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Montreux, Switzerland, 10-12 June 2001

Initiative for Vaccine Research
Vaccines and Biologicals

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Abbreviations

AIDS	acquired immunodeficiency syndrome
ATT	Access to Technologies
BCG	Bacillus Calmette-Guérin (vaccine)
BL-3	biosaftey level 3
CDC	Centers for Disease Control and Prevention (USA)
CDS	Communicable Diseases (WHO)
CRO	Contract Research Organization
CT B	B-Submit of Cholera Toxin
DC	developing countries
DT	diphtheria–tetanus (vaccine)
DTP	diphtheria–tetanus–pertussis (vaccine)
ETEC	Enterotoxigenic *E-coli*
GAVI	Global Alliance for Vaccines and Immunization
GMP	good manufacturing practice
HBV	hepatitis B virus
HepB	hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
IFN	Interferon
IVR	Initiative for Vaccine Research
MVA	Modified Vaccinia Ankara strain of vaccinia virus
NIH	National Institutes of Health (USA
PATH	Program for Appropriate Technology in Health (USA)
PCR	polymerase chain reaction
pfu	plaque-forming units

QSB	Quality Assurance and Safety of Biologicals
RSV	respiratory syncytial virus
SAGE	Scientific Advisory Group of Experts
SCUDDS	Self-contained Unit Dose Delivery Systems
SOP	standard operating procedure
TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TT	tetanus toxoid
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
V&B	Vaccines and Biologicals (WHO)
VAM	Vaccine Assessment and Monitoring (V&B/WHO)
VVM	vaccine vial monitor

Executive summary
(prepared by Dr Rino Rappuoli)

Introduction

The Montreux meetings were initiated in 1996 by Dr Paul-Henri Lambert, who was then Head of the Vaccine Development Team of the Department of Vaccines and Biologicals. The first meeting, held before the Strategic Advisory Group of Experts (SAGE) had been formed, gathered technical information on the basis of which informed decisions and recommendations on vaccine development could be made. When the Global Alliance for Vaccines and Immunization (GAVI) came into the picture, the organization of the Montreux meetings was shared by WHO, which hosted them, and the GAVI Research and Development Task Force. The aim of the meetings is now to bring together the major players in vaccine development and implementation, to communicate and discuss the activities and strategies adopted by the Task Force, to explore what is new in the field, to find out which issues are open, and to make recommendations. The 2001 meeting was chaired by the industrial co-chair of the Research and Development Task Force, and its goal was to bring to the forefront all the problems that vaccine manufacturers were facing in developed and developing countries.

Introductory session

Following brief introductory remarks by Dr M. Teresa Aguado and Dr Rino Rappuoli, a keynote lecture was delivered by Dr Jacques-François Martin, President of the Vaccine Fund, an expert with extensive experience as a senior manager in the vaccine industry and with much recently acquired know-how in the public sector. Infectious diseases are the main reason for economic problems in the developing world. However, for the first time, the vaccine community is coming together in a true alliance (GAVI) in order to combat these diseases, even in the poorer countries. Within the alliance it is essential for the public and private sectors to collaborate with one another. Clearly, in order for this to be possible they have to understand each other. The private sector has to make a profit in order to be able to contribute financially to GAVI. Some vaccines are still perceived as a public benefit which ought to be inexpensive. It has to be realized, however, that they provide the best value in terms of medical intervention and that the appropriate price is not being paid for the service they represent.

The Global Fund was initiated by the generosity of Bill and Melinda Gates with a donation of US$ 750 million. This has encouraged further donations from other charitable organizations and from governments, taking the figure to $1.1 billion. The target for donations is 1.8 billion. Of these funds, $370 million has already been committed to the acquisition of products and $75 million has been dedicated to

infrastructural purposes. The week before the meeting the first immunizations with vaccines provided by the Vaccine Fund were given to children in Mozambique. Once vaccinated, they were given yellow vaccination cards as "passports for life".

Brief addresses were given by Mr Michel Zaffran from WHO, replacing Dr Tore Godal, and by the Co-Chairmen of the GAVI Research and Development Task Force, Dr Yasuhiro Suzuki and Dr Myron Levine, who presented an update on GAVI activities and the progress of the Task Force. The following strategic objectives of GAVI are:

- improvement of access to immunization services;
- expansion of the use of existing cost-effective vaccines;
- acceleration of the development and introduction of new vaccines;
- acceleration of research and development efforts in respect of vaccines and related products specifically needed by developing countries, particularly vaccines against HIV/AIDS, malaria and tuberculosis;
- to make immunization an integral part of international development efforts.

It is advisable to consider this as an economical investment rather than as a charitable operation, and therefore attempts should be made to raise more money for the Vaccine Fund, possibly through G8 involvement, in order to increase the interest of the private sector in preventive vaccines. The private sector is actually shifting its attention from preventive to therapeutic vaccines, which are believed to be more profitable.

The mission of the Task Force is to catalyse action in research and development in support of GAVI's overall objectives. In particular the Task Force should support the objectives of:

- accelerating the development and introduction of new vaccines and technologies;
- accelerating research and development work on vaccines needed primarily in developing countries.

In order to achieve these goals the Task Force had initially decided to focus on three specific projects and three new short-term technologies of high impact and high probability of success. Project selection was carried out by circulating a questionnaire and reviewing the responses at a meeting held in Boston in the autumn of 2000. The candidate vaccines considered in the questionnaire related to:

- HIV/AIDS
- Malaria
- Tuberculosis
- *Streptococcus pneumoniae*
- Rotavirus

- *Neisseria meningitidis* group A (and C)
- *Shigella*
- Respiratory syncytial virus (RSV)

The Task Force recognized that HIV, tuberculosis and malaria merited high priority. However, given the massive global effort that was involved in these projects, little could be done to push them any further at present. The Task Force also recognized that if suitable vaccines became available there was no infrastructure available to put them into efficient public health use. It was therefore decided to focus on vaccines of lower technical risk (e.g. where proof of concept had already been obtained). Success with these vaccines would alleviate the burden of important diseases in developing countries and would build the infrastructure for the efficient delivery of vaccines emerging later, such as HIV, tuberculosis and malaria vaccines. On the basis of all the relevant criteria it was recommended that the Task Force initially concentrate on vaccines against:

- *Streptococcus pneumoniae*
- Rotavirus
- *Neisseria meningitidis*

Once the groundwork is laid by work on these vaccines, attention could turn to the more difficult candidates such as HIV, malaria and tuberculosis vaccines. A process has been initiated for the selection of new technologies, focusing on those which would provide increased access to immunization, provide safety of vaccines and vaccination, and improved disease surveillance and management of immunization services.

The introductory session was concluded with presentations on the strategies and activities of the other GAVI task forces by Dr Amie Batson, Co-Chair of the Task Force on Financing, Ms Diana Chang-Blanc, Task Force on Country Coordination, and Dr Heidi Larson, Chair of the Task Force on Advocacy. Close collaboration and communication on the activities of the different task forces is necessary in order to maximize GAVI's overall impact.

Another important common goal of GAVI consists of finding mechanisms to encourage the private sector to invest in vaccines dedicated to the poorest countries.

World Health Organization and the Global Alliance for Vaccines and Immunization

Overall Chairperson:	Rino Rappuoli
Moderators/Co-Chairpersons:	Gus Nossal Claire Broome Mike Levine Jan Holmgren Gordon Dougan Rosanna Lagos Rino Rappuoli
Rapporteurs:	Uli Fruth Margaret Liu Mark Miller Giuseppe del Giudice George Curlin Howard Engers Ron Dagan Amie Batson
GAVI Representative:	Tore Godal
WHO/IVR Representative:	Teresa Aguado
Participants:	See Annex 1

Progress towards vaccines for HIV/AIDS, malaria and tuberculosis: overview and highlights

HIV/AIDS: The biological basis of an AIDS vaccine
(Neil Nathanson and Donald Francis)

The difficulties facing the development of a vaccine against HIV/AIDS includes the biology of viral persistence and disease progression which is poorly understood. This is also true for the mechanisms of protection against infection and/or disease. It remains unclear whether a vaccine against HIV/AIDS should induce sterilizing or partial immunity, as existing vaccines usually provide only partial immunity. The immune correlates of protection against AIDS have not been defined, although it has been reported that protection is associated with the presence of antibodies, CD4+ proliferating cells, and/or CD8+ cytotoxic lymphocytes. The different findings could be explained by the utilization of different model systems and different immunization protocols. It remains entirely possible that a combination of the three effector systems would be ideal for the induction of vaccine-mediated protection.

Another crucial open issue relevant to the development of an effective AIDS vaccine concerns the intrinsic variability of the virus and the question as to whether clades, 10 at present, represent distinct immunotypes at the antibody and/or cellular level, or whether a "common" vaccine against HIV-1 is conceivable. Five groups have products in phase I trials, one group (priming with avipox expressing the gp120, followed by boosting with the recombinant protein) has a construct in phase II trials, and one group (VaxGen) is in phase III trials. Eighteen groups have products at the pre-clinical stage, more or less close to clinical trials. Promising data (significantly reduced viraemia, although without sterilizing immunity) are coming from studies pursuing the approach of priming with DNA and boosting with the same gene (gp120) expressed in MVA.

To summarize the outline of phase III trials currently in progress with the VaxGen vaccine, it contains gp120 protein adjuvanted with alum and has shown 100% protectionin chimpanzees against a homologous challenge. In phase I/II trials the vaccine has demonstrated a very good safety profile and very good immune responses. The ongoing phase III trials are being conducted in the USA (B clade, infection rate 1.5% per year, 5400 individuals, 61 clinical sites) and Thailand (B/E clades, infection rate 6% per year, 2500 individuals, 17 clinical sites). The primary endpoint will be prevention of infection. The secondary endpoint will be the reduction of viraemia as measured by PCR. Safety, adverse events, behavioural changes, and potential correlates of protection will also be evaluated. An interim analysis of the study in the USA will be carried out in November 2001 and the study will be completed at the end of 2002. The interim analysis of the Thai study will be performed at the end of 2002 and this study will terminate in November 2003.

Malaria: Vaccines against blood stages of malaria parasites
(Chetan Chitnis)

Plasmodium falciparum causes 300–500 million cases of malaria and 1.5–2 million deaths annually, mainly in sub-Saharan Africa. *P. vivax* causes 75–90 million cases per year. Malaria is also appearing in non-immune migrant populations in Asia and South America. The frequency of drug-resistant strains of parasites is increasing worldwide, as is the resistance of mosquitoes vectors to insecticides.

Numerous obstacles hinder the development of a malaria vaccine. There are several species of parasite (*P. falciparum*, *P. vivax*, etc.) and multiple stages (liver, blood, sexual), which induce species and stage-specific immunity. It is not possible to culture *P. falciparum* in axenic conditions and *P. vivax* cannot be cultured at all. The predictability of animal models of infection with human malaria parasites is not well established. No correlates of protection have been defined and the malaria parasites have developed multiple immune evasion mechanisms (antigenic diversity, antigenic variation, etc.). Finally, the private sector has shown decreasing interest in the development of a malaria vaccine.

Nevertheless, several observations suggest that the development of a vaccine against malaria is conceivable.

At the International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi, research and development has focused on the merozoite surface antigen 1 ($MSP\text{-}1_{19}$) and on the erythrocyte-binding antigen 175 (EBA-175). MSP-1 is a highly variable 195 kDa protein expressed on the surface of merozoites. However, it contains a well- conserved C-terminal sequence ($MSP\text{-}1_{19}$) that may be a very promising candidate. EBA-175 in *P. falciparum* is the equivalent of the Duffy binding protein of *P. vivax*, which is considered as a candidate antigen for a vaccine against infection by *P. vivax*. The production of both recombinant proteins is now being scaled up.

Efforts are being concentrated on the identification of the best adjuvant or adjuvants to generate functional antibodies (e.g. QS21, MF59, Montanides, SBAS2, etc.) and on the evaluation of efficacy against *P. falciparum* challenge in Aotus monkeys, with a view to clinical trials in 2003. A potential field site for future vaccination trials has been identified in the Sundergarh District of Orissa. Transmission occurs throughout the year in this area; 96% of infections are attributable to *P. falciparum* and 2–3% to *P. vivax*; children aged 1–5 years experience multiple episodes annually; older individuals exhibit anti-disease immunity.

Malaria: Pre-erythrocytic malaria vaccines
(Adrian Hill)

Vaccination with irradiated sporozoites has been shown to protect mice, monkeys and humans (apparently through CD8 cytolytic T-cells), thus demonstrating that it is possible to eliminate the parasite at the time of infection. Challenge models are available in humans and small animals.

In the area of pre-erythrocytic malaria vaccines, two strategies have shown some protective efficacy in humans, both of them involving effector mechanisms mediated by T-cells. One consists of a protein-adjuvant vaccine (RTS,S antigen plus the SBAS2 adjuvant); the other involves DNA priming followed by boosting with the same gene expressed in MVA.

The RTS,S antigen is a fusion protein containing most of the CS protein of *P. falciparum* and HbsAg. SBAS2 is a cocktail adjuvant containing MPL, QS21 and an oil-in-water emulsion; it induces good antibody and CD4 responses. In challenge experiments this vaccine protected six out of seven immunized volunteers. When the infectious challenge was repeated after six months however, only one in six remained protected. The overall efficacy of the vaccine in a homologous challenge model involving over 50 volunteers was 40–45%. In a phase IIb efficacy trial involving 306 volunteers in the Gambia, the efficacy against infection for the whole surveillance period was 34–71% during the first nine weeks but 0% for the following six weeks. A single booster dose produced 47% efficacy during the following malaria season. This vaccine induced high levels of cells producing IFN-gamma, but the duration of the T-cell response was short. Thus the RTS,S vaccine can induce cross-strain protection of limited duration. This vaccine is currently being improved by the addition of a blood-stage antigen (MSP-1).

The prime-boost approach developed by Adrian Hill's group uses non-replicating poxviruses to boost the cellular immune response primed with DNA. This approach is powerful for inducing proliferation of specific CD8 cells and for enhancing Th1-type CD4 cell responses. The modified vaccinia virus Ankara (MVA) is a highly attenuated vaccinia virus strain that replicates in chicken embryo fibroblasts but not in mammalian cells. More than 120 000 people have been vaccinated with non-recombinant MVA as a vaccine against smallpox with an excellent safety profile.

A DNA construct was produced which consisted of a polyepitopic sequence coding for several CD8 epitopes (with various HLA class-I restrictions) fused with the TRAP/SSP2 coding sequence. This construct was inserted into a plasmid for use as a DNA vaccine, as well as into the MVA vector. The DNA vaccine was then administered intradermally (500 micrograms) or using a PowderJect gene gun to volunteers in a phase I trial in the United Kingdom. An MVA boost was given intradermally. As in similar phase I trials in the Gambia, no safety issues were reported. Priming with the gene gun and boosting with MVA induced the best CD8 responses. DNA-MVA was more immunogenic than either alone. In a human challenge experiment in the United Kingdom, two of six volunteers immunized in accordance with this vaccination schedule exhibited a significant delay in the appearance of parasites in their bloodstream. T-cell responses were stronger in Africans than in non-immune Europeans. DNA-MVA clinical trials have started or will start soon in other disease models: HIV (United Kingdom and Kenya), tuberculosis (BCG priming + MVA-Ag85 boost, United Kingdom), hepatitis B (therapeutic, the Gambia). Work in progress aims at the optimization of dosage, route and intervals, as well as the evaluation of the replacement of DNA by fowlpox virus for the priming vaccination.

Other ongoing pre-erythrocytic malaria vaccine trials include: (i) five plasmids tested in up to 40 challenged volunteers with or without a plasmid coding for GM-CSF, United States Navy; (ii) phase I clinical trial with long CS peptides plus Montanide ISA 172 as adjuvant, University of Lausanne; (iii) phase I trial with long LSA-3 peptides plus adjuvant, Pasteur Institute.

Tuberculosis: Tuberculosis vaccines (Harriet Mayanja-Kizza)

Tuberculosis still causes high mortality and morbidity, especially in developing countries. The situation is worsened by the HIV epidemic and the emergence of multiple-drug-resistant strains of mycobacteria. Control measures include case-finding, treatment, environmental control and vaccination with BCG. BCG, which was introduced in 1921, provides reasonable protection against childhood manifestations of tuberculosis such as tubercular meningitis. However, it gives inadequate and inconsistent protection against cavitating pulmonary tuberculosis, with efficacy varying between 0% and 80%. BCG-mediated protection declines with the age at vaccination and no protection is seen in subjects older than 15 years, possibly because of interference with environmental mycobacteria to which older individuals are exposed.

The animal models (mice, guinea pigs, rabbits) available for testing new vaccines are not optimal and no precise surrogate of protection is currently available. Several approaches are being followed for the development of new vaccines against tuberculosis: (i) development of new attenuated strains of the pathogen, *Mycobacterium tuberculosis*; (ii) knock-in mutations of the current vaccine, BCG, to improve its immunogenicity; (iii) protein subunit vaccines with antigens such as MTB72, Ag85, fusion protein of Ag85 and ESAT-6, major secretory protein of 30 kDa; (iv) DNA vaccines have been tested in animals using the Ag85 as a model; (v) the same model has also been tested in the DNA prime/protein boost approach. The development of therapeutic vaccines is also being considered with a killed preparation of *M. vaccae.*

Tuberculosis: Report on the Global Forum on Tuberculosis Vaccines Research and Development (Mike Brennan)

Eight million new cases of tuberculosis are diagnosed every year, causing roughly 2 million deaths. Thus a vaccine with an effectiveness as low as 50% would save more than a million lives annually. The Global Forum on Tuberculosis Vaccines Research and Development was held in Geneva on 7–8 June 2001. It was recognized that the availability of at least 10 candidate tuberculosis vaccines for testing in humans represented a turning point in tuberculosis vaccine development. The clinical testing of tuberculosis vaccines will now be the driving force in this field.

A five-year action plan has been developed with the following milestones: (i) testing a minimum of five tuberculosis vaccines in phase I/II clinical studies; (ii) building a clinical site infrastructure to begin testing a minimum of one tuberculosis vaccine in phase III efficacy studies; (iii) standardizing and optimizing preclinical testing in animal models.

The following recommendations have been made.

A. For preclinical testing strategies:

1. Standardize animal models for tuberculosis.
2. Establish international testing centres with BL-3 capacity.
3. Use animal models to test human infection and immunization paradigms, including latency and reinfection, dose and immunization schedules, development of potency assays, immunization strategies (e.g. prime-boost strategies, exposure to environmental mycobacteria, etc.).

B. For clinical trials:

1. Establish a clinical trials network for tuberculosis vaccines.
2. Establish an adult immunization strategy.
3. Develop standardized guidelines for clinical evaluation of tuberculosis vaccines.
4. Integrate new tuberculosis diagnostics into clinical studies.
5. Synergize with other research programmes (e.g. tuberculosis drugs, tuberculosis diagnostics, AIDS, malaria).
6. Address tuberculosis-specific issues, e.g. vaccines for tuberculosis-infected and BCG-immunized populations, populations with high incidence of AIDS.

C. For manufacturing:

1. Partner academic vaccine developers with facilities capable of producing vaccine trial lots under GMP.
2. Promote efforts to harmonize regulatory standards for tuberculosis vaccines.
3. Address tuberculosis-specific issues, e.g. BL-3, manufacturing facilities, potency assays, safety studies.
4. Perform vaccino-economic and cost-effectiveness analysis to assure global access to tuberculosis vaccines.

The three disease-specific vaccine research and development projects selected by the Task Force

Pneumococcal vaccines (Orin Levine and Ron Dagan)

Pneumococci are the major causative organisms of invasive infections, bacterial pneumonia and acute otitis media. It is estimated that they cause annually over a million deaths in children under five years of age. Over 90 serotypes have been identified but a relatively small number of them account for most invasive disease. A 7-valent conjugate vaccine has been licensed. It has proved efficacious against invasive disease and bacterial carriage but less so against otitis media. 9-valent and 11-valent vaccines are at the phase III stage of development. The following questions have to be considered:

- Will the efficacy observed in developed countries be repeated in developing countries?
- Will the serotypes included in the vaccines be replaced by other serotypes?
- Will resistance increase in these serotypes?
- Will conjugate vaccines be available for poorer countries in the coming years?

One of GAVI's objectives is to accelerate the introduction of pneumococcal conjugate vaccines. The Task Force on Research and Development met at NIH in April 2001, with representatives of industry, academia and regulatory agencies, in order to identify priority research and development activities on Pneumococcal Conjugate Vaccines necessary for accelerating the development and use of these vaccines. Among the activities identified the following were considered to be of the highest priority:

- development of methods to assess disease burden in various settings;
- standardization of diagnosis of pneumonia by X-ray;
- expansion of surveillance of laboratory-confirmed disease;
- measurement of pneumonia burden;
- establishment of long-term surveillance to measure vaccine impact;
- generation of more local advocacy from research.

The final document is not a comprehensive agenda of all research needs in pneumococcal diseases and vaccines. It includes only those high-priority activities that would lead to the development and introduction of conjugate vaccines in developing countries. However, it also acknowledges the importance of research in adults and on approaches other than that involving conjugate vaccines, such as the

use of protein vaccines, but goes not further on this subject. The process should see the involvement of the broad research and development community and coordination with other task forces and their communities.

Rotavirus vaccines (Roger Glass and Bernard Ivanoff)

Rotavirus is the most common cause of diarrhoeal deaths among children in developing countries and of diarrhoea leading to hospitalization worldwide. A vaccine licensed in the USA in 1998 was administered to over 800 000 children. Vaccine-associated intussusception was identified within nine months, the recommendation to use the vaccine was withdrawn, and production was stopped. The risk of intussusception being one event in 12 000 to 56 000 vaccinees, the first 800 000 vaccinees would have experienced 13 000 fewer diarrhoeal hospitalizations but 67 more intussusceptions (one per 200 rotavirus hospitalizations). In developing countries, rotavirus kills one child in 200. The risk of intussusception in these countries is unknown. However, assuming that the rates are similar to those observed in the USA, one vaccine-associated intussusception death would be expected for every 250 rotavirus deaths averted. The need for rotavirus vaccine in developing countries thus remains clear. Currently, two international vaccine manufacturers and two local producers are making and testing new rotavirus vaccines. It is necessary to establish the safety and efficacy of the next generation of rotavirus vaccines and to ensure their availability in adequate amounts and at an affordable price for children in developing countries. WHO has therefore made the following recommendations:

- The development of new candidate rotavirus vaccines should be encouraged.
- Parallel testing of new vaccines should be performed in developed and developing countries.
- The potential risk of intussusception should be assessed.
- Research on the pathogenesis and epidemiology of intussusception should continue, especially in countries interested in testing new rotavirus vaccines.
- Studies on the rotavirus disease burden should be performed in selected developing countries.
- Laboratory surveillance of rotavirus strains should continue, especially in Africa and Asia.

WHO has already initiated several of these activities.

Meningococcal vaccines (Luis Jodar)

A substantial reduction of meningitis-associated mortality and morbidity could be achieved in Africa by the introduction of group A/C conjugate vaccines. Several companies suspended development of these vaccines during the 1990s because of high costs and insufficient returns. GAVI has sought to develop a tailor-made vaccine for Africa through the Meningitis Vaccine Project, which foresees public-private partnerships and detailed analysis of costs and timelines. In order to stimulate industrial interest the Project envisages capital investment for production capacity, support for clinical activities, support for a fast-track licensing strategy, and guaranteed purchase. The future activities will include:

- Appointing a director and staff.
- Negotiating partnership agreements.
- Making site visits to companies.
- Making a presentation to GAVI.
- Holding meetings for strategy development with African countries.
- Formulating an implementation plan with partners.

The prevention of meningococcal epidemics is a matter of high priority for the countries in the African meningitis belt. Conjugate vaccines could prevent and eventually eliminate these epidemics. The introduction of conjugate A or A/C vaccine is feasible and affordable in the short-term. The potential exists for strengthening immunization services, achieving sustainability and synergizing with other disease control programmes. The Project could become a model for public-private sector partnerships in respect of other "orphan" vaccines.

New immunization technologies

A process for identifying and selecting new technologies

(Teresa Aguado and Peter Wilson)

The objective was to select up to three new technologies capable of improving safety, compliance and effectiveness in immunization. By early 2002 the GAVI Task Force on R&D will make recommendations on the selected technologies.

New technologies cover a wide range of possible applications and are at various stages of development. For the purpose of ranking a list of these technologies was prepared and some 65 questionnaires were distributed in developed and developing countries. The questions, suggested by the Research and Development Task Force, were as follows:

- How can new technologies or research improve immunization?
- What are the criteria for selection?
- What is the prioritization of the broad technology/research areas?
- How are specific technologies/research identified and prioritized?

Of the 41 responses analysed, 12 came from developing countries and four from industry. The responses gave the following clear indications.

- There is a desire to make immunization simpler and easier by reducing the number of patient interactions, improving management and tracking systems, and solving short-term engineering problems (e.g. in the cold chain).
- Dependency on the cold chain, which appeared to be a major source of difficulty, should be reduced.
- The use of sharps should be reduced in the long term and there should be a move to non-parenteral immunization.
- New ways of making immunization safer should be investigated.
- There is a need to understand the effectiveness of the immunization service and factors affecting access to and coverage of immunization, with a view to achieving improvement in these matters.

Three study teams have been set up on **safety** (e.g. administration, risks of contamination), **efficiency** (e.g. reduction of wastage, reduction of dependency on the cold chain, reduction of contacts, use of multidose/multivalent vaccines) and **effectiveness** (e.g. access, coverage, practical engineering problems, logistics).

These teams are expected to perform the synthesis necessary for recommendations to be made to the GAVI Board. The major tasks of the study teams are: to define goals and criteria of success; to identify the main issues and constraints; to review alternative strategies for achieving goals and addressing the issues (short term and long term); to identify technologies or research areas critical for success; to identify how new technology can be applied to a particular vaccine project; and to evaluate and recommend specific technologies and research.

Priority area: assuring safe and effective vaccine administration

(Michael Free)

Current challenges in immunization include unsafe administration, wasted vaccine, spoiled vaccine, decaying cold chain, inaccurate dosing, syringe shortages, poor infrastructure, outreach, and addition of new vaccines. Various means are available for assuring safe and effective vaccine administration. They include: detection and prevention of heat damage and freeze damage, the prevention of vaccine contamination, provision of means of administration, provision of sterile administration and correct doses, and prevention of collateral sharps injury.

Heat damage is monitored with vaccine vial monitors (VVMs). First used for OPV, VVMs are now available for most vaccines and have also been accepted by WHO, GAVI and UNICEF as a means of reducing vaccine wastage. The prevention of heat damage, i.e. the improvement of vaccine stability, can be achieved by glassification (using sugar stabilizers such as trehalose), which has been successfully tested with measles vaccine, DT and DTP. Other systems for preventing heat damage include fail-safe refrigeration systems, spray-drying (for dry injection or inhalation), and cochleation (for oral delivery). The prevention of freeze damage is critical for hepatitis B vaccine (HepB), DTP, TT and other vaccines. This can be achieved by means of freeze indicators, although this technology is only applicable to batches, i.e. not to individual vials.

The contamination of vaccines can be prevented by using monodose vaccines (however, this increases costs and volumes), auto-disable reconstitution syringes (plastic needles), and auto-reconstitution (enables storage as stabilized dry vaccine). Reusable administration systems are frequently associated with the transmission of HBV infection (30% risk). Disposable administration systems assure sterile injections with auto-disable syringes, self-contained unit dose delivery systems (SCUDDS, such as UniJect™). Collateral sharps injuries can be prevented by needle-free administration (jet injector, needle-free SCUDDS).

With a view to assuring safe and effective vaccine administration the GAVI research and development agenda may include the following.

For the short term, i.e. under 5 years:

- Roll-out of VVMs for all vaccines, monodose vials, auto-disable syringes for routine use, injection SCUDDS, campaign jet injectors.
- Validation of high-efficiency refrigerator, ice-free cooling, out-of-the-cold vaccines, sharps disposal solutions.
- Development of sugar/glass stabilizers, injection SCUDDS, reconstitution auto-disable syringes.

For the long term, i.e. 5–10 years:

- Research and development on auto-reconstitution systems, non-invasive SCUDDS, other stabilization systems (for new vaccines).

Priority area: systems efficiency (Gordon Dougan)

The aim of improving vaccine efficiency is to reduce the morbidity and mortality burden of infectious diseases as safely and cheaply as possible. Systems efficiency can work at many levels against a background of improvements in safety and programme effectiveness.

The first area relates to the stability of vaccines, with reference to both shelf-life and field-life. This can be achieved through the stabilization of the vaccine preparation. Examples of these systems are lyophilization, glass technology (which still requires validation by using a single vaccine such as TT), and slow-release methods (which also require validation).

The second area relates to the enhancement of immunogenicity, with the final objective of reducing the number of contacts. This can be achieved by means of better adjuvants and immunostimulators, slow-release systems such as biodegradable particles, and better delivery systems such as guns, inhalers, and DNA versus protein. It is still undecided as to what impact the combination of strong adjuvants would have.

The third area relates to the safe delivery mode of vaccines, in terms of guns, sprays, patches, etc., via the mucosal, oral, nasal and transcutaneous routes. Little is known about the latter in humans with respect to safety, mechanisms and immunogenicity, and short-term validation is required (phase I and II trials). Mucosal delivery has produced a large volume of scientific literature but few potential products because of the need for the optimization of improved formulations and delivery systems.

The current needs for systems efficiency are as follows:

- For stabilization: glass/sugar stabilizers and others.
- For immunogenicity: improved adjuvants, impact on combination of strong adjuvants.
- For delivery: non-invasive delivery (devices, transcutaneous), devices for gut and nose delivery (possibly SCUDDS), studies in humans (adjuvants/formulations), geographical differences in responsiveness.

Priority area: programme effectiveness (Rosanna Lagos)

The main goal is to evaluate the effectiveness of immunization services in a manner which is accurate, sustainable and synergistic with other public health interventions. This requires competent management, accurate monitoring of achievements, and safe and efficient immunizations.

How can the efficiency of immunization services at the operational level be improved? Immunization services are very efficient in urban areas, with up to ten immunization contacts and vaccination records per hour. In rural areas, however, reaching a handful of children may involve expensive logistical arrangements and costs are therefore much higher than in cities.

Technologies are needed for: (i) assessing the costs of immunization services; (ii) information systems for monitoring vaccination at the level of the individual vaccine; (iii) information systems for assessing impact on diseases; (iv) reliable and easy evaluation of immune protection.

In order to improve the effectiveness of immunization at the operational level, great importance is attached to reducing the number of immunizations, dependence on the cold chain, wastage and contamination.

New developments in selected areas

***Shigella* vaccines** (Karen Kotloff)

Shigellosis affects more than 160 million people and causes 1.2 million deaths every year. It is highly contagious, oral rehydration provides little benefit, and antibiotic resistance is increasing. Several studies in human volunteers have shown that the use of vaccines against shigellosis is feasible. Parenteral conjugates, nasal proteosomes and invasive live attenuated deletion mutants are being tested. Some of these vaccines, especially a live oral attenuated vaccine, have shown promising efficacy against challenge in volunteers. However, recent results from phase I/II trials in children are less promising. Because of serotype specificity in protection, a multivalent *Shigella* vaccine approach is being pursued with a cocktail of *Shigella* species carrying appropriate gene mutations.

ETEC (R. Abu-Elyazeed)

Enterotoxigenic E-coli remains a leading cause of diarrhoea in developing countries and travellers. An oral vaccine consisting of killed whole-cell ETEC plus recombinant CT B subunit has shown promise in adult volunteers. This vaccine had proved very safe and strongly immunogenic among adults and young persons in trials conducted in developed and developing countries. Efficacy trials of the vaccine are now in progress in the Nile Delta region in Egypt among children aged 6–18 months. Data on the trial will be available by early 2002.

RSV (Theodor Tsai and Eric Simoes)

RSV infects 90% of children by 2 years of age and causes lower respiratory tract disease in children aged up to 5 years. The most severe cases occur in infancy, especially in children aged under 6 months. RSV accounts for between 250 000 and 900 000 deaths annually in children over 5 years of age. Passive immunization with specific intravenous immunoglobulins has reduced RSV hospitalization by about 50%. The development of a vaccine has met several obstacles, the most significant deriving from the observation that formalin-inactivated vaccine enhanced lung pathology and mortality during the 1960s.

Several RSV subunit vaccines are now under development, involving fusions of both recombinant F or G proteins or fusions of parts of them. These vaccines have been shown to be efficacious in animal models and safe in humans in phase I/II trials. Cold-adapted mutants of the virus have been obtained and used for intranasal delivery. In humans these strains have shown acceptable safety.

New adjuvants

CpGs (Heather Davis)

CpG motifs are unmethylated C-G dinucleotides in a particular base context. They strongly stimulate innate immunity. In microorganisms, C-G dinucleotides are expected at a random frequency of one in every 16 base pairs. In vertebrates their frequency is suppressed from one-third to one-fourth. In mammals, C residues are highly methylated and thus lose their immunostimulating properties. Acting through Tol Receptor-9, CpG motifs stimulate a variety of immune cells. This stimulation includes: (i) direct activation of B-cells; (ii) direct activation of macrophages and dendritic cells; (iii) activation of NK cells; (iv) activation of CD4+ and CD8+ cells, leading to the development of an immune response of the Th1 type. CpG motifs augment adaptive immune responses and have proved superior to well-known adjuvants in the induction of Th1-biased immune responses. The adjuvanticity of CpG motifs has been demonstrated in monkeys through the use of hepatitis B vaccine. In phase I trials in humans with CpG-adjuvanted hepatitis B vaccine, a strong and early vaccine-specific immune response has been induced. Further pre-clinical studies have indicated the potential use of CpG as an adjuvant for a variety of vaccines.

MF59 (Giuseppe Del Giudice)

MF59 is an oil-in-water emulsion containing squalene, Tween-80 and other components. Although the exact mechanisms of adjuvanticity are not known, it seems to work through the activation of antigen-presenting cells. In mice, MF59 has shown strong adjuvanticity for influenza vaccines, enhancing the immune responses in old animals at levels normally encountered in young individuals. MF59 appears to induce a pronounced immune response of the Th2 type. Extensive clinical data demonstrate that MF59 strongly enhances the immune response to influenza vaccine in older individuals. On the basis of these data the MF59-adjuvanted influenza vaccine was licensed in Europe in 2000. This was the first adjuvant to be admitted for human use after alum. More recently, MF59 has significantly improved the immunogenicity of a vaccine against a pandemic strain of influenza virus and reduced the amount of antigen required to achieve protection. Similarly, MF59-adjuvanted hepatitis B vaccine has shown induced protective immunity in human volunteers after two doses of the vaccine, instead of the usual three.

Virosomes (Reinhard Glück)

Virosomes are spherical vesicles with a diameter of 140 nm. They have been used to formulate hepatitis A and influenza vaccines and are licensed in various European countries. A virosomal influenza vaccine adjuvanted with wild-type *Escherichia coli* enterotoxin (LT) has been licensed in Switzerland for intranasal delivery. It was shown to be safe and efficacious in several animal models and shows good immunogenicity in humans.

Clinical trials

Scientific considerations on quality, safety and regulatory issues for vaccines under development: HIV as a model

(Elwyn Griffiths and José Esparza)

Many new vaccines are under development for several priority infections. Some approaches are following traditional lines, while others are moving into novel biotechnologies. It is essential that early consideration be given to regulatory issues associated with these products so as to ensure that safety and quality control are adequately addressed and that regulatory decisions have the soundest possible scientific basis worldwide. This should facilitate the licensing process and minimize delays in product availability.

Historically, assuring the consistent safety and efficacy of vaccines has been primarily a problem-led exercise, i.e. major problems have led to improvements in quality control procedures. In the biotechnology field, however, guidelines on production and control have been laid down early in the development of new products and have been instrumental in establishing their safety and quality, have assisted national regulatory authorities to regulate them successfully, and have facilitated the rapid introduction of new products into mainstream clinical use. With respect to vaccines, WHO guidelines have been developed for some novel technologies, e.g. for DNA and peptide vaccines. In order to develop an international consensus on safety and quality control in new vaccines, however, it is necessary to identify the issues so that they can be adequately addressed by the time of clinical trials and license application. Agreement is also required on criteria for vaccine efficacy and it is necessary to develop procedures for ensuring comparability in the measurement of potential correlates of protection and for providing adequate regulatory oversight.

The development of HIV vaccines provides a model for addressing such considerations. There is an intense public health interest in developing safe and effective preventive HIV vaccines because, as yet, there is no definite cure for AIDS. HIV vaccines represent the best long-term hope for controlling the HIV/AIDS epidemic, especially in developing countries, but their development presents unique and complex scientific, social, ethical and economic challenges.

A consultation on "Scientific considerations for evaluation of HIV vaccines and related regulatory perspectives", organized by the Quality Assurance and Safety of Biologicals Team and the WHO/UNAIDS HIV Vaccine Initiative was held in Geneva on 13–16 March 2001. The principal recommendations that emerged are indicated below:

- HIV vaccine trials should be conducted only in countries with adequate regulatory resources; specific support for strengthening such resources should be sought where they are limited.
- Because of the use of several novel biotechnology approaches for vaccine production, new ways should be sought to provide appropriate specialized scientific support for national regulatory authorities of developing countries in the evaluation of candidate vaccines and clinical trial protocols and in licensing, in addition to the strengthening of regulatory processes.
- Criteria for vaccine efficacy should be clearly defined (prevention of infection, reduction of viral load) and it should be recognized that end-points may vary between countries.
- Because the production of some HIV vaccines raises issues about cell substrates which are not described in current regulatory guidelines, regulatory research should be conducted with a view to the development of further guidance based on sound science rather than on conjecture.
- Generic or specific guidelines on HIV vaccines delivered using viral and bacterial vectors should be developed.
- Consensus should be sought on methods for determining serological and cellular immune responses to HIV vaccines, as well as virus load, and appropriate reference materials should be developed for assay standardization at the international level in order to achieve global comparability of data.
- The WHO/UNAIDS Network for HIV Isolation and Characterization should be further developed in response to the continued spread of HIV, and molecular, biological and immunological information on incident viruses should be disseminated in a timely manner.

Issues in clinical trials (Mike Levine)

Dr Levine highlighted some principles and issues concerning bioethical, regulatory, design and financial aspects of clinical trials.

1. What is the impetus for organizing large-scale vaccine field trials?

Field sites generally fall into one of the following two categories.

- Site seeking a vaccine to test: A health ministry, contemplating vaccination as a future means of controlling disease, seeks one or more candidate vaccines for evaluation, e.g. the typhoid vaccine sought by Chile.
- Site sought by a vaccine developer: A vaccine developer seeks an appropriate site where the safety, immunogenicity and efficacy of a vaccine can be tested, e.g. cholera vaccines were developed and a site for testing them was subsequently sought.

2. Who should finance large-scale phase III vaccine field trials?

- Industry finances clinical development and large-scale trials for industrialized market vaccines and global market vaccines, a return being expected on this investment, e.g. initial Hib vaccine studies, Lyme disease vaccine.

- Public sector should supports trials of developing market vaccines, e.g. asexual-stage malaria, typhoid, cholera, leishmaniasis.
- Public-private partnerships should foster trials of global market vaccines in developing countries, e.g. Hib, pneumococcal conjugates, rotavirus.

3. Several ethical issues in vaccine efficacy trials in developing countries:

- What control preparation should be used? This could be chosen on the basis of technical or ethical aspects, e.g. what is the standard of care?. The control preparation might be a true placebo; a licensed vaccine against another infection that can have no effect on the outcome events of the study, providing a benefit for control subjects (however, it is sometimes difficult to find a suitable vaccine which does not compromise double blindness of the trial).
- An experimental vaccine against another infection that has no effect on the outcome of the study.
- The cross-cultural complexities of informed consent should be recognized.
- Vulnerable populations, e.g. incarcerated individuals or poor populations receiving health services from the source responsible for the trial.
- What should be the responsibilities of the sponsor after the trial ends? Do they concern the study population and the larger reference population of the country or region in question. This issue should be discussed before the study is initiated.

4. Study design - reasons to randomize by units other than individual subjects:

- Nature of the vaccine, e.g. live vaccine with potential for person-to-person transmission, or vaccine conferring protection at the community level, as with transmission-blocking malaria vaccine.
- Logistics and practicality.
- Attempt to measure herd immunity.

5. Other issues in the design of various efficacy trials: who should decide when to stop a trial and break the code: industrial sponsors, who generally want to stop at the earliest possible time, or public health authorities, which generally prefer that a trial should run for an extended period of follow-up in order to obtain data on the duration of vaccine efficacy.

6. Strengthening the infrastructure in order to support large-scale vaccine field trials in developing countries; the microbiological infrastructure has to be strengthened, e.g. automated blood culture in children in preparation for pneumococcal vaccine trials. The health care delivery infrastructure often has to be reinforced as well.

7. Good clinical practices (GCP): Comprehensive regulations and guidelines on the conduct of clinical trials have to be followed if the results are to be included in an application for the licensing of a vaccine. They cover protocol design, record-keeping, laboratory standard operating procedures (SOPs), informed consent, data-reporting, and the reporting of adverse events.

8. Unexpected morbidity and mortality detected during efficacy trials. Trials should be examined carefully for unexpected events. Well-known examples include a phase III trial of formalin-inactivated RSV vaccine – where increased incidence of severe RSV disease in vaccinees vs. controls was observed; phase IV immunogenicity trials of high-titre measles vaccine *(*= 10^5 pfu) in young African and Haitian infants – increased long-term mortality in females.

9. The complexity of record-keeping, data management and formal randomization procedure is growing, e.g. increasing automation, remote data entry. This creates a tension between efforts to validate collected data and laboratory data (high-quality data) on the one hand and the simplification and economization of clinical trials on the other. Consequently, there has been a growth of contract research organizations (CROs). Among the most important roles of CROs in large trials are the management of data files, the random allocation of subjects to experimental vaccine or control regimens, and assisting in surveillance for serious adverse events. Unfortunately, CROs become very costly.

10. Efficacy versus effectiveness of vaccines. This issue is extremely important. Dr Levine believes that postlicensing effectiveness studies are of great value in helping towards understanding vaccine impact.

Views of industry and economic incentives for vaccine development

Manufacturers in developed countries (Michel Greco)

Dr Greco presented the views of the vaccine manufacturers of developed countries. He summarized the vaccine development process and showed that the research phase cost approximately 10% of the total budget necessary for the development of a vaccine. The early development phase accounted for approximately 20% of the costs, and 70% of the budget was required for the late development phase and registration.

Industry thus has selected projects very carefully before embarking on the development phase. The criteria used for selection include scientific and industrial feasibility combined with anticipation of an appropriate return on investment, which is usually calculated in relation to sales in developed countries only.

The vaccine industry is willing to help to achieve GAVI's objectives in making vaccines available to developing countries at a lower price on the following conditions:

- The industry has to obtain most of the expected return from sales to the industrialized world.
- Products sold only in the developing world have to generate a reasonable profit.

This implied that dual pricing should not lead to price decreases in developed countries and that the protection of intellectual property should be enforced.

The push-and-pull mechanism could be an incentive to manufacturers to conduct research and develop and to supply vaccines that might not otherwise be available, as it will provide additional resources for vaccine development (push) and create a more visible market downstream (pull). Other mechanisms for encouraging the vaccine industry involves supplying epidemiological data, strengthening local clinical development infrastructures, creative regulatory support, vaccine advocacy, good estimation of the capacity needed for developing markets, and commitment to purchase.

Manufacturers in developing countries (Isais Raw)

On 18 April 2001, 18 public and private laboratories in developing countries had organized a meeting under WHO auspices in order to establish a network of vaccine manufacturers in these countries. The network aims at sharing bulk vaccines stocks and exchanging knowledge on technology, research and development. Manufacturers in developing countries already supplied EPI vaccines to half of the world and they intend to play an increasing role in GAVI activities.

The European Union: a new supporter of GAVI's activities
(Arnd Hoeveler)

Dr Hoeveler reported that the European Union had decided to support the fight against HIV/AIDS, malaria and tuberculosis in developing countries, with the aim of reducing poverty.

In addition to over 100 million Euros spent in support of research on the three diseases, a major new activity planned by the European Union involves the development of a clinical trials platform for developing countries. This infrastructure will be of value when candidate vaccines became available.

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The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* team ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

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