and local levels.

### **Vaccine vial monitors**

While it was commendable to advocate that all children be immunized *safely*, it was essential not to drop the emphasis on *potency*. Vaccine vial monitors (VVMs) should not be omitted from the picture. SAGE was assured that UNICEF remained committed to VVMs. They were part of the policy of involving parents in monitoring vaccination. It was also important that VVMs accompany vaccine left in villages so that its potency could be monitored.. Further discussion was needed on making VVMs a commercial reality. UNICEF was in close touch with WHO about this issue.

### **Recommendations**

1. SAGE endorses the recommendations made by the Steering Committee on Immunization Safety at its second meeting held on 26 and 27 October 2000.
2. SAGE recommends that, in order to reach the target that all countries use AD syringes by 2003, appropriate support be given to countries for the transition to these syringes, with particular reference to sterilizables, and that there be wider endorsement of the joint statement of WHO, UNICEF and UNFPA.
3. SAGE recommends that waste disposal be given sufficient attention and encourages WHO to work with UNICEF in order to achieve this, giving special attention to environmentally friendly options.

### **3.4 BCG vaccine – the next 10 years**

#### ***Presentation (C.J. Clements)***

BCG vaccine was one of the longest-used vaccines and was still administered in most countries.

It was a low-cost, stable vaccine that left a scar useful for monitoring and it exerted some protection against leprosy. Most importantly, it worked well in infants against invasive tuberculosis. However, it was a controversial vaccine. *How* it worked in infants was not known. Nor was it known *if* it worked in adults. It gave mild side-effects, presented the usual potential risks on being reconstituted, and had caused a small number of deaths of HIV-infected people. There were different strains of BCG and there was no single correlate of protection. Furthermore, a third of BCG vaccine was produced by local producers in the absence of quality assurance.

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Nevertheless, as tuberculosis was a rising threat to public health, BCG was still the best defence for babies.

Notwithstanding the problems associated with the continuing use of BCG, it was needed until a new anti-tuberculous vaccine was tested and available, and this would not be for at least another decade. High-risk countries should not stop using BCG.

Unfortunately, the uncertain circumstances surrounding BCG and the costs of modernizing old manufacturing plants were undermining commercial production, and the number of suppliers had fallen dramatically. It was desirable to take steps that would guarantee a continuing supply.

### ***Discussion and issues***

#### **Encouraging continued production**

There was general agreement that the administration of BCG vaccine should have strong support and that it should continue to be used routinely until a new vaccine became available in the next decade.

It was considered important to create an environment in which manufacturers were encouraged to continue producing BCG vaccine. Its availability was at risk because of the stringent requirements that had to be placed on producers and because of uncertainty about the future.

#### **Vaccine quality**

The possibility existed of beginning to improve the quality of BCG vaccine because the gene had been sequenced. It was necessary to investigate the differences between the various strains by means of molecular techniques and to improve the strains through the application of genetic science. Dr Griffiths pointed out that although extended control of NRAs was important in assuring quality, the regulations were old and the assays used for quality control needed updating.

#### **Vaccine wastage**

Questions were raised about the wastage of 95% of the vaccine. No solution seemed to be available. Requirements for a different vial size might deter manufacturers, as the vial represented a major part of the cost. Moreover, since the actual vaccine cost so little the wastage was generally considered insignificant.

#### **Tuberculosis Control Initiative**

There was a need for better coordination between BCG vaccination and the Stop TB Initiative. It was desirable for WHO to try to convey the message that BCG was still the only defence against invasive disease in neonates. It was agreed there was no point in giving booster doses. Meanwhile, many industrialized countries were moving to selective use. The recommendations of IUATLD should guide countries that were considering discontinuation of the vaccine.

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## ***Recommendations***

SAGE strongly endorses the continued use of BCG in national immunization services as a means of minimizing the harmful effects of tuberculosis infection in the first year of life. SAGE recommends that the vaccine be used until there is an alternative improved anti-tuberculosis vaccine. This is probably at least a decade away. In the meantime, national immunization services are encouraged to maintain the highest possible coverage of infants.

1. SAGE endorses the need to maintain an adequate supply of high-quality BCG vaccine. This will entail working closely with industrial partners.
2. As increasing numbers of industrialized countries are likely to consider shifting from routine to selective use of BCG during the next decade, the recommendations of IUATLD are considered to be the appropriate guidelines for countries thinking of discontinuing BCG vaccination.
3. SAGE reinforces WHO's recommendation that no booster dose of BCG be given, as there is no evidence that booster doses are efficacious.

### **3.5 Thiomersal**

#### ***Presentation (N. Dellepiane)***

Theoretical concerns had been raised over the use in vaccines of the organomercuric preservative, thiomersal, and a policy of elimination, reduction or replacement of thiomersal in paediatric vaccines had recently been introduced in the USA and the European Union (EU).

Experience with methyl mercury ingested with food had shown that low doses of mercury can cause hypersensitivity and that high doses can cause neurological and nephrological toxicity. WHO had set the safety limit for ingested methyl mercury at 0.5 micrograms, leaving a generous margin of error. Thiomersal was an ethyl mercury compound for which there were no guidelines for safe exposure, and studies had not shown any neurological effects. On the basis of the safety levels established for methyl mercury, however, three doses of DTP, Hib and HepB in the first 14 weeks of life would, theoretically, exceed the safety limit.

Consultations between WHO and three prequalified manufacturers had shown differences in the implementation of new policy, as well as some common features. A policy of elimination, reduction or replacement of thiomersal in paediatric vaccines had implications for vaccine quality, the WHO multidose vial policy, and future vaccine supply.

Manufacturers generally agreed that complete elimination of thiomersal could be obtained for some monodose vaccines, although the changes could be costly. In the case of multidose vials it was believed that some preservative was essential, and 2-phenoxyethanol was the main alternative candidate. Changing the preservative would raise regulatory issues that could take up to five years to resolve. Efficacy might have to be redemonstrated in new clinical trials.

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## ***Discussion and issues***

WHO was extremely anxious to preserve the production and availability of vaccines. Industry was expecting clear signals from WHO on the thiomersal issue, as had been confirmed by informal consultations with some manufacturers during the first half of 2001.

### **Substitution qualifications and implications**

There was general agreement that manufacturers should be encouraged to remove thiomersal from monodose vaccines, even though this was based merely on theoretical concerns. On the other hand it was considered that there should be more caution about encouraging its removal from multidose vials, at least until studies showed that alternative preservatives were effective and regulatory procedures were in place.

Whereas the position of the USA was to eliminate or substitute for another preservative as soon as possible, the EU recommended that manufacturers consider elimination, reduction or substitution of thiomersal in accordance with quality and efficacy.

It was suggested that WHO should review various strategies that would help to reduce the intake of thiomersal. These included the use of Uniject™ monodose cartridges and greater use of combination vaccines. It was suggested that equity in immunization might be compromised if concerns about thiomersal were to be resolved by a move to more expensive technologies.

The need for caution was underlined during the plenary session, particularly as the reality of multidose vials would remain for some considerable time.

Dr Greco stated that manufacturers were working hard towards removing thiomersal from vaccines. However, changing to a less proven preservative had supply, cost and safety implications. Dr Folb confirmed that the safety advisory committee endorsed the position that there was no scientific basis for concern.

### **Regulatory procedures**

The decisive role of NRAs was discussed. Thiomersal elimination and substitution had created an area of uncertainty with regard to regulation by NRAs. One country might look on a vaccine in which the level of thiomersal had been reduced or in which thiomersal had been replaced with another preservative as a new product and might require trials, while another country might not. It would thus be constructive to arrange a workshop to define criteria on changes in preservative and related matters.

### **Safe intake criteria**

SAGE agreed that WHO should consider redefining the criteria for intake so that they were more relevant.

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## ***Recommendations***

SAGE considers that the benefits of vaccination with thiomersal-containing vaccines far outweigh the risks, if any, of exposure to thiomersal in vaccines. However, as the consumption of mercury of any sort is considered less than optimal, it is considered wise to promote efforts towards the reduction of the thiomersal content of vaccines whenever feasible. WHO is also encouraged to undertake activities related to the assessment of risk from thiomersal-containing vaccines and of the safety of using vaccines with reduced amounts of thiomersal. SAGE makes the following recommendations.

1. WHO should examine the options for redefining its criteria for maximum safe intake levels of mercury in the context of thiomersal in vaccines.
2. V&B should work with manufacturers towards the reduction of thiomersal in monodose containers and in monodose prefilled devices.
3. V&B should determine whether vaccines with reduced amounts of thiomersal, or vaccines containing alternative preservatives, can be used safely in the context of the current multidose vial policy.
4. V&B should review programmatic strategies relating to the use of multidose presentations in high-use settings.
5. V&B should convene a meeting with national regulatory authorities in order to develop criteria for reviewing products with changes in preservative content.

### **3.6 BSE/TSEs and vaccines**

#### ***Presentation (E. Griffiths)***

Bovine spongiform encephalopathy (BSE) had first appeared in cattle in the United Kingdom in 1986. By the 1990s it had become a major epidemic and had spread to a few other countries. In 1996, in the wake of this epidemic, there were 10 cases of an unusual form of Creutzfeldt-Jakob disease (CJD) in the United Kingdom and this was linked to the possibility that the patients had eaten infected beef. Since then the number of cases of the new disease, called variant CJD, had exceeded 100 in the United Kingdom and there had been three cases in France. The prion hypothesis as to the cause of the disease held that the agent of BSE and variant CJD was not self-replicating but was a protein with an abnormal conformation that influenced normal counterparts around it to develop the same abnormality, a process that took a long time. This agent could cross the species barrier and was unaffected by chemical and heat treatments that normally disabled viruses and other organisms.

The major concern had been how to minimize the transfer of this agent to humans through food, blood, blood products and vaccines. Precautionary measures had been taken to prevent the theoretical possibility of transmitting variant CJD through blood products or vaccines (or other biologicals) whose manufacture involved the use of human plasma or bovine materials at some stage. Particular attention had been given to excluding from vaccine production all categories of materials known to carry TSE infectivity. According to the safety regulations, even those bovine materials not known to carry any infectivity, such as bovine serum, should not be obtained from a BSE-infected country, herd or animal. The safety of vaccines and other biologicals

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in respect of TSEs was thus considered to be assured by a combination of appropriate geographical sourcing of materials and the exclusive use of tissues with no demonstrable infectivity. Precautionary measures had also extended to the working seeds. For example, an Hib vaccine was taken off the market because the working seed for the organism had been produced using brain-heart infusion medium. Vaccine was now manufactured by using a new working seed produced using another medium. There had, however, been caution about changing master seeds. This was because the risk in this case was extremely remote and the process of changing to a new master seed raised other real and uncertain risks for vaccine safety and efficacy.

All the major regulatory agencies agreed that the risks of transmitting TSEs via biological products were theoretical and negligible. Among the reassuring findings was the fact that, after five years, healthy cattle given serum from BSE-infected cattle had not shown any signs of infection. In addition a recent analysis of the age-related distribution of variant CJD cases in the United Kingdom showed no evidence of an association with vaccination. Nevertheless, in view of the rapid developments in this area, WHO's Expert Committee on Biological Standardization (ECBS) recommended that WHO should review the situation and update its 1997 recommendations. WHO was also developing and evaluating international reference materials for the diagnosis and study of human TSEs. This was considered by ECBS to be a priority activity. Furthermore, a multiagency technical consultation on BSE, public health and trade would consider broader aspects such as infectivity, testing programmes and public health policies.

Dr Griffiths said that risk assessments would probably be introduced in order to indicate countries from which bovine products could safely be obtained.

### ***Discussion and issues***

It was agreed that BSE/TSEs had important implications for vaccine safety. Impressive collaboration between WHO and NRAs had involved risk evaluation, assessment of the products on the market, and the development of a strong international consensus on risks and how to avoid them.

### **Safe supply of materials**

It was agreed that the risk of acquiring variant CJD from vaccines was negligible. Nevertheless, there should be constant vigilance and ongoing review of the use in vaccine production of materials derived from ruminants and human plasma.

Dr Clements asked if it was possible to be sure that bovine materials did not come from countries where there was BSE. Dr Griffiths explained that documents accompanying supplies made it possible to check their origin. It was a criminal offence to falsify supply information. Initially, the "paper trail" had sometimes been less rigorously followed with respect to seed materials and a number of vaccine manufacturers had been asked to replace their working seeds. Manufacturers were now automatically producing new seeds from materials that had no demonstrable infectivity and had been appropriately sourced.

It was suggested that an important aim of research would be to find synthetic substitutes with a view to abandoning, where possible, the use of animal materials in the manufacture of vaccine.

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## **Role of NRAs**

The group agreed on the importance of NRAs in monitoring the safety of materials used in vaccine production. It was necessary to bear this in mind during the consultations on BSE/s and vaccines. At the same time it was desirable to consider the predicament of NRAs in assessing products. There was a wealth of experience to be shared. It was suggested that an ongoing position statement would assist NRAs in their assessments of products and avoid much unnecessary replication of work.

## **Regulations on geographical sourcing**

In particular, WHO should help to clarify which were BSE-positive or BSE-negative countries and which were high-risk or low-risk countries. It might be argued that any country where bovines were allowed to eat offal would be in a risk category.

During the plenary session Dr Salisbury stressed the need for complete clarity on the geographical sourcing of materials. If a country declared itself BSE-free the credibility of this depended entirely on the quality of surveillance and risk assessment. It was far more important that no bovine materials be used if they could be replaced.

## **Public confidence**

Even if experts were convinced that the risk was negligible, public perceptions about safety remained extremely important. It was necessary to communicate properly and convincingly to and with the public. Dr Griffiths reminded the meeting that public perceptions of safety could severely damage an immunization service, as happened in the United Kingdom with whole-cell pertussis vaccine.

## **International reference materials**

It was important to complete the development and evaluation of international reference materials for the diagnosis and study of human TSEs.

## ***Recommendations***

1. SAGE endorses the activities of WHO in the area of TSE/BSE vaccines.
2. The planned review on medicinal and other products in relation to human and animal TSEs should focus, in particular, on the use in vaccine production of bovine serum, other ruminant-derived materials and products derived from human plasma. WHO is encouraged to keep this issue under constant review.
3. SAGE recommends that adequate resources be made available in order that the development and evaluation of international reference materials for the diagnosis and study of human TSEs be completed as soon as possible.

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## 4. Accelerated disease control

*Chair: Dr M. Dahl-Regis*  
*Rapporteur: Dr D. Kunasol*

### 4.1 Polio eradication

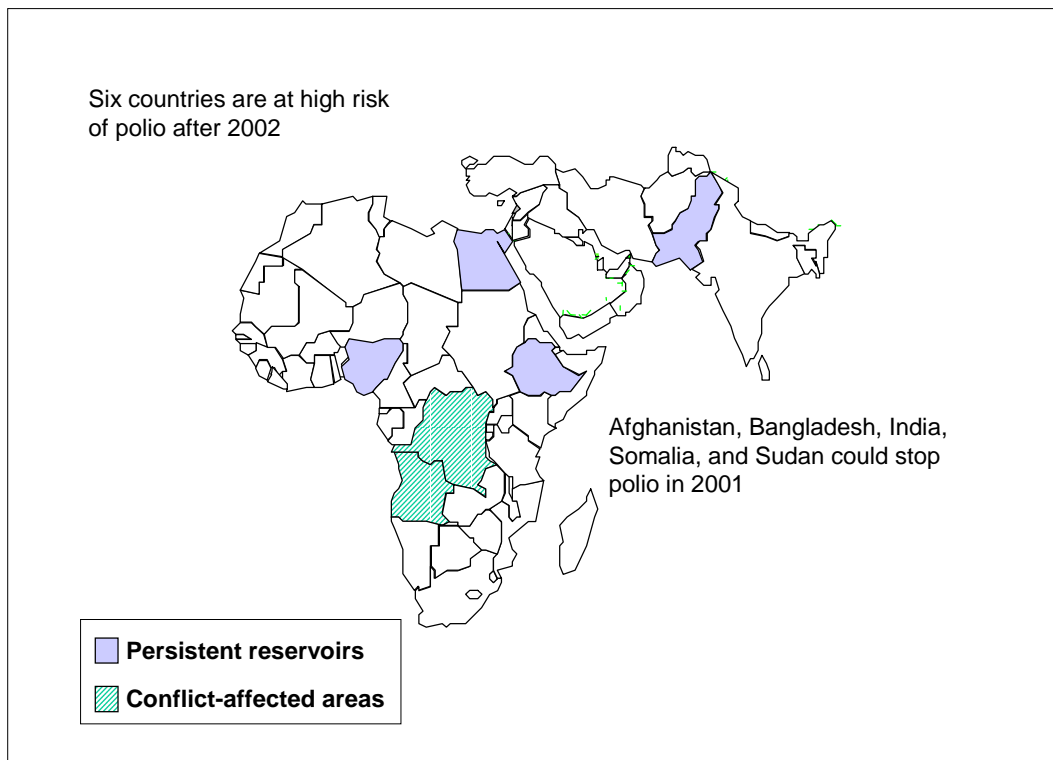
*Presentation on the impact of acceleration and priorities for 2001–2002*  
*(B. Aylward)*

Tremendous progress was made in poliomyelitis eradication between 1999 and 2000, demonstrated by the 20% increase in the sensitivity of surveillance for acute flaccid paralysis (AFP), the 33% reduction in the number of countries where the disease was endemic, and the 60% decline in the number of confirmed cases. Type II poliovirus was last detected in October 1999. This progress was the result of continued extensive efforts by countries in which polio was endemic, working in partnership with an international coalition of organizations, spearheaded by WHO, Rotary International, CDC, and UNICEF.

The conclusions of TCG at its meeting in May 2001 were reviewed. Particular attention was given to the TCG recommendations on: (i) the geographical and strategic priorities for interrupting wild poliovirus transmission (strategies to sustain access, maintain political commitment, and close the funding gap of US\$ 400 million); (ii) the challenges and priorities for the period 2001–2002; and (iii) the polio end-game (defined as laboratory containment, the certification process and the eventual cessation of the use of oral polio vaccine (OPV)).

The current key targets for the polio eradication initiative were to reduce the number of countries where polio was endemic to below 10 by the end of 2001, and to interrupt polio worldwide by the end of 2002. In order to achieve this the quality of activities in all remaining countries of endemicity, particularly Angola, the Democratic Republic of Congo, Ethiopia, Nigeria, and Pakistan had to be enhanced, aggressive mopping-up had to be carried out in countries of low transmission, and surveillance had to be brought to the required standard worldwide. Figure 5 shows the geographical priorities.

**Figure 5: Geographical priorities for the polio eradication initiative**



***Presentation on OPV cessation and the post-immunization era (D. Wood)***

SAGE reviewed in detail the WHO programme of work that had been endorsed by TCG for the post-certification era. This programme would provide the information needed for informed decisions about: (i) how to safely stop polio immunization; and (ii) how to minimize the risk of, and respond to, polio reintroduction in the post-immunization era. In reviewing this programme, SAGE took the deliberations of TCG into account as well as additional data on the challenges and risks to the successful conclusion of the global eradication initiative.

TCG had confirmed the criteria for determining when OPV immunization should stop: (i) certification of eradication of wild polioviruses (absence of wild poliovirus for at least three years in the presence of excellent surveillance); (ii) laboratory containment (finding and controlling wild poliovirus in laboratories and production facilities); (iii) evidence that vaccine-derived viruses would circulate for only a short period (when OPV cessation policies were implemented); and (iv) the existence of a global vaccine stockpile. The global action plan of 1997 for laboratory containment would be reviewed in order to develop risk assessments of potential infective material and make recommendations for the validation of high-containment laboratories.

Dr Wood emphasized that it was necessary to plan as though vaccine-derived poliovirus circulation would continue unless effective OPV cessation policies were implemented. On Hispaniola in 2000/2001 there had been 17 cases of paralysis due to a circulating Sabin type I vaccine-derived poliovirus and in Egypt there had been 32 cases of Sabin type II vaccine-derived poliovirus between 1982 and 1993, showing that, on rare occasions, vaccine-derived polioviruses could establish sustained chains of transmission.

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The potential immunization policy options for the post-eradication era were identified as follows.

1. Continuation of OPV immunization indefinitely (not supported by TCG).
2. Development of new strains to replace Sabin strains (not supported by manufacturers and regulators).
3. Discontinuation of OPV in an appropriate way without offering a replacement polio vaccine.
4. Replacement of OPV with inactivated polio vaccine (IPV) for a limited period.
5. Application of a mixture of strategies.

The latter three potential policy options were still being evaluated. Primary research issues included:

- how to protect populations while stopping OPV in the presence of vaccine-derived poliovirus circulation;
- how to minimize the risk of poliovirus reintroduction from laboratories and long-term excretors and how to respond if such an event were to occur.

It was important to further evaluate the risk of circulation of Sabin-derived viruses. In addition, an outbreak response strategy was necessary, as were vaccine stockpiles. The TCG would develop policy options for consideration by SAGE.

## ***Discussion***

### **Countries suffering emergencies**

In addition to the priority countries highlighted in the presentation, SAGE members reaffirmed the importance and challenges to polio eradication presented by countries experiencing complex emergencies, and were particularly concerned that special attention be given to polio eradication in Angola. It was noted that the problems associated with the implementation of surveillance strategies in these areas were often even greater than those related to supplementary immunization activities.

### **Funding gap**

The SAGE subgroup discussed the special importance of the funding gap to the overall success of the eradication initiative. Reference was made to the role of ICCs in mobilizing resources. Dr Aylward confirmed that much additional funding could be sought on a bilateral basis, and this was why it made good strategic sense to strengthen ICCs.

### **Polio end-game research**

Members stressed that progress towards the interruption of wild poliovirus transmission increased the need to hasten research on the polio end-game. The complex set of interconnected activities in the polio end-game had economic and other implications that required long-term planning. It was important that further high-quality collaborative research in this area be properly costed and supported.

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There was a limited number of potential policy options for stopping polio immunization. Members stressed that it was essential for WHO to ensure that countries did not make premature or epidemiologically inappropriate policy decisions before the information generated by research was available.

The possible role of IPV in the end-game had substantial unknown costs. Furthermore, there were still questions about the efficacy of IPV in interrupting the transmission of vaccine-derived polioviruses.

Vaccine manufacturers needed the greatest possible advance notice of potential scenarios for the use of polio vaccine over the next 10 years. This was particularly challenging as the scientific work that would influence policy recommendations was still in progress. WHO/UNICEF had to work closely with the manufacturers and perhaps develop new paradigms for managing the end-game supply of vaccine.

### **Surveillance and immunization response**

Surveillance of high quality was needed to ensure that any circulating vaccine-derived polioviruses could be detected as quickly as possible. The maintenance of such surveillance after certification would be a major challenge. It was essential to achieve timely publication of information on important vaccine-derived strains and to exchange information on them between the laboratories of the polio laboratory network.

If outbreak response strategies for the post-immunization era were used in highly susceptible populations they would have to reflect the possibility of different vaccine transmission characteristics.

### **Polio infrastructure for the broader health agenda**

The infrastructure and systems developed for polio eradication would be essential for advancing immunization in developing countries, particularly in respect of the measles mortality reduction and routine immunization coverage goals set for 2005.

### **End-game scenarios (plenary discussion)**

At the plenary session there was further discussion of the polio eradication initiative and, in particular, of the end-game.

Dr Miller noted that the option remained of *not* stopping immunization. This had been extensively discussed at a meeting of the United States National Academy of Sciences. Dr Aylward stressed the need to ensure that public positions put forward by SAGE reflected the best available evidence and majority opinion.

Dr Greco expressed concern that the time horizon for establishing a clear end-game policy kept moving. An increase in IPV capacity took between three and five years, and new combination vaccines, if needed, would only be available after five to seven years.

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In response, Dr Aylward reiterated that TCG had reviewed the events of 2000 and the Hispaniola outbreaks, and had clearly stated that OPV would be needed until at least 2010. However, some countries might consider introducing IPV into their national programmes before that time. WHO and UNICEF had put much effort into improving communications with manufacturers on these issues during the preceding year. There would be a meeting in late 2001 or early 2002 on factors affecting vaccine supply. More information would be available by mid-2002, including OPV scenarios until 2010 and IPV timeframes.

Professor Nossal urged SAGE to focus on industry's achievement in supplying billions of doses of OPV at a very low price, and called for continued communication.

Regarding the recommendation to review management and administrative support, especially at country level, Dr Salisbury noted that the Director-General of WHO had already called for such a review. This was in progress and would be presented to the WHO Executive Board in January 2002.

### ***Recommendations***

SAGE notes the tremendous progress made in poliomyelitis eradication, demonstrated by the reduction in the number of confirmed cases by 60% between 1999 and 2000.

SAGE endorses the recommendations of TCG for continued acceleration of polio eradication activities, recognizing that especially intensified efforts are required in the six countries currently at highest risk of continuing transmission after the end of 2002: Angola, the Democratic Republic of Congo, Egypt, Ethiopia, Nigeria, and Pakistan.

1. SAGE reaffirms that, in order to derive the maximum benefit from polio eradication, immunization should ultimately be stopped, and endorses the programme of work developed by the polio research steering committee under the direction of TCG. SAGE further reaffirms that adequate resources must be made available so that it can be rapidly carried out.
2. The urgent need to mobilize resources in order to close the estimated funding gap of US\$ 400 million for activities between 2002 and 2005 requires extraordinary efforts on the part of WHO at the highest level. Closing the funding gap must be an institutional priority, not one for V&B alone. Specifically, SAGE suggests the following approaches to closing the funding gap.
  - Although national ICCs have to address the entire immunization agenda, in the remaining countries of endemicity the ICCs should give priority to closing the polio funding gaps.
  - WHO should host a special donor event in late 2001 or early 2002 in order to launch the revised resource requirements for the period up to 2005.
  - GAVI should encourage the remaining countries where polio is endemic to use the Vaccine Fund to cover those elements of the national polio funding gaps that represent routine immunization infrastructure costs.

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3. SAGE recognizes that the immediate priority in conflict-affected areas must be to improve the quality of activities in accessible areas. WHO and partner agencies should give increased attention to overcoming the challenges posed in conflict-affected areas. The approaches adopted should include the following.
    - Political advocacy should be directed at increasing access to currently unreached children.
    - There should be a recognition that, compared with stable countries, these areas require increased per capita funding for effective strategy implementation.
    - Contingency plans should be developed in case access to children is further compromised by new conflicts.
  4. With the recent expansion of V&B's polio eradication infrastructure, particularly in terms of human resources, SAGE considers that the management and administration of these resources may need to be strengthened in some countries. SAGE recommends that WHO regularly review the performance of its management and administrative support for polio eradication and take corrective action as needed.
  5. Recognizing the importance of broad engagement of the scientific community in the polio end-game, WHO should review the mechanisms that the influenza network has established for rapidly sharing new virological data as they become available.
  6. In the course of revising the resource requirements for polio eradication up to 2005, WHO should ensure that the figures include the funding needed for the completion of research for guiding decisions on the cessation of immunization.
  7. Vaccine-derived polioviruses that have circulated in the population should be subjected to laboratory containment procedures similar to those used for wild polioviruses. Further work should be undertaken to ensure the collaboration of the research community in all parts of the world in the containment plan, which should include better definition of the risks associated with potentially infectious laboratory materials.
  8. Because substantial international consensus-building will be required to ensure that the end-game strategies obtain broad support in the scientific and political communities, SAGE recommends that the end-game issues be placed on the January 2002 agenda of the WHO Executive Board and on the subsequent WHA agenda.
  9. SAGE should be responsible for recommending specific policy options for stopping polio immunization to WHA. It is further recommended that these options be defined by TCG for consideration by SAGE. Using the best available information, WHO should develop a tentative timeline for the cessation of polio immunization, commencing when no cases have been reported globally for 12 months.
  10. Recognizing that the remit of TCG will increasingly focus on polio end-game issues, SAGE should adopt the principal responsibility for overseeing the expansion of the polio infrastructure in order to address the broader immunization agenda. SAGE requests that the WHO Secretariat work with partner agencies to develop an appropriate strategy for ensuring that these resources are sustained, and that a detailed report be submitted to SAGE on this issue in 2002.

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## 4.2 Measles: almost a million preventable deaths a year

### *Presentation (A.M. Henao-Restrepo)*

Globally, measles was still the leading cause of vaccine-preventable child mortality: there were approximately 30 million cases and 875 000 deaths each year. This was an unacceptable disease burden, given that there was an effective and inexpensive vaccine. Dr Henao-Restrepo pointed out that immunization against measles was an extremely cost-effective intervention: US\$ 0.26 per dose, including safety injection equipment; US\$ 1.20 per dose administered in campaigns; US\$ 0.60 if given during a polio national immunization day (NID).

The Global Measles Strategic Plan, developed by WHO, UNICEF, CDC and others, presented new goals for measles control. These included: (i) the reduction of annual global measles-related mortality by half by 2005, relative to 1999 estimates; (ii) the achievement and maintenance of interruption of indigenous measles transmission in large geographical areas with established elimination goals; (iii) the convening of a global consultation in 2005, in collaboration with other major partners, to review progress in measles mortality reduction and to assess the technical and political feasibility of global measles eradication.

In addition, a measles research agenda had been developed in order to confront the remaining barriers to the control and elimination of the disease. This agenda also takes account of key issues related to the feasibility and appropriateness of measles eradication.

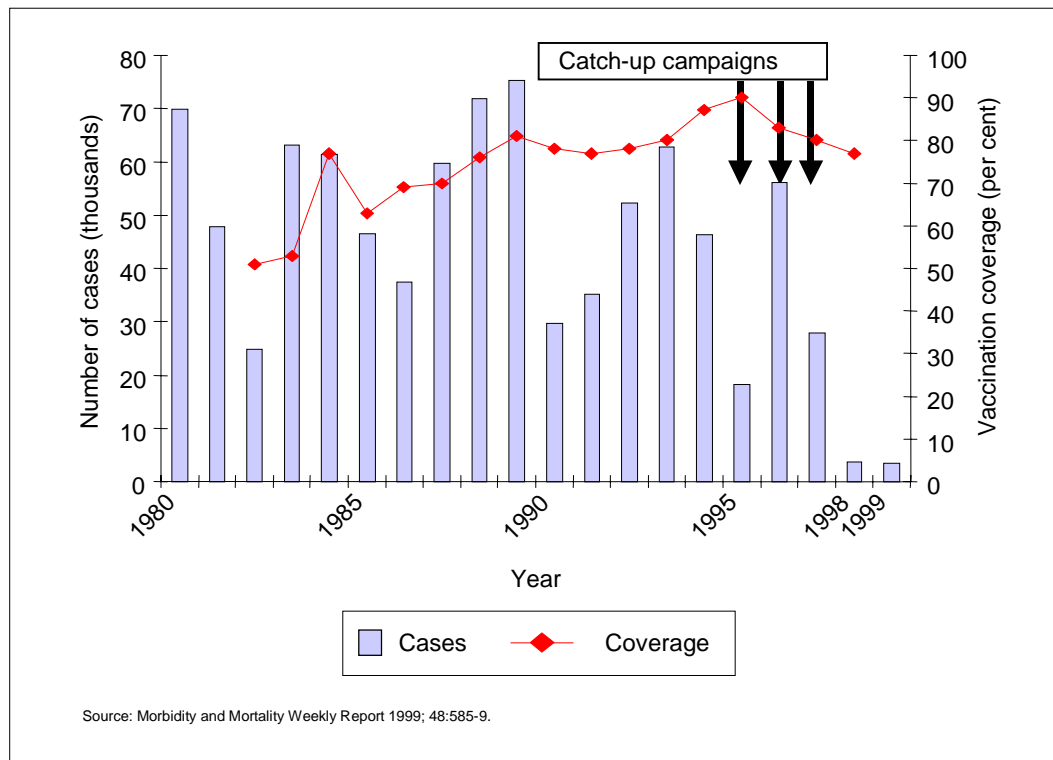
The Global Measles Strategic Plan includes the following strategies:

- improving the coverage and quality of routine immunization services in all countries;
- ensuring a second opportunity for measles immunization (supplemental or routine);
- establishing effective surveillance for measles disease and monitoring vaccine coverage;
- improving case management, including vitamin A supplementation.

In 1999, measles coverage below 50% was reported by 13 countries in the African Region (Burkina Faso, Burundi, Cameroon, Congo, Democratic Republic of Congo, Gabon, Guinea-Bissau, Liberia, Madagascar, Niger, Senegal, and Togo) and by three countries in the Eastern Mediterranean Region (Afghanistan, Djibouti, and Somalia). A second opportunity would make it possible to provide immunization to children who had not been vaccinated previously or who had not responded to an initial dose. This second opportunity could be delivered through regular routine or supplemental immunization activities, as appropriate. The implementation of a routine two-dose vaccination schedule was only recommended in countries with highly developed immunization services capable of coverage exceeding 90% through routine services and with a functioning system for identifying and following defaulters. Furthermore, many countries lacked adequate monitoring systems for detecting weaknesses in immunization services and guiding programme activities.

Experiences with measles control in the African Region were described by Dr Okwo-Bele. The evaluation of measles campaigns in 12 African countries showed that the impact on burden and mortality was enhanced when all children under 15 years of age were targeted. A strategy pursued in seven southern African countries which included catch-up campaigns among children aged between 9 months and 14 years reduced the incidence of measles dramatically and brought down the mortality rate to zero (figure 6).

**Figure 6: Reported measles cases and routine measles vaccination coverage among infants in six southern African countries, 1980-1999**



The five-year measles plan for the African Region had been updated and strategies for long-term aggressive measles control had been clarified and used in southern, eastern and western Africa. Plans existed for supporting targeted countries to increase routine vaccination, supplemental measles vaccination, and case-based, laboratory-based surveillance. Dr Okwo-Bele explained that measles control in Africa was a response to a deeply felt need of mothers, families, health communities and politicians.

Both presenters emphasized the need to ensure that certain operational criteria were in place:

- a five-year plan for measles control;
- a 12-month planning process for the initial campaign;
- strong capacity for evaluation, surveillance and problem identification;
- quality of campaign issues;
- high coverage in both routine immunization and campaigns;
- satisfactory injection safety and waste disposal.

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## ***Discussion***

### **Second opportunity for measles vaccination**

There was agreement on the need for all children to have a second opportunity for measles vaccination. The way in which this might be achieved would depend on a number of variables. It was highly unlikely that a single approach would fit all cases. Differences in health systems and epidemiological conditions would be important determinants of the models adopted in countries and regions. It was important to continue to work vigorously on reducing measles morbidity in as many countries as possible.

Some preliminary cost-effectiveness studies of measles immunization strategies had been performed by the Secretariat and the meeting encouraged the continuation of such studies.

### **Measles and polio alignment**

One way in which supplementary measles doses were delivered in a very effective way in many countries was through the alignment of measles vaccination with polio eradication activities. Field experience showed that it was possible to deliver measles vaccine and conduct high-quality polio NIDs at the same time. The importance was stressed of carefully planning the phased integration of measles vaccine activities into polio immunization activities in a way that supported the polio control efforts. Speakers made it clear that they did not want to overshadow the priority given to the polio effort in any way.

Surveillance for measles was being linked to polio surveillance, and field experience had shown that, in some cases, the integration of measles had helped to sustain polio surveillance. This approach was to be welcomed.

### **Measles targets**

A strategy for controlling measles needed to be very carefully stated. It was particularly important to determine whether any goal would be time-limited, as the economic implications would be very different for different scenarios.

Whether it would be possible to eradicate measles was a matter of debate, as it was far more transmissible than polio, and this matter came up again during the plenary session. Dr Arita asked whether an effective control programme might be better than one of eradication in the long run.

Regarding the recommendation of a WHA resolution on the measles reduction plan, Dr Melgaard noted that the target for death reduction departed significantly from previous targets and was realistic for the first time. It would be put forward at UNGASS in September 2001 (see footnote 3 on page 2 of this report). It would be important to align WHA with the UNGASS considerations. Furthermore, the new measles goals responded to requests from Member States. Dr Sakai requested an addition to the meeting report stating that the cornerstone of measles control was increasing access through the routine system.

## Recommendations

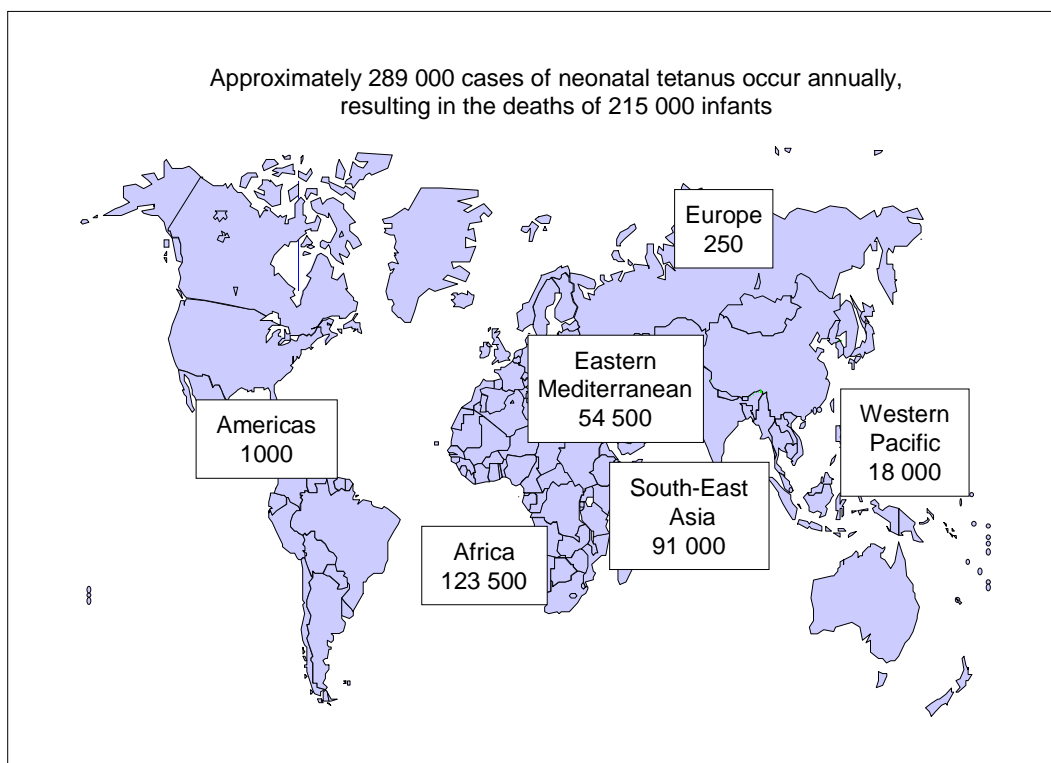
1. SAGE recommends that the WHO Secretariat take the necessary steps to draft a resolution supporting the WHO/UNICEF Measles Mortality Reduction and Regional Elimination Strategic Plan 2001-2005 for presentation at the WHA in 2002. This is in recognition of the fact that the targets depart significantly from previous targets, and should therefore reflect the perspective of countries and align with the UNGASS agenda.
2. SAGE strongly advocates the use of measles immunization as the most cost-effective intervention to reduce childhood mortality and deaths caused by vaccine-preventable disease.
3. SAGE endorses the targets and strategies outlined in the WHO/UNICEF Measles Mortality Reduction and Regional Elimination Strategic Plan 2001–2005, including the provision of all children with a second opportunity for measles vaccination. SAGE notes that the cornerstone of measles control is access to the vaccine through the routine system.

### 4.3 Elimination of maternal and neonatal tetanus

#### *Presentations (F. Gasse and M. Birmingham)*

Every year some 20 million pregnant women were at risk of maternal tetanus or of having their babies succumb to neonatal tetanus (NT). It was estimated that 215 000 infants had died from NT in the preceding year. By 2000, 57 countries had still not achieved the goal of NT elimination set by the WHA in 1989 (figure 7).

**Fig. 7: Countries with neonatal tetanus risk**



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An updated strategic plan to achieve the elimination of maternal and neonatal tetanus (MNT) by 2005 was developed jointly by UNICEF, WHO and UNFPA. MNT elimination was defined as occurring when there was less than 1 case of NT per 1000 live births in every district. The elimination strategy recommended the use of supplemental immunization activities in areas where women were not reached by routine services, as well as the strengthening of routine immunization services in poorly performing districts. The tactics included a targeted high-risk approach:

- identification of high-risk districts;
- administration of three properly spaced tetanus toxoid (TT) doses to all women of childbearing age in the high-risk areas identified;
- use of AD syringes/prefilled devices;
- promotion of clean birth delivery practices;
- monitoring of progress and achievements;
- integration of NT surveillance with active AFP surveillance;
- creation of a microplan in high-risk districts to strengthen outreach immunization services, reduce the dropout rate and improve hygienic birth practices.

Operational strategies called for a phased approach over the next two to four years, depending on the number of high-risk districts identified and the intensity of polio eradication efforts in the country concerned. UNICEF had raised US\$ 60 million with a view to achieving the goal of eliminating MNT by 2005. The challenges included:

- keeping MNT elimination on the political agenda (MNT mostly occurred in politically non-threatening communities);
- documenting and validating the achievement of the elimination goal set by the WHA (less than 1 NT case/1000 live births) in a cost-effective way.

NT was difficult to monitor. It was highly underreported and there was no sensitivity indicator. The monitoring of TT2+ coverage was often unreliable. The proposed approach for monitoring and validating MNT elimination involved:

- reviewing WHO/UNICEF-recommended indicator data by district;
- analysing the impact of supplemental immunization activities in high-risk areas;
- external reviewing, including a community-based survey of NT mortality in the districts at highest risk;
- finding evidence of a good plan to sustain MNT elimination.

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## ***Discussion and issues***

### **Impact assessment and surveillance**

The proposed plan could be expected to have a strong impact since it was similar to that already successfully implemented in the Americas. However, there were requirements for improved disease burden estimates and indicators in order to assess the sensitivity of the surveillance system.

The definition of “childbearing age” could vary from country to country. Flexibility was being built into the plan in order to allow for this. Defining denominators of at-risk women was potentially problematic, and countries were being encouraged to conduct studies that would validate their coverage data.

### **TT prefilled injection devices**

There was a discussion of the cost and quality control of the use of TT prefilled devices. Uniject™ was to be fitted with VVMs, and there was evidence suggesting that this allowed the use of effective vaccine outside the cold chain. Five countries had agreed to the performance of pilot projects with Uniject™. These projects would provide valuable experience on the introduction of the new vaccine delivery technology in diverse settings. However, there was concern that there might be a bottleneck in production capacity.

## ***Recommendations***

1. SAGE endorses the WHO/UNICEF strategic plan for MNT elimination by 2005, and stresses the importance of implementing the high-risk approach by increasing routine immunization coverage with at least three doses of TT-containing vaccines to at least 80% of women of childbearing age in high-risk areas.
2. SAGE recommends that the proposed approach to monitoring and validating MNT elimination be adopted.
3. SAGE recommends that a progress report on MNT elimination be presented at each annual meeting until 2005. For 2002, SAGE recommends that WHO and UNICEF document and report significant achievements to SAGE, including progress in strengthening the monitoring/surveillance of MNT elimination as well as the alignment of this initiative with other disease control activities.

### **4.4 Vitamin A supplementation and immunization activities**

#### ***Presentation (B. Mathews)***

Globally, 140–250 million children under 5 years of age were at risk of vitamin A deficiency. They consequently suffered an increased risk of morbidity and mortality, particularly from measles and diarrhoea. Between 250 000 and 500 000 children became blind every year. Supplementation in populations deficient in vitamin A was estimated to result in a reduction of 23–34% in childhood (6 months to 5 years) mortality from all causes and a 33% reduction in mortality attributable to diarrhoeal disease.

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In 1990 the World Summit for Children set the goal of eliminating vitamin A deficiency by 2000. Although this was not achieved there had been significant progress in controlling the deficiency in many countries. Worldwide, approximately 70% of children living in countries at risk of deficiency were now receiving at least one high dose of vitamin A per year.

Currently, polio eradication activities and other supplemental immunization campaigns provided the most successful vehicles for vitamin A supplementation. It was estimated that 242 000 deaths were averted through the distribution of vitamin A during polio NIDs in 1999/2000: 53 countries included vitamin A with their NIDs and more than 90 million children were reached with at least one dose each year. Routine and supplemental measles immunization contacts also presented an excellent opportunity for vitamin A supplementation, and vitamin A had an important role to play in the case management of measles.

The gradual phasing out of polio NIDs meant that there was a need to ensure longer-term sustainability and a potentially greater health impact by linking vitamin A supplementation with routine immunization contacts. In 1999, 40 countries reported the integration of vitamin A supplementation into routine immunization activities. However, coverage data were reported by only 10 countries, five of which reported coverage below 50%.

With a view to expanding opportunities and increasing impact, an informal consultation of experts on Vitamin A supplementation, held at Yverdon in March 2000, recommended:

- supplementation for infants under 6 months of age during DTP contacts at 6, 10 and 14 weeks, in addition to the dose given with measles vaccination at 9 months;
- an increase in the maternal postpartum dose.

Action to strengthen the integration of vitamin A with immunization services included:

- immune response studies and evaluation of the use of DTP contacts with children under 6 months of age;
- continued use of existing opportunities to include vitamin A supplementation with immunization activities;
- improved coverage and reporting of vitamin A delivery as part of the strengthening of routine services;
- improved coordination between nutrition and V&B.

It was considered essential that countries with vitamin A deficiency should develop a clear plan and defined responsibilities for each of the key partners involved in the planning and implementation of activities.

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## ***Discussion and issues***

### **Outreach possibilities through immunization services**

Coverage needed to be improved. It was desirable to recognize the particular advantages of delivering vitamin A through immunization contacts, since this programme offered possibilities of deep outreach into communities that might otherwise not be covered.

### **Other means of delivery**

It was also desirable to encourage opportunities for vitamin A delivery through programmes other than EPI. While immunization allowed maximum opportunities for contact with infants under 1 year of age, other programmes might reach older age groups that were also at risk. Food fortification, which was being achieved through nutrition programmes, should be encouraged. EPI should be encouraged to exchange information with other programmes so as to demonstrate what might be achieved in vitamin A supplementation.

Where two programmes were involved, i.e. immunization and nutrition, there was always the possibility of the abandonment of responsibility. Every effort had to be made to prevent this from happening.

### **Coverage data**

Coverage data needed to be improved. There was evidence that in some places vitamin A supplementation was not being performed. Elsewhere it was being performed but not reported. Attempts were being made to simplify reporting systems in order to deal with the latter shortcoming.

## ***Recommendations***

1. SAGE recommends that WHO support better coordination between national focal points for nutrition and immunization, including plans that define areas of responsibility for implementation and monitoring.
2. SAGE supports the continued use of opportunities to include vitamin A supplementation in routine and supplementary immunization services, including the contact with measles immunization at 9 months of age and the treatment of childhood illnesses as per IMCI guidelines.
3. SAGE supports the inclusion of other interventions with immunization contacts if and when there is evidence to support them.
4. SAGE requests that at its 2002 session a report be submitted on progress in improving the monitoring of vitamin A delivery with routine immunization services.

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# 5. Plenary session

*Chair: Dr M. Ali Jaffer*

*Rapporteur: Dr A. Kraigher*

## 5.1 Presentations by subgroups

The major discussion points and recommendations of the subgroups were presented by their chairs. The complete list of recommendations adopted by SAGE is given in the Executive Summary.

## 5.2 Global Alliance for Vaccines and Immunization

### *Presentation (M. Zaffran)*

The objectives of GAVI were: (i) to improve access to children needing immunization; (ii) to expand the use of established vaccines; (iii) to accelerate the introduction of new vaccines; (iv) to accelerate research and development relating to such diseases as HIV/AIDS, malaria and tuberculosis, as well as pneumococcal and meningococcal diseases; and (v) to bring immunization coverage on to the international agenda. GAVI was particularly concerned with developing countries.

Mr Zaffran reviewed the structures, operations and funding policies of GAVI. The structures included:

- a board with 15 high-level members who committed their institutions to the GAVI objectives;
- a working group of 10 members which ensured that work in support of GAVI's objectives was reflected in the strategic plans and work plans of their respective agencies; this group also attended to joint policy development;
- four task forces, in which V&B staff provided expertise; WHO co-chaired the Research and Development Task Force together with industry and academia, and headed the Task Force on Country Coordination.

The Task Force on Country Coordination had placed special emphasis on coordinating technical support for countries and providing assistance to regional and subregional groups. Other points of focus had been capacity-building and the development of tools for monitoring and evaluation.

WHO had also played a pivotal role in research and development projects on meningococcus A/C, rotavirus and pneumococcus.

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The Vaccine Fund was a newly established tool that would enable the GAVI partners to provide seed funding to the poorest countries. Countries with a gross national product per capita of less than US\$ 1000 were eligible to receive support from the Vaccine Fund. International donor partners had pledged 1.03 billion dollars to the Vaccine Fund or to multilateral agencies as support for the objectives of GAVI.

If the targets for countries already obtaining support through the Vaccine Fund were met, 5 million additional children would be fully immunized; 45 million additional children would be immunized against HBV, an additional 1 million would be immunized against Hib, and 3 million more would receive immunization against yellow fever.

The regional structure of working groups was advantageous for both WHO and UNICEF because the regions did not overlap. The example of the Subregional Working Group in West and Central Africa was presented by Dr Nshimirimana. It first met in April 2001 following the division of the African Regional Working Group into two subregional groups. Its membership consisted of major partners in the region, including country representatives. On a monthly basis they shared information relating to country activities, with reference to coverage by district, disease surveillance data, and vaccine availability and use. They also provided technical support to countries that were preparing applications to the Vaccine Fund. Among other issues covered by the subregional group was the synchronization of polio NIDs and measles campaigns.

### ***Discussion and issues***

A major part of the discussion centred on financing.

#### **Vaccine Fund able to meet commitments**

Regarding pledges to GAVI objectives (either through the Vaccine Fund or through partners) it was estimated that about US\$ 300 million per year would be available. There would be no difficulty in meeting commitments for HepB and Hib vaccines and for shares for the 74 eligible countries. However, there would not be much scope for additional endeavours unless substantial extra funding were raised.

#### **Low overheads**

With regard to funding for partner activities, Dr Melgaard noted that of the amount pledged for GAVI objectives only 2% had gone to WHO and approximately the same amount had gone to UNICEF. This meant that WHO was having difficulty in providing the technical support required at all levels, a lot of which was being given by polio-funded staff at the country level.

GAVI support could be given to the Vaccine Fund, to multilateral agencies, and directly to countries on a bilateral basis. All three levels of financing had to be pursued simultaneously.

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### **Unfinished agenda: GAVI support?**

Polio and measles still had an unfinished agenda. Dr. Ciro de Quadros pointed out that donors should be aware that if they put money in the Fund it could not be used for measles vaccine. On the other hand, it was suggested that Fund and GAVI regulations should be reviewed, as should such indicators as district coverage, to allow more flexibility for extending support to the unfinished agenda.

The disease control session had recommended that the Fund be used to cover elements of the polio-funding gap. This could not happen, however, under current guidelines. One answer would be to call for new GAVI funding specifically for polio. Alternatively, there were areas of overlap where funds could work for both the polio eradication initiative and the strengthening of immunization systems.

### ***Recommendations***

1. SAGE recommends that WHO continue to play an active role in all aspects of GAVI policy development and implementation, and affirms the importance of dedicating significant V&B staff time to accomplishing the objectives of the GAVI Working Group and GAVI task forces.
2. SAGE endorses WHO's role as the lead technical agency of GAVI and urges V&B to continue contributing its expertise in the areas of product supply and quality, logistics, financing, service delivery and surveillance, including immunization safety.
3. SAGE acknowledges WHO's responsibility for providing technical assistance to countries and encourages the further development of GAVI regional working groups that aim to strengthen coordination mechanisms at the country level and build national capacity in programme management and priority-setting.
4. SAGE affirms WHO's responsibilities for coordinating efforts in vaccine research and development and strongly endorses the role of the leader of the Initiative for Vaccine Research as Secretary of the GAVI Task Force on Research and Development. While the task force focuses chiefly on research and development goals achievable within five to seven years, WHO's research and development agenda should encompass a longer period.
5. SAGE notes with satisfaction the considerable progress achieved by GAVI since its inception and urges WHO and V&B to capitalize on opportunities offered by GAVI for strengthening national immunization services in a manner that generates sustainability.
6. SAGE recognizes that it is essential for national ICCs to be strengthened in order to ensure that resources are mobilized locally from national governments as well as from multilateral agencies, bilateral donors and private organizations.
7. SAGE recognizes that vaccine manufacturers from both industrialized and developing countries play a critical role in meeting global immunization needs. Support should be given for initiatives aimed at ensuring that new vaccines and immunization-related technologies are available to enhance access to affordable products of high quality.

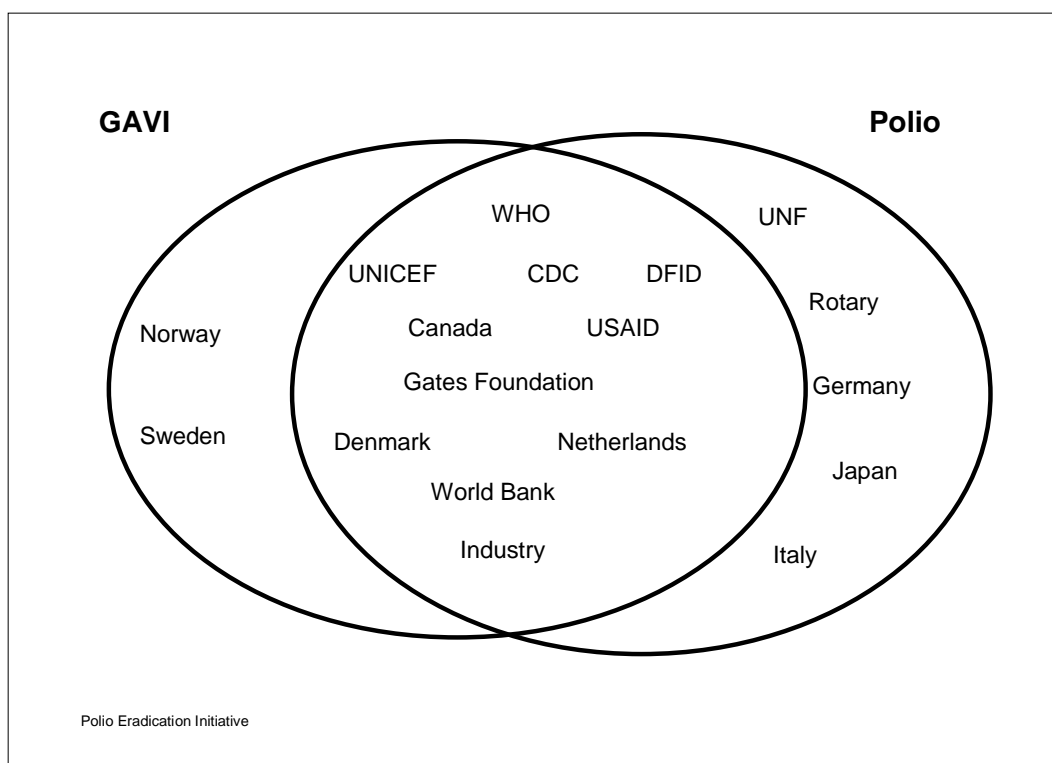
### 5.3 GAVI and accelerated disease control initiatives

#### *Presentation (T. Goodman)*

Ms Goodman presented an overview of the extensive analysis and consultation process that had been carried out over the preceding six months to develop a framework for the alignment of GAVI objectives with ADC initiatives, including polio eradication, measles control, MNT elimination and vitamin A supplementation. The GAVI Board had requested an investigation of this issue at its meeting in Noordwijk in November 2000. A report was presented to the GAVI Board in London in June 2001.

The first methodological step involved mapping the various immunization initiatives in accordance with their objectives, milestones, targets, partners, strategies, disease impacts, available funding, and funding gaps. This clearly demonstrated areas of overlap while pinpointing differences. It confirmed that there was a strong foundation and clear justification for planning better synergies among initiatives. (Figure 8 shows the extensive overlap of partners between GAVI and the polio eradication initiative.)

**Figure 8: Major stakeholders in GAVI and the polio eradication initiative**



Through the mapping exercise and subsequent stakeholder consultation, a framework of possible scenarios for alignment was developed for evaluation against four key areas of activity common to all initiatives (advocacy, fundraising, coordination, country operations). (Figure 9 provides a summary of the alignment framework and the results of the stakeholder consultation on the preferred scenario.)

It was clear that, in many areas, alignment was already happening. Two extreme scenarios were rejected, one because it did not address the perceived problem, the other because it was not yet feasible. So the current proposal involved working on shared objectives and milestones plus some cost-sharing between the two initiatives. The proposal also suggested that new disease outcome indicators be selected after consultation with partners, and that GAVI support the integrated delivery of other interventions, e.g. vitamin A supplementation during immunization contacts.

**Figure 9: Summary of stakeholder consultation on GAVI/ADC alignment scenarios**

Scenario	Implications			
	Advocacy	Fundraising	Coordination	Country operations
1. Status quo	-	+	-	-
2. Adopting new objective/milestone and indicators	+	+	-	-
3. New objective, milestone/indicators and cost-sharing	+	+	+	+/-
4. Full integration of processes and funding	+	-	+	+

In discussions with the GAVI Working Group it emerged that there was support for GAVI placing more emphasis on access. A new accelerated disease control objective (supporting national targets) and milestone (world polio-free by 2005) would help to improve access and equity. In the area of shared investment the focus was the human resources infrastructure (1550 polio-funded staff, costing US\$ 25-50 million per year), which had been built up through the polio eradication initiative. It was vital to retain this human resource infrastructure, which could be adapted to work on the broader immunization agenda. It was proposed that GAVI consider establishing a mechanism to provide support for the human resources infrastructure by 2002, but support from the Vaccine Fund appeared unlikely.

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## ***Discussion and issues***

SAGE strongly supported the concept that planning for immunization activities be integrated at country level and recognized the value of using immunization contacts to provide other interventions for disease reduction. There was general support for the principle of alignment and the proposed new disease control objectives and milestone. However, a number of questions on the implications for GAVI and ADC emerged during the discussion.

- Dr de Quadros noted that it was necessary for GAVI to be focused if it were to succeed. Historical lessons were important: immunization deteriorated when a loss of focus occurred during the 1990s. He supported the proposal for using equity and access as guiding principles but reiterated the need for focus.
- Several speakers noted the long history of the ADC initiatives and questioned whether they should fall under the umbrella of GAVI. Mr Zaffran mentioned that 95% of partners were supporters of both ADC and GAVI initiatives, and said that the ADC objectives and the new milestone could be seen as a huge step forward. Although the implications of this for financing and human resources were not yet known, alignment could be expected to benefit all initiatives.
- The subject of diseases not covered by ADC was raised, such as meningitis. The proposal for alignment mentioned *national* disease control priorities, thus leaving the way open for support for the control of other diseases prioritized by countries.
- Dr Salisbury emphasized that there was an expectation that GAVI would take a vital role in maintaining the routine infrastructure in the transition phase between the cessation of campaigns and the eventual eradication of polio. This reliance that GAVI would maintain the interruption of polio transmission presented a high degree of risk, as GAVI had no history of achievement in the strengthening of infrastructure. In this regard the whole alignment process was enormously helpful in narrowing the gap between these two important initiatives. There was perhaps a case for prioritizing demonstration projects in order to show how infrastructure built by the polio programme could be preserved and strengthened for routine systems. This would increase confidence in the alignment process.
- Questions were raised about the reaction of countries to changes in the GAVI goals before there had been an assessment of impact, and about the transparency of the whole GAVI structure.

## ***Recommendations***

1. SAGE reaffirms its conviction that the ADC principles are fundamental to the reduction of vaccine-preventable morbidity and mortality. These principles include surveillance-based outcome monitoring, epidemiologically-driven supplementary immunization activities, and innovative strategies and technologies for accessing unreached children. The sustainability of these gains is premised upon achieving and maintaining high routine immunization coverage.

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2. SAGE recommends WHO to advocate that GAVI:
- a) approve the immediate establishment of a new accelerated disease control objective, a new milestone, and new indicators:
    - **new objective:** support the *national* accelerated disease control targets for vaccine-preventable diseases;
    - **new milestone:** by 2005, the world to be certified polio-free;
    - **new indicators:** addition of disease outcome indicators; selection of the most appropriate indicators (polio, measles, MNT, vitamin A) to be proposed by the working group after consultation with partners;
  - b) place renewed emphasis on GAVI's first objective, i.e. "*improve access to sustainable immunization services*". This would serve to unify all immunization initiatives by making their primary aim "*access to all children and target populations*";
  - c) immediately revise the second objective as follows: "*Expand the use of all existing safe and cost-effective vaccines, and promote the delivery of other appropriate interventions during immunization contacts*";
  - d) request that GAVI partners provide financial support for a human resources infrastructure for immunization. As a first step, UN agencies should develop for consideration by the GAVI partners an immunization human resources plan (i.e. minimum staff for each country) and costing based on the current human resources, including those that are funded under ADC. GAVI partners should have a funding mechanism in place for supporting this plan by 2002 (e.g. by designating GAVI funding for this purpose at source).

#### 5.4 Vaccine selection: implication of two tracks

##### *Presentation (J. Milstien)*

There was a divergence of products in national immunization services between developing and industrialized countries. The briefing paper looked at the implications of this and how it would be possible for the public and private sectors to collaborate in order to ensure that goals were not threatened.<sup>4</sup>

One aspect of divergence was that for the same disease there were different products for different settings. Thus the developing countries favoured OPV, combinations based on whole-cell pertussis, and monovalent measles vaccine, while the industrialized countries favoured IPV, combinations based on acellular pertussis vaccines, and MMR vaccine. There was also a tendency to use single-dose presentations in industrialized countries, whereas multidose products were the rule in the developing world.

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<sup>4</sup> Milstien J, et al. *Divergence of vaccine product lines in industrialized and developing countries*. Geneva, World Health Organization, Access to Technologies (unpublished document).

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Meanwhile, suppliers' vaccine portfolios were changing. Dr Milstien gave the following examples.

- Wyeth-Lederle, an industrialized country supplier, had decreased its supply of traditional products and increased its supply of newer products serving the industrialized world.
- Since 1990, Biofarma (Indonesia), a developing country manufacturer, had been steadily adding to its portfolio of traditional vaccines. Biofarma planned to expand into combinations and other new products that served global markets.

Changes in demand were apparent in the markets of both the developed and developing countries.

- Industrialized countries had changed their vaccine demands, sometimes reflecting epidemiological findings but often responding to fear of adverse reactions. On the basis of epidemiological considerations, the United Kingdom introduced meningococcal C conjugate and the USA introduced Hib vaccine. Fear of adverse reactions caused Canada to replace whole-cell pertussis with acellular pertussis and led Japan to abandon mumps vaccine.
- United Nations agencies, the primary sources of supply for many countries, demanded large but unpredictable volumes of traditional vaccines but also demanded new combination products tailored for the developing market.

Other developments covered by Dr Milstien included the following:

- The supplier mix was changing. Over the past 20 years, PAHO and UNICEF had changed the supplier base for EPI vaccine procurement to a mix of industrialized and developing country/emerging economy manufacturers, the latter outpacing the former. Industrialized country suppliers were increasingly targeted on the industrialized market. As demand for new vaccines increased, manufacturers in developing countries were also turning to new and future vaccines, increasingly targeted at markets other than their own.
- Demand and availability were converging for traditional vaccines supplied by UNICEF. There was no longer an excess. This demand was largely being met by developing country/emerging economy manufacturers as the market diverged. Thus divergence made supply more tenuous.
- Prices of traditional vaccines had remained static as developing country manufacturers had kept their prices low. For vaccines without excess capacity, e.g. yellow fever vaccine, the prices were rising, as were those of new vaccines.
- Regulatory requirements had become considerably more stringent, affecting the cost of production. One manufacturer had claimed that prices had gone up threefold in relation to production space in the last five years because of regulatory requirements. Regulatory pathways might be limited by product divergence: the EU was only licensing products that were used within its boundaries. Options were being explored and the situation seemed resolvable; nevertheless, product divergence raised the question of regulatory oversight.

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Dr Milstien said that divergence was not likely to change in the near term. This made the supply chain fragile. A manufacturing failure by one supplier could threaten immunization services. It was necessary to increase investment and capacity and to improve quality. Because new vaccines were much more expensive than the traditional ones, a fundamental change was required in the willingness of the public sector to pay.

In order to meet the demand for developing market vaccines it would be important to encourage both industrialized country and developing country/emerging economy manufacturers to stay in the market. WHO and its partners would have to issue a strong message that product line divergence was not a reflection of quality but a conscious choice to optimally meet the needs of immunization services in developing countries.

### ***Discussion and issues***

#### **Technology transfer**

Dr Arita pointed out that 60% of vaccine requirements in large countries such as Brazil, China, and India might be met by the countries themselves. There was a need for technology transfer in order to achieve this, and the answer lay in bilateral assistance using public sector funding. He appealed for support for development along these lines. Dr Milstien remarked that developing countries were increasingly interested in supplying vaccines for the international markets. Many manufacturers in developing countries with high quality standards and huge capacities were no longer interested only in their own markets. Meanwhile, some manufacturers in developing countries that in the past met national needs had dropped out of the market because of changes in vaccine mix and regulatory requirements. WHO was not focusing on technology transfer but on assisting countries to ensure the appropriate environment and leaving them to interact freely among themselves.

Dr Streefland asked about production in the public sector, and wondered about the relevance of globalization to international vaccine production. Dr Milstien said that WHO no longer made a distinction between public and private sector, as most surviving public sector industries were no longer confined to that sector and those that competed internationally maintained good manufacturing practices. With respect to globalization, WHO supported the position of the World Trade Organization and the principles of intellectual property protection.

#### **Costs of quality control**

A high proportion of the costs of quality control was attributable to *in vivo* testing. Dr Schild suggested that NRAs and manufacturers might work together to reduce and refine tests and thus keep costs down. It was desirable to reduce or replace animal tests wherever possible.

#### **Secure supply and funding**

Mr Jarrett told the meeting that UNICEF was concerned about potential threats to vaccine security. In the past, UNICEF had been preoccupied only with obtaining the lowest prices but now recognized the importance of keeping manufacturers in business. The organization had commissioned a detailed report on this issue. It was concerned about the predictability of demand, especially for basic vaccines.

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UNICEF was also concerned about stable and secure funding. At present UNICEF was working with only a four-month security of funding for OPV. How to ensure predictability of demand and secure funding were major challenges that were being discussed with partners and would be addressed by the Executive Board in 2002.

Dr Greco agreed that there was a need for clear demand forecasting and long-term purchasing commitments. He also explained that manufacturers in industrialized countries had a problem with the increasing need for certain antigens for other products, e.g. tetanus toxoid required for the conjugation process. Licences should be available from the countries of origin. This was becoming a problem in Europe and should be managed by WHO.

### **Cost adjustments and attitudes**

Dr Broome said that increases in costs for new products might help towards an appreciation of the extremely low costs of traditional vaccines. Perhaps it was necessary to point out that new products should be appropriately valued. She felt the focus should be on approaches to sustainable financing, and suggested that there was an excessive emphasis on price. Mr Jarrett responded that UNICEF had accepted criticism for pressing down prices, but wondered how the real value of DTP or measles vaccines could be assessed. He requested help in this matter.

### **Quality issues**

Dr Slamet asked what assurance of quality there was for vaccines that were not made for international, i.e. United Nations, supply. A regulatory system was required to ensure quality while allowing incentive for the manufacturers. Dr Milstien said that manufacturers did not become suppliers internationally unless they were on WHO's prequalified list, which, thanks to WHO advocacy, had virtually become a procurement guide. The foundation of this assurance was the competent functioning of the NRAs, to which WHO attached special importance.

### ***Recommendations***

SAGE advises WHO and its partners as follows.

1. Strong positions should be developed and communicated on product selection in order to minimize issues related to perceived safety and quality of developing market products.
2. Key manufacturers should be kept in the market through clear communications, improved demand forecasting, and advocacy for the intrinsic value of vaccines. The possibility of multiyear contracts and commitments to purchase should be examined.
3. It is necessary to ensure that appropriate systems exist for licensing and regulatory oversight of these products.

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## 5.5 Yellow fever

### *Presentations (F. Avokey and A. Dabbagh)*

There was a resurgence of yellow fever in Africa and South America, and at the same time a drastic shortage in vaccine supply. Furthermore, resources were inadequate, immunization coverage was low and surveillance was poor. The vaccine had received adverse publicity when four deaths associated with its administration had occurred in Brazil and the USA in recent years.

The resurgence in yellow fever, particularly in Africa, was attributable to increased contact with the mosquito vector and a build-up of unprotected populations. In West Africa, outbreaks were recorded in both urban and rural areas, whereas in South America the majority of outbreaks had been associated with sylvatic infection. Most of these cases were diagnosed or reported in or near urban areas, thus presenting a real risk of urban transmission.

In Africa there was poor integration of yellow fever immunization into routine immunization services, only one African country having reached 80% coverage. Drs Avokey and Dabbagh endorsed the 1988 UNICEF and WHO recommendation that yellow fever vaccination should be integrated into EPI, which should be strengthened so as to achieve at least 80% coverage. They urged that catch-up campaigns be conducted, particularly in high-risk districts, and that resources be mobilized in order to implement preventive vaccination programmes.

Africa also suffered from poor surveillance and outbreak response. Strategies had been proposed for establishing case-based active surveillance for yellow fever in the context of integrated disease surveillance, for involving community groups in the early detection of cases, and for developing a yellow fever/measles laboratory network that would provide prompt diagnosis through the establishment of IgM testing capacity at the national level. In Liberia, where there was surveillance through the AFP system, 137 suspected cases had been detected, of which seven were confirmed as yellow fever cases in two outbreaks.

Recent outbreaks had demonstrated the need to improve routine immunization, yet there was a crisis in the supply of yellow fever vaccine. In recent years the number of suppliers of this vaccine had decreased and there were currently only two prequalified suppliers. Manufacturers had not been responsive to demand and in 2000 a tender by the PAHO Revolving Fund for 30 million doses had not been filled.

GAVI was willing to give this vaccine to all high-risk countries eligible for support from the Vaccine Fund which were prepared to introduce yellow fever immunization into the routine immunization services.

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Considering the scarcity of vaccines and the need to respond to outbreaks, it was decided that a stockpile of 2 million doses should be set aside for mass emergency vaccinations in the event of outbreaks being declared and requests for vaccines being made. A mechanism similar to that adopted by the ICG for meningococcal A/C vaccines had been set up in collaboration with other partners, including representatives of the vaccine producers, in order to allocate these doses for outbreak response. Supplies for routine coverage would be suspended until the stockpile level was achieved. A plan had been proposed for emergency response. WHO and UNICEF had agreed on priority, calculated in accordance with countries' needs and risk categories. It was necessary to inform suppliers of projected requirements. In addition, there was a need to provide incentives to suppliers to increase capacity and take up production, as well as to improve communication so that long-term plans could be developed.

Illness associated with the use of 17-D yellow fever vaccine had been described, and there had been three fatal cases among young females in Brazil. There had also been three deaths related to the use of the 17-D strain in the USA. Persons older than 65 years were at highest risk. The reactions were not thought to be attributable to genetic variation in the attenuated virus but rather to extremely rare abnormal host responses to the vaccine. However, speakers from the floor stressed that it was necessary to maintain an open mind on this matter.

### ***Discussion and issues***

While satisfied with the emergency supply measures and the intention to improve coverage and surveillance, speakers from the floor expressed concern about supply, poor immunization coverage (as low as 1% in Nigeria), and, in particular, problems of quality and adverse events.

#### **Adverse events following immunization**

Dr Schild explained that point mutation could conceivably explain recent adverse events. In polio even a single mutation in the nucleotide could make a difference between virulence and non-virulence. He suggested that some genetic studies could be added to the quality control guidelines, which had been in existence for a considerable time. Dr Olivé agreed that molecular studies could be included in the quality control of the vaccine, and Dr Griffiths mentioned that WHO was looking into improving the characterization of the strains as well as other aspects of potency assays and standardization. However, the hypothesis of genetic variation in the host had gained considerable strength because the sister of a person who had died had previously experienced a similar reaction. The virus isolated from two Brazilian cases was found to be identical to the seed lots, and studies in monkeys had shown no neurological differences between seed lots, vaccine lots and isolates.

Dr Clements acclaimed the improved surveillance but wondered if there was a relationship between yellow fever and HIV positivity. Dr Olivé believed that this was not a problem in asymptomatic HIV infection.

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## Supply issues

Dr Greco confirmed that Aventis Pasteur was scaling up the production of yellow fever vaccine and that by 2004-2005 this firm should be producing some 50 million doses per year, depending on presentation. However, feedback was urgently needed. Dr de Quadros predicted that supply problems would be associated with the increased danger of outbreaks in South America and urged that consideration be given to supporting former producers of yellow fever vaccine in Colombia and Senegal to resume production. Dr Dellepiane said that Biomanguinhos (Brazil) was undergoing the prequalification process and would provide an important increase in capacity.

## GAVI and yellow fever vaccine

Dr Dahl-Regis remarked that, in Africa, some countries were not applying for the vaccine. This was an urgent problem additional to those of vaccine supply, poor surveillance and the frequency of adverse events. It was desirable that GAVI's working group consider this matter. Mr Zaffran stressed that money was available for poor countries that required the vaccine. By waiving the conditionality of DTP3 coverage, GAVI had given industry a signal that money was available. Dr Avokey explained that the GAVI West and Central Africa Regional Working Group was sensitizing countries on the waiver and on the need to seize this opportunity to make applications for introducing yellow fever vaccine into EPI, and that in 2002 more at-risk countries would apply. Dr Broome reminded the meeting of the need for technical assistance in this connection.

## *Recommendations*

1. SAGE recognizes the short-term crisis in yellow fever vaccine supply and endorses the policy adopted by WHO, UNICEF and ICG to prioritize the use of limited supplies. For the longer term, SAGE recommends that WHO urgently work closely with countries to determine real demand by time period, including desired vial sizes. Once these demand estimates are completed, WHO should work closely with manufacturers, UNICEF Supply Division, and the PAHO Revolving Fund to explore the available supply, the potential capacity, and the need for expanding capacity.
2. SAGE strongly endorses the AFRO regional strategy and milestones for yellow fever control.
3. The policy of vaccinating persons who are going to travel to areas where yellow fever is endemic should be continued.
4. All countries at risk should strive for a rapid response to outbreaks. This is particularly significant in view of the current vaccine shortage, as it ensures a more efficient use of yellow fever vaccines.
5. SAGE requests that the Global Advisory Committee on Vaccine Safety review the safety of yellow fever vaccination.

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## 5.6 Report of the Global Advisory Committee on Vaccine Safety

### *Presentations (P. Folb and M. Griffin)*

Dr Folb, Chair of GACVS, presented the main conclusions and recommendations of meetings held in June and December 2000. The following topics were among those considered: (a) the relationship between macrophagic myofascitis (MMF) and the injection of aluminium-containing vaccines, and the possible link with a systemic syndrome; (b) the purported risk of auto-immune diseases associated with immunization; (c) issues related to thiomersal and vaccines; (d) the issue of child survival following routine immunization.

Dr Folb explained that MMF was a unique lesion described almost only from France. GACVS had spent much time with French neuropathologists and with the French pharmaceutical industry and regulatory authorities in order to elucidate the matter. Agreement had been reached that no more work would be done to establish causality. One explanation was that biopsies performed at the site of injections had revealed what happened when aluminium was injected into muscle.

Dr Folb also discussed the survey in Guinea-Bissau published by Dr Aaby and others in the *British Medical Journal* in December 2000. The survey had found adverse effects on mortality with DTP vaccine but positive effects with measles and BCG vaccines. After discussing the findings with Dr Aaby and examining the data and their analysis, GACVS decided that the conclusions could not be verified. Faults in the study method included the small sample, the short duration, and the lack of information on the numbers of vaccinations the subjects had received before entry. The whole argument depended critically on the outcome of two of 19 cases, which allowed for a considerable margin of error.

Nevertheless, because of the serious nature of the conclusions, further studies in countries with both high and low mortality would be commissioned in order to determine whether a general picture emerged of increased mortality after DTP immunization. An intervention study would be carried out in Guinea-Bissau.

A literature review of non-specific beneficial or detrimental effects of vaccines had been commissioned. Dr Griffin presented the preliminary results. In respect of measles vaccine, these seemed to indicate that the reduction of mortality was within the expected rates. For DTP and BCG vaccines there was not enough evidence to confirm or reject Dr Aaby's hypothesis.<sup>5</sup>

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<sup>5</sup> See the minutes of the meetings of the Global Advisory Committee on Vaccine Safety for detailed information on topics considered in June and December 2001.

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## ***Discussion and issues***

### **Retrospective studies**

Elaborating on the follow-up to the Guinea-Bissau study, Dr Duclos said that retrospective studies had been contracted by WHO and that preliminary results would be available within three months. They would be reported to GACVS, which would give further advice on how to proceed.

Dr Stoeckel asked whether the retrospective studies considered children that had received the normally recommended schedule or a special schedule. Dr Duclos explained that, as yet, there was no evidence of an association or even a positive effect. The studies already analysed could not answer this question. However, in the current retrospective study these issues had been taken into account.

### **Weaknesses in study design**

Returning to unsatisfactory elements of the Aaby study, Dr Folb pointed out that assessment of mortality was made after one immunization, not necessarily the first. He emphasized the need to answer basic questions such as the effect on mortality following one immunization. Referring again to possible bias in the Aaby methodology, he recalled that in the study on BCG only children weighing more than 2500 g at birth were considered. The possibility that there had been selection for sick infants or exclusion of these infants could not be dismissed, a point not disputed by Dr Aaby.

Responding to a question from Dr Dabbagh, Dr Griffin said that other factors, e.g. vitamin A, would not give the wrong results if the groups vaccinated and unvaccinated were the same with respect to vitamin A deficiency. In this situation vitamin A deficiency would not be a confounding factor but just a contributing factor, and would not bias the results. However, vitamin A deficiency and other factors contributing to childhood mortality could influence the results if the factors were distributed differently among vaccinated and unvaccinated children. This would constitute selection bias as discussed by Dr Folb.

### **Public perception and communication**

Dr Clements remarked that although some studies had concluded that there was no evidence of risk, the public remained unsatisfied. Whereas scientific reports stated that there was no evidence of risk, the public wanted to hear that vaccine had been proved safe. Dr de Quadros concurred that the public was not reassured by statements indicating that there was no evidence of risk but that in some cases there might be associations.

The difficult task of seeking the right wording was summed up by Dr Greco, who pointed out that it was almost impossible to demonstrate an absence of correlation between vaccines and mortality, since vaccines were given to the entire birth cohort population. Furthermore, there had been a change in attitudes. Previously, a causal relationship had to be proved. Now it was assumed that there was a causal relationship and the onus was on the scientists to prove the contrary.

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Dr Melgaard said that there was a discrepancy between scientific evidence and perception of risk. A communication problem clearly existed. On this basis he saw the need for the Secretariat to prepare a communication programme. Dr Duclos agreed on the need to improve communication but remarked that there would always be a marginal yet influential group of people who would disbelieve whatever was said.

Recommendations were adopted that applauded the work of GACVS in examining the Guinea-Bissau findings on DTP. Dr Melgaard's suggestion on a communications strategy was adopted.

### ***Recommendations***

1. SAGE commends the work of GACVS in carefully examining the evidence on the nonspecific effects of vaccines on mortality, and endorses the conclusion reached by GACVS that on the evidence currently available an association between DTP and increased mortality has not been demonstrated.
2. SAGE commends the efforts of GACVS to commission additional studies aimed at determining whether the findings reported from Guinea-Bissau (British Medical Journal, 9 December 2000) are reproducible in Guinea-Bissau and elsewhere in developing countries, and awaits the outcome of these studies.
3. SAGE endorses the proposal for the development by V&B of a communications strategy meeting public concern about the adverse effects of vaccines in general.

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# Annex 1:

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