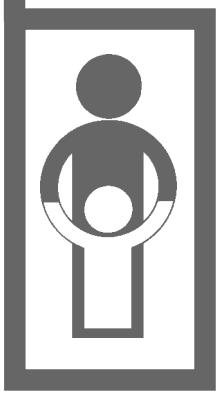
WHO/V&B/01.21
ORIGINAL: ENGLISH
DISTR.: GENERAL

Proceedings of the first Global Vaccine Research Forum

Montreux, 7-9 June 2000



DEPARTMENT OF VACCINES AND BIOLOGICALS

World Health Organization
Geneva
2001

The Department of Vaccines and Biologicals
thanks the donors whose unspecified financial support
has made the production of this document possible.

This document was produced by the
Vaccine Development Team
of the Department of Vaccines and Biologicals

Ordering code: WHO/V&B/01.21
Printed: June 2001

This document is available on the Internet at:
www.who.int/vaccines-documents/

Copies may be requested from:
World Health Organization
Department of Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* + 41 22 791 4227 • *E-mail:* vaccines@who.int •

© World Health Organization 2001

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced and translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

Contents

Abbreviations

AAV	adeno-associated viral vector
AEFI	adverse event following immunization
AIDS	acquired immunodeficiency syndrome
ALM	autoclared leishmania major
BCG	bacillus Calmette-Guérin (vaccine)
CRF	case report forms
CSP	circumsporozoite protein
CTL	cytotoxic lymphocyte
ELISPOT	enzyme-linked immuno-spot
EPI	Expanded Programme on Immunization
ETEC	enterotoxigenic *E. coli*
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GMP	good manufacturing practice
HAART	highly active anti-retroviral therapy
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation
IND	investigational new drug
IVR	Initiative for Vaccine Research
LPS	lipopolysaccharides
MAP	multiple antigen peptide
MMR	measles-mumps-rubella (vaccine)
MVA	modified vaccinia Ankara
NID	national immunization day
PCR	polymerase chain reaction
PERT	product-enhanced reverse transcriptase
RSV	respiratory syncytial virus
SOP	standard operating procedure
STD	sexually transmitted disease
TRAP	thrombospondin-related anonymous protein
UNICEF	United Nations Children's Fund
VCT	vaccine clinical trial
VLP	virus-like particle

Global Alliance for Vaccines and Immunization
and
World Health Organization

Overall Chairperson:	Myron (Mike) Levine
Moderators/Co-Chairpersons:	Rino Rappuoli John LaMontagne David Kaslow Carole Heilman Reinhard Gluck Sine Bayo Umberto Bertazzoni Hanna Nohynek William Hausdorff Wiliam Makgoba
Rapporteurs:	George Griffin Altaf Lal Claudio Lanata Margaret Liu Pedro Alonso Stefan Kaufmann Geoffrey Schild Brian Greenwood Gordon Dougan Cesar Gonzalez-Bonilla Orin Levine Margaret Burgess Douglas Young
GAVI representative:	Tore Godal
IVR representative:	Teresa Aguado
Participants:	See Annex 1

Introduction

The delegates were warmly welcomed to the First Global Vaccine Research Forum by Mike Levine, who thanked Teresa Aguado and her staff for their efficiency in organizing the meeting and the Programme Committee for their diligence in setting the programme.

David Heymann described the wide range of infectious disease targets that WHO had addressed in vaccine development activities in recent years. Infectious disease syndromes responsible for the highest mortality burden among children aged under 5 years in developing countries included acute respiratory infections, diarrhoeal diseases, measles and malaria. Important causes of mortality among adults were acute respiratory infections, AIDS, tuberculosis and malaria. Dr Heymann summarized the impact that increasing resistance of bacteria and parasites to antimicrobial agents was having on disease control activities. Many infections that had been easily treatable in the past, often with inexpensive oral antimicrobial agents, had become resistant to multiple therapeutic agents. This alarming situation demonstrated the need for vaccines.

Yasuhiro Suzuki indicated WHO's advocacy and support for vaccines and immunization and its desire to be a leading partner in the Global Alliance for Vaccines and Immunization (GAVI). He stressed the importance of research and close liaison between the public sector and industry.

Tore Godal gave an update on GAVI, including its mission, objectives and accomplishments. He drew attention to three gaps that GAVI would address: the millions of infants in developing countries each year who did not receive the vaccines that they needed or who were only partially immunized; the slow pace of introduction of new vaccines (e.g. hepatitis B, *Haemophilus influenzae* type b conjugate) into the immunization services of the least developed countries, even though such vaccines had been routinely administered for years to infants in industrialized countries; and the inadequate investment in research and development on vaccines particularly needed by populations in developing countries. He described the structure of GAVI and the interactions of its components and reviewed the Global Fund for Children's Vaccines and its fundamental importance as an instrument for achieving GAVI's objectives.

Teresa Aguado described WHO's Initiative on Vaccine Research and the pivotal role in advocacy, coordination and support played by WHO in vaccine research and implementation. She listed WHO's research activities on vaccines other than AIDS vaccines and indicated where responsibility for these activities resided in the WHO structure.

José Esparza described the vaccine research activities of the WHO/UNAIDS HIV Vaccine Initiative particularly in relation to sub-Saharan Africa. He emphasized the crucial role that a future vaccine might be expected to play in the control of AIDS in Africa and in developing countries elsewhere. However, the high expectations initially held in respect of HIV vaccine development had been tempered by a realization of the immensity of the task in immunological and virological terms. Dr Esparza outlined the long road that had led to the current Phase III trial of an HIV vaccine in Thailand, and indicated the role of WHO/UNAIDS in tackling the complex ethical issues of HIV vaccine research.

Mike Levine presented the rationale and objectives of the Global Vaccine Research Forum as an important mechanism that would help to address GAVI's research and development objectives. A fundamental tenet of GAVI was that partners should collaborate (albeit in different ways) with a view to achieving common goals, creating synergy and avoiding duplication of effort so as to make the most of limited resources. The Global Vaccine Research Forum would fulfil an important communication function and would serve as an interface with the broad and disparate research and development community.

Mike Levine explained that priorities in the global allocation of resources for vaccine research and development did not correspond to global burdens of mortality and morbidity associated with disease. Few resources were allocated for tackling diseases that disproportionately affected populations in developing countries. He indicated four categories into which vaccine development projects could be fitted on the basis of the current situation (see table below).

Four generic categories of vaccines in relation to disease burden and reliability of markets

Category of vaccine	Developing countries		Industrialized countries		Examples
	Disease burden	Current markets	Disease burden	Current markets	
Global market vaccines	Large	Small	Large	Large	Hib conjugate; HBV; rotavirus; pneumo conjugate
Industrialized market vaccines	Small	Small	Large or moderate; (may be small, but public perception high)	Moderate	Lyme disease
Impeded vaccines	Large	Small	Large	Large	RSV; Group A *S. pyogenes*
Developing market vaccines	Large	Small	Small	Small	Malaria; tuberculosis; typhoid; *Shigella*

Creating incentives for industry to invest in developing market vaccines: role of public sector in forging partnerships with industry

Alf Lindberg pointed out that a rather limited number of major vaccine manufacturers were producing most of the global supply of vaccines. The demand for vaccines was growing but many disincentives were discouraging industry from increasing production in order to supply developing countries. For example, the production of biologicals was repeatedly subjected to new regulatory changes and quality requirements, many of which were not harmonized among the major regulatory agencies. Most importantly, pricing constraints limited the ability to recover investments. With respect to the desired future generations of vaccines, research and development costs for industry had increased enormously. Research on many new vaccines was quite risky because of their complexity or the lack of a strong scientific understanding and rationale for the approaches adopted. Finally, prioritization and opportunity costs were significant. Clearly, the dedication of resources to a vaccine project of global public health importance meant that they were not available for other purposes.

The three main barriers to investment by industry in vaccines of global public health importance were:

- insufficient scientific understanding;
- lack of economic rationale;
- access to investment.

He discussed ways in which potential public/private partnerships might be successful in advancing the development of a desired developing market vaccine. On the push side, direct public investment to diminish the costs of early high-risk Phase I and Phase II clinical trials and to share the costs of Phase III efficacy trials would be useful. Improved estimates of disease burden and financing assistance to create expanded production capacity would also be helpful. On the pull side, some clear incentives for vaccine manufacturers would be tax credits on vaccine sales to developing countries, patent extension on a preferred product, modification of orphan drug legislation and precommitments to vaccine purchase. Other pull mechanisms would include Development Bank loans to developing countries for vaccine purchase, a vaccine purchase fund (like the Global Fund for Children's Vaccines), strong advocacy for the use of existing and future vaccines, and the strengthening national control authorities.

Amie Batson noted that the development of vaccines and their use in the sphere of public health for the alleviation of disease problems in the developing world was a priority of the World Bank. A study had shown that ill health, largely attributable to communicable diseases, was one of the primary causes of the slide into poverty. The Bank considered that research and development leading, for example, to a safe and efficacious AIDS or malaria vaccine, would be a global public good yielding benefits for all humanity. Strategically, the Bank considered that communicable diseases were a global problem requiring global solutions. World Bank funding accounted for 20% of ODA for health in developing countries.

A World Bank multidisciplinary task force had found that few of the major vaccine manufacturers had the development of an AIDS vaccine as a high priority in their research and development portfolios. Most research in this field was being conducted by biotechnology companies that lacked vaccine marketing experience and assumed that if a vaccine was shown to be efficacious a market for it would somehow come to exist in developing countries. Some major vaccine manufacturers doubted whether the industrialized country market for an HIV/AIDS vaccine would be significant. The Bank had found that the lack of a strong scientific basis and rationale for the development of an AIDS vaccine was a strong barrier to development. In practical terms this meant that an expensive, complicated large-scale Phase III efficacy trial would have to be completed in order to validate a candidate vaccine. Such a trial would carry a high risk in comparison with efficacy trials on many other types of vaccine for which the scientific rationale was strong. The task force concluded that, in order to accelerate the development of an AIDS vaccine, a paradigm shift involving the application of both push and pull incentives would have to occur.

Update on activities to map gaps and strengths in vaccine research and development

Dr Levine mentioned that a GAVI pre-task force, in conjunction with WHO and other partners, had undertaken work on mapping certain generic gaps and strengths in the global infrastructure with respect to the performance of vaccine research and development needed for developing countries. Taraz Samandari, Julie Milstien and Marti Vall respectively reviewed three of the associated activities: the development of a questionnaire that would help to prioritize vaccine development projects; a survey of the capacity in developing countries to produce pilot lot formulations of candidate vaccines; and the preparation of an inventory of sites in developing countries which could carry out clinical trials in accordance with good clinical practice (GCP).

Dr Samandari presented a questionnaire (Annex 2) that had been developed as an instrument to help with the selection of a few vaccine projects particularly needed by developing countries (other than ones relating to tuberculosis, malaria and AIDS) which might be targeted for accelerated development (Annex 3). The questionnaire took account of disease burden, various public health issues, the feasibility and complexity of the candidate vaccines, and vaccine evaluation issues. Each of these characteristics was ranked on a scale of 1 (least desirable) to 5 (most desirable). The disease burden could be further classified as global and regional. Several options for adjusting the score were available.

Julie Milstien reported on a survey that identified facilities in developing countries which had the capability to prepare pilot lots of candidate vaccines in accordance with GLP and good manufacturing practice (GMP). This exercise was undertaken because, at a meeting of the GAVI Pre-Task Force on Research and Development in November 1999, both public sector and industry researchers had identified difficulty in gaining access to pilot lot production as a significant obstacle impeding the pace of development of candidate vaccines. Fourteen manufacturers in five developing countries had been identified and all sites but one had been visited. Six vaccine production companies in India, four in Brazil, two in Iran, one in China, and one in Indonesia were targeted for visits in the initial cycle. Information was collected on the type of facility, production capability and capacity, experience, staffing, support facilities, equipment, regulatory support, capacity to develop products under GMP, track record and other matters. Information was collected on the capability of these companies to produce recombinant proteins, live attenuated bacteria, DNA vaccines, bacterial and viral live vector vaccines, synthetic peptides, and polysaccharide-carrier protein conjugates.

A preliminary analysis revealed that: none of the companies had experience in contract manufacturing; all had commercial and governmental commitments that would take priority; evaluation would be difficult without a specific project in mind; the costs of production and personnel were combined in many of the facilities; all but two had GMP certification from their countries but functional regulatory bodies were not in place; two producers in two countries were UNICEF suppliers.

Marti Vall Mayans presented an analysis of the various sites in both industrialized and developing countries where, based on past experience, clinical trials to evaluate developing market vaccines could be carried out. The aim was to identify sites that could be called upon to perform clinical trials under the harmonized rules and regulations of GCP. It emerged that 260 clinical trials of developing market vaccines had been conducted in the last ten years. The sources of the information were PubMed and Medline as of April 2000, WHO's vaccines and biologicals directory as of August 1999, and interviews with experts in the field of vaccine trials. Forty per cent of the trials had been conducted in developing countries and 60% in industrialized countries. Before 2000 almost all HIV trials had been performed in industrialized countries, more than 100 having been conducted in the USA. Approximately 90% of trials had been in the Phase I or Phase II categories, the remaining 10% in Phase III or Phase IV. Notably, almost all Phase III trials of developing market vaccines had been carried out in developing countries. Dr Vall Mayans presented information on the field-testing of vaccines and indicated the countries in which these studies were conducted.

A checklist was prepared with a view to assessing the capability of the sites to conduct vaccine testing in compliance with GCP, helping to identify gaps that needed to be filled in order to promote GCP in vaccine testing, developing an inventory of vaccine testing sites, and developing the infrastructure required for vaccine testing sites.

Rebecca Sheets and Brian Greenwood discussed how GCP trials might be strengthened and expedited. Dr Greenwood noted that, in the era before GCP procedures were harmonized and enforced, clinical vaccine trials had been performed more quickly and simply, had been investigator-driven, had taken greater risks, had often used inappropriate procedures and had performed inappropriate analyses. Under GCP the trials were better conceived and executed, had more appropriate design and analysis procedures, and involved lower risk to participants and lower post-licensure costs. However, too many forms had to be completed and they were too complicated. Many procedures and forms were not appropriate for local cultures, were not driven by local investigators but by foreign agencies, and were much more expensive. Furthermore, the procedures had become more important than the substance. Scientists were no longer in control of the trial procedures. The recommendations were to balance the need for GCP with reasonable procedures that were culturally acceptable, to allow more input from local scientists and vaccine manufacturers, to diminish the number of regulatory non-scientist personnel, and to look for ways of decreasing the complexity of trials without increasing the risks.

HIV vaccines

Neal Nathanson reviewed the challenges faced by the scientific community in connection with research into and the development of an AIDS vaccine. He argued that a vaccine that induced even partial protection might provide a significant public health benefit, assuming that the vaccine could be made available to high-risk target populations. Both antibody and cellular immune mechanisms were thought to be important in keeping HIV infection under control. Whether the approximately ten HIV clades were distinct immunotypes was questionable, since data existed showing cross-clade neutralization titres and cytotoxic lymphocytes (CTLs) to *gag* protein. Therapeutic vaccines – perhaps in addition to HAART – might allow quicker determination of the efficacy of some candidate vaccines.

Donald Francis argued for the involvement of the private sector in the development of AIDS vaccines but emphasized that industry had to have a satisfactory return on investment. He discussed the obstacles that still had to be overcome in order to achieve this goal, and reviewed progress made with VaxGen's BB North American and BE Thai vaccines.

Seth Berkeley described the mixture of push and pull approaches to the development of a vaccine for HIV which was being pursued by the International AIDS Vaccine Initiative (IAVI), including efforts to build local demand for a vaccine in developing countries. He noted that the effort being put into prophylactic HIV vaccine development was small in comparison with the investment in developing the next generation of therapeutic strategies. IAVI was funding three vaccine development projects: a DNA prime/modified vaccinia Ankara (MVA) boost project; an AAV project; and an attenuated *Salmonella* live vector vaccine project. These were either in early clinical trials in developing countries or were rapidly approaching this stage. It was necessary to start work on access issues immediately in order to allow rapid introduction should one or more of these strategies prove viable.

Edward Mbidde described the preparedness of researchers and government in Uganda to participate in research and development on an HIV vaccine. He cautioned that if testing was conducted in a developing country the inhabitants should not be denied access to any vaccine that was eventually produced. Among the specific benefits that a developing country might expect to derive from the performance of clinical trials on an AIDS vaccine were:

- generation of mutual trust between the vaccine trial sponsors and developing country investigators and health authorities;
- infrastructure development;
- training of local investigators and personnel in the performance of clinical trials;
- opportunities to negotiate arrangements for preferential acquisition of the vaccine should it become a licensed product.

Discussion followed on the issue of clades. Could animal and human data be compared? Would a non-clade B vaccine be tested in developing countries? The question also arose as to whether a developing country could gain access to intellectual property rights to a vaccine while maintaining incentives for industry.

Malaria vaccines

Regina Rabinovich examined the biological and logistical challenges facing the development of malaria vaccines. Some of these were:

- incomplete understanding of immunity in populations at risk;
- lack of a good animal model for human malaria;
- fewer tools to evaluate *P. vivax* in primates or humans (compared to *P. falciparum*);
- inability to culture malaria parasites in cell-free systems;
- inadequate access to pilot lots of candidate vaccines produced under GMP conditions;
- lack of a single strategy because of parasite antigenic diversity and human genetic diversity;
- lack of agreement on specific end-points for assessing vaccine efficacy in clinical trials with subjects of different ages.

Dr Rabinovich described various facilities that were capable of preparing vaccine pilot lots in accordance with GMP criteria and listed institutions capable of carrying out Phase II challenge trials. It was essential to improve capabilities in the performance of clinical trials and field trials by the application of industrial project management practices, human capital development, trial site development and market assessment and development.

Experimental challenge studies for the preliminary assessment of the efficacy of candidate pre-erythrocytic stage vaccines had been critical in screening candidate vaccine approaches. The only sites and teams that had carried out such studies in recent years were at the following institutions.

- Walter Reed Army Institute of Research, Maryland, USA.
- Center for Vaccine Development, University of Maryland, USA.
- Naval Medical Research Center, Maryland, USA.
- Oxford University, United Kingdom.
- Nijmegen University, the Netherlands.

Clinical trials had been conducted at various sites on all the continents affected by malaria. As well as assessing malaria vaccines, these trials had allowed the building of capacity to test other vaccines. Trial sites had to be nurtured through long-term commitment to the training of local teams and the strengthening of the vaccine-testing infrastructure.

Adrian Hill summarized the state of progress of the Oxford University group's endeavours, involving the use of a DNA prime/non-replicating poxvirus (MVA) boost strategy. Results in animals where the *P. berghei* model had been used indicated that the immunization sequence was critical. As shown in the following table, DNA prime followed by live vector boost conferred the highest level of protection in the mouse model.

Level of protection in mice with different sequences of parenteral immunization with DNA or MVA carrying genes encoding *P. berghei* circumsporozoite protein (CSP) and TRAP

Priming immunization	Booster immunization	Level of protection (%)
DNA	DNA	0
MVA	MVA	20
DNA	MVA	100
MVA	DNA	0

Phase I trials have confirmed a superior interferon-g response in 18 human subjects. Preliminary studies showed that 4 ìg delivered by gene gun were as immunogenic as 500 ìg given by intramuscular needle injection. Stronger *ex vivo* ELISPOT interferon-g responses were induced in humans by MVA than by DNA immunization. However, in five subjects studied, the boosting of a DNA-primed response with MVA led to a substantial increase in *ex vivo* ELISPOT responses.

It was planned to follow Phase II challenge trials in the United Kingdom with a Phase I trial in the Gambia. Dr Hill also noted that interest had been generated among other researchers in the general DNA prime/live vector boost approach as a strategy for the development of HIV and tuberculosis vaccines.

Joe Cohen described the history and status of the RTS,S/SBAS2 malaria candidate vaccine and gave details of a small randomized controlled Phase II field trial in the Gambia in which its safety, immunogenicity and preliminary efficacy were assessed. Highly encouraging results were obtained, a protective efficacy of 63% being obtained against symptomatic *P. falciparum* infection in semi-immune adults (see table below). Although the short-term efficacy was quite promising, protective efficacy in the field lasted only two months. This result was similar to that obtained with North American volunteers in whom the vaccine had been tested against experimental challenge: significant protection had lasted for only a few months.

Incidence of symptomatic malaria infection per 100 person-months during first two months of surveillance after vaccination, Gambia trial		Vaccine efficacy (95% confidence interval)
RTS,S vaccine	Control (rabies vaccine)	
3.5	8.8	63% (15-84%) p = 0.019

RTS,S continued to be a leading candidate malaria vaccine on the basis of the following observations.

- More than 1000 doses of RTS,SSBAS2 had been administered to malaria non-immune and semi-immune adult volunteers.
- The vaccine had been shown to be safe and well tolerated but more reactogenic than the hepatitis B and rabies vaccines used as controls in randomized double-blind trials.
- Exceptionally high humoral immune responses against CSP epitopes had been recorded, as well as potent and broad cell-mediated immune responses.
- Unprecedented protection against *P. falciparum* sporozoites had been obtained under experimental and field challenge.
- The field study results had been consistent with experimental challenge model results, thereby validating the volunteer challenge model.

In its current form the candidate vaccine had the following limitations.

- Its efficacy was closely related to the formulation (type of adjuvant, etc.).
- The significant efficacy observed in experimental challenge and field studies waned rapidly.

Future plans for RTS,S/SBAS2 included:

- Assessing its safety, immunogenicity and efficacy in young children and infants in regions of endemicity.
- Identifying, if possible, immune corrleates of protection.
- Improving the vaccine profile (higher efficacy, longer duration).

Kalifa Bojang argued that Phase I and II trials with candidate malaria vaccines should be initiated as soon as possible among target populations in developing countries since the reactogenicity and immunogenicity profiles of the vaccines might differ from the responses observed in immunologically naive adults in developed countries. Even in developing countries it was important to conduct trials in a range of epidemiological settings where the vaccine was likely to be used. It was essential that clinical trials of malaria vaccines in developing countries followed GCP guidelines and that informed consent was obtained on the basis of culturally sensitive procedures involving the entire community, e.g. using audiovisual aids. High ethical standards

had to be maintained in clinical trials, and oversight had to be provided by appropriate monitoring committees. Clinical trials, and particularly large-scale field trials, had to include long-term follow-up so that both safety and the duration of protection could be assessed. The information thus derived would be invaluable as a means of convincing governments to adopt vaccines for malaria control once they became available. The opportunity had to be taken to train local personnel in clinical trials methodology and to achieve capacity-building in local institutions.

Tuberculosis vaccines

Ann Ginsberg provided an overview of the status of the development of new vaccines for the prevention of tuberculosis. It was necessary to identify the correlates of protection in humans and to develop improved animal models and simple diagnostic techniques. Some notable recent advances had included the sequencing of the complete genome of *Mycobacterium tuberculosis* and the creation of tools for the genetic manipulation of *Mycobacterium*. The genomes of *M. bovis* and *M. smegmatis* were being sequenced, and this also would contribute towards the development of tuberculosis vaccines for humans.

Many new candidate tuberculosis vaccines had been created. Some of them appeared promising in animal models. A brief summary of the principal strategies is presented in the following table.

Type	Advantages	Disadvantages	Promise
Recombinant BCG vaccines (e.g. expressing cytokines, protective antigens, listeriolysin)	Safe, inexpensive to produce, lessens ethical issues related to replacing BCG	Safety must be demonstrated in immunocompromised hosts	Moderate/high
Attenuated *M. tuberculosis* strains	Mimic natural infection	Safety must be conclusively demonstrated	Moderate
Other mycobacteria (*vaccae, microti, habana*)	Safe	Weakly immunogenic	Low
Live vectors (e.g. *Salmonella*, vaccinia) expressing *M. tuberculosis* antigens	Novel delivery methods possible	No evidence yet of protective immunity better than that given by BCG	Moderate
Subunit vaccines (proteins, peptides, lipids, carbohydrate conjugates)	Safe, well-characterized, strong protection in animal models	Will probably require adjuvants and multiple doses	Moderate/high
DNA vaccines	Easy manufacture, heat-stable	Unproven efficacy; adjuvant required; safety concerns	Moderate/high

Carol Nacy of the Sequella Global Tuberculosis Foundation stated that this organization would try to develop a new vaccine through its own development programmes, while facilitating new vaccine development by other groups. She described the Foundation's current scientific programme and planned grants. Two BCG vaccine strains would be tested in clinical trials at a site in South Africa.

Mauricio Barreto outlined the difficulties of assessing the efficacy of tuberculosis vaccines. The safety of all new live vaccines would have to be demonstrated in HIV-positive subjects. From the clinico-epidemiological standpoint, tuberculosis comprised several diseases. It was desirable to develop improved animal models that not only measured protection against primary disease in immunologically naive hosts but also allowed candidate vaccines to be evaluated against reinfection and reactivation disease. A background of extensive prior environmental mycobacterial exposure would have to be allowed for in this endeavour.

There were three prerequisites for undertaking a large-scale Phase III efficacy trial of a candidate tuberculosis vaccine:

- sufficient convincing human safety data available from Phase I and II clinical trials;
- evidence of sustained vaccine protective activity in animal models;
- elicitation of a relevant immune response.

Because of the cost of large Phase III studies in communities at moderate risk of tuberculosis, a triage system was required whereby a preliminary assessment could be made of the efficacy of new vaccines in small populations at very high risk of developing the disease (e.g. coal miners, health care workers) before large-scale trials were undertaken. Such an evaluation could, perhaps, utilize an efficacy surrogate.

Dr Baretto described a current randomized trial involving 356 804 children in Brazil, in which the efficacy of a second dose of BCG in the prevention of tuberculosis and leprosy was being assessed.

Developing market vaccines, Session I

The aim of "developing market vaccines" is to prevent infectious diseases that constitute major public health problems in developing countries but pose little, if any, risk to populations in industrialized countries, with the exception of travellers who go from developed to developing countries.

Thomas Monath described the development and preclinical testing of a chimeric dengue fever vaccine, based on the genetic modification of live attenuated yellow fever vaccine strain 17D so as to express envelope proteins of other flaviviruses, including the four serotypes of dengue virus. A similar approach was described for a Japanese B encephalitis vaccine in which a chimeric yellow fever virus bearing the Japanese encephalitis envelope gene was constructed. This Japanese B encephalitis chimera was protective in animal models and non-infectious in the mosquito. Several advantages derived from starting with the 17D strain. It provided a high level of long-term protection against yellow fever with a single dose. Over 400 million doses had been administered, attesting to its safety. The viral envelope genes of the 17D strain were replaced with corresponding genes of the heterologous target flavirirus. The resulting chimera was expected to have the safety of 17D while stimulating immune responses against the heterologous flavivirus. This strategy lends itself to the construction of chimeric viruses encoding antigens of Japanese encephalitis virus, dengue virus 1-4 and West Nile virus.

Dr Monath said that the tetravalent dengue virus vaccine would be a mixture of four chimeric strains administered as a single inoculation. The chimeric 17D-dengue virus strains were not neurovirulent in monkeys. They were immunogenic as tetravalent combinations as well as when inoculated as monovalent vaccines, and they protected monkeys against challenge with wild- type dengue viruses.

Natth Bhamarapravati described progress in the development of a tetravalent live attenuated dengue vaccine prepared by conventional serial passages in cell culture. In clinical trials with 200 adults a single dose of tetravalent vaccine had been well tolerated and had elicited seroconversion in all the subjects; neutralizing antibody titres had persisted for at least four years. Clinical trials with this vaccine had been initiated in children. A single dose of vaccine had generally been well tolerated in children aged 10-14 years, only a small proportion experiencing fever and rash. Seroconversion to all four serotypes had occurred in 80% of paediatric subjects and to three serotypes in 95%. Different strategies would be pursued with a view to raising seroconversion to all four serotypes in close to 100% of paediatric subjects.

The work of Dr Bhamarapravati and Dr Monath involved close collaboration between WHO, vaccine manufacturers and academic institutions.

Developing market vaccines, Session II

Dan Granoff and Luis Jodar described a model of public-private partnership called Epidemic Meningitis Vaccines for Africa. In the meningitis belt of sub-Saharan Africa, approximately 80-90% of endemic meningococcal disease was caused by group A *Neisseria meningitidis* and 10-20% by group C *N. meningitidis*. Large-scale explosive epidemics were overwhelmingly caused by group A. Data from Niger showed that immunization of young infants with a meningococcal group A conjugate vaccine followed by a dose of polysaccharide vaccine resulted in a high level of seroconversion and elevated antibody titres. WHO had sponsored the development of a business plan exploring the feasibility of producing group A meningococcal polysaccharide, the critical first step towards the creation of a conjugate vaccine. Liquid vaccine would be less expensive than lyophilized vaccine. Vaccine would be licensed on the basis of the ability to stimulate bactericidal antibodies rather than on the results of efficacy trials.

A proposed plan was presented for the introduction of the group A/C conjugate vaccine in Africa. Ideally, the vaccine would be used both for the routine immunization of infants with two doses through the Expanded Programme on Immunization and in mass campaigns involving older children, adolescents and young adults. It was further proposed that, when the vaccine became available, demonstration projects be carried out in two countries prior to more extensive introduction in 12 other high-risk countries.

Philippe Sansonetti reviewed candidate shigellosis vaccines and indicated that in order to provide broad-spectrum coverage they would have to include at least five serotypes. He described progress in the evaluation of non-living vaccines with reference to:

- a parenteral conjugate vaccine consisting of detoxified LPS linked to a carrier protein;
- a parenteral nuclear protein/ribosomal vaccine approach;
- mucosally administered *Shigella*-proteosome vaccine consisting of *Shigella* LPS non-covalently linked to micelles from the outer membrane protein of group B *Neisseria meningitidis*.

Dr Sansonetti also described progress with two candidate live oral vaccines in clinical trials:

- attenuated *S. flexneri* 2a strain SC602 (constructed at the Pasteur Institute, Paris);
- attenuated *S. flexneri* 2a strain CVD 1207 (constructed at the Center for Vaccine Development, University of Maryland).

Lin Du presented data from clinical trials in China where a bivalent *S. flexneri* 2a-*S. sonnei* hybrid strain constructed at the Lanzhou institute of Biological Products was tested for safety and efficacy. In a clinical trial involving approximately 48 000 subjects, adverse reactions, including diarrhoea and fever, were observed no more commonly in vaccinees ($20.6/10^4$) than in recipients of placebo ($22.2/10^4$). In a field trial in Henan, China, in 1997, 13 057 subjects received three oral doses of vaccine at intervals of five days and there were 13 173 controls. Levels of protective efficacy of 72% and 61% were achieved against *S. sonnei* and *S. flexneri* 2a respectively, and there was evidence of cross-protection against other *S. flexneri* serotypes.

John Clemens described the funding, focus and administration of the International Vaccine Institute, created by the United Nations Development Programme and based in Seoul, Republic of Korea. For the immediate future, this body would concentrate on clinical trials and demonstration projects in Asia relating to vaccines against diarrhoeal disease and enteric fever and to conjugate vaccines against bacterial respiratory pathogens.

Farrokh Modabber described clinical trials of first-generation vaccines for the prevention of leishmaniasis in Iran and Sudan. These vaccines were based on what was presently available and included killed whole parasites (ALM) vaccine plus BCG as adjuvant. The ALM + BCG vaccine was shown to be well tolerated but poorly immunogenic, and it was of low efficacy. Nevertheless, these trials had allowed the establishment of a suitable infrastructure for the performance of clinical trials. Trials of different immunization schedules of ALM + alum + BCG were in progress. A challenge model of cutaneous leishmaniasis involving inoculation with wild-type *L. major* had shown promising results as a method of assessing the efficacy of candidate *Leishmania* vaccines.

Guilles Riveau reported on clinical trials with a *Schistosoma* 28 KDa GSTs vaccine against schistosomiasis in Senegal. There had been a reduction of reinfection as well as of the parasite burden as indicated by egg counts. After successful Phase I trials in adults and children, sera from vaccinated children had been shown to inhibit enzymatic activity in the parasite. Phase II clinical trials were in progress.

Rosanna Lagos reported that post-licensure trials of an Hib conjugate vaccine in Chile demonstrated its efficacy in preventing invasive disease and pneumonia, and had expedited its practical introduction into the immunization system of this non-industrialized country. A level of protection of 92% was achieved against invasive Hib disease. Vaccination also resulted in a 22% proportionate reduction in probable bacterial pneumonia among children under 2 years of age. Policy-makers in Chile were initially concerned about the relatively high cost of the vaccine in comparison with other EPI vaccines and wished to obtain evidence of the impact that it would have.

Keith Klugman discussed some of the complexities of vaccination against pneumococci, of which there were many serotypes. A large study in South Africa had revealed that vaccination with pneumococcal conjugate vaccines had led to reduced nasopharyngeal carriage of vaccine serotypes but also to replacement with non-

vaccine serotypes. Dr Klugman summarized the results of trials that had shown pneumococcal conjugate vaccines to be outstandingly efficacious against invasive pneumococcal disease. There had also been a decrease in the incidence of otitis media and significant reductions in antibiotic use.

Kim Mulholland presented a global view of pneumococcal disease and its prevention by immunization. More precise estimates of the total global burden of pneumococcal disease were required. It was thought that for every recorded case of invasive disease there were many additional cases of pneumococcal pneumonia. However, quantifying the burden of pneumococcal pneumonia was difficult, as no diagnostic test accurately identified the etiology of the disease. Several conjugate vaccines were undergoing clinical trials in developing countries, including 9-valent Wyeth-Lederle vaccine, 11-valent Aventis Pasteur vaccine and 11-valent SKB vaccine. Further work relating to pneumococcal conjugate vaccines was needed on alternative immunization schedules that might be more practical and economical, on vaccine efficacy in very young and malnourished infants, and on identifying the correlates of protection.

Clinical trials were under way with common pneumococcal protein vaccines. Among the antigens of interest were PsPA, PsAA and pneumolysoid. The advantage of this approach was that such vaccines could be expected to provide protection against all serotypes of pneumococcus.

William Hausdorff of Wyeth-Lederle briefly outlined experience gained in the USA with the live rhesus tetravalent reassortant rotavirus vaccine during the year when universal infant immunization was recommended and vaccine use was fairly widespread. Approximately 1.8 million doses were administered to infants before an association with intussusception was reported. The true rate of intussusception associated with ingestion of the vaccine was still being investigated.

Daniel Soland described SmithKline Beecham's commitment to the development of a candidate live attenuated rotavirus vaccine (a monovalent human G1:P8 strain) and to its eventual use in infant populations of both developing and developed countries. He indicated his company's willingness to participate in clinical trials in developing countries. However, manufacturers would find it difficult to undertake the extremely large safety trials that might be necessary in order to demonstrate that new vaccines were not associated with intussusception. Dr Soland suggested a possible development plan for clinical trials, which, if successful, could bring forward the availability of these vaccines in less developed countries.

Alan Shaw of Merck Research Laboratories outlined the development of a rotavirus vaccine based on at least four bovine-human reassortant strains (WC3) and drew attention to what were believed to be its more promising safety features in comparison with the rhesus vaccine. Because intussusception was associated with the rhesus reassortant vaccine, newer candidate live oral rotavirus vaccines would have to be subjected to safety studies on a much larger scale than the efficacy studies on rhesus vaccine. In advance of licensure, the safety studies would lead to a reasonable degree of confidence that no severe adverse events were associated with vaccination.

Maharaj Bhan discussed the misgivings of developing countries about the use of a rotavirus vaccine:

- there was a need for better data on disease burden attributable to rotavirus;
- there was concern about intussusception because of the high case-fatality rate linked to this syndrome in developing countries;
- there was concern that safety and efficacy data generated in one country might not apply in another.

There was a need for a candidate vaccine that could be orally administered, was affordable, had no major side-effects, was compatible with the Expanded Programme on Immunization and was more than 70% efficacious against severe rotavirus diarrhoea attributable to multiple serotypes.

Discussion of draft terms of reference for the GAVI Task Force on Research and Development

Dr Levine provided an overview of GAVI's vision and specific objectives. In particular he drew attention to the concept that research and development was an integral part of an overall vaccine continuum. Efforts to develop new vaccines would be unproductive if the barriers to the introduction of existing vaccines were not removed. Current projects in research and development were tomorrow's front-line vaccine tools for fighting disease. It was vital that the members of the vaccine and immunization community should work together in order to develop the most appropriate tools possible.

A question was raised about GAVI's interaction with agencies involved in research and development. Mike Levine and John LaMontagne explained that GAVI was an alliance of various partners and not an implementing agency. It would act in concert with and through existing organizations. Bjorn Melgaard endorsed this strategy on behalf of WHO.

Steve Hoffman asked for clarification of the mechanisms whereby GAVI would interact with individual countries with a view to the strengthening of infrastructures. Amie Batson outlined a recently launched scheme enabling countries to ask GAVI for support for vaccine implementation programmes. Carlos Morel and Gordon Dougan said that GAVI should give careful consideration to sustainability at the outset of the programme, particularly in respect of personnel and technology transfer. Amie Batson described the current phase of GAVI organization as the tip of a volcano: the GAVI process was still evolving.

Mike Levine read through the draft terms of reference for the Research and Development Task Force. Don Francis commented that too few clearly defined end-points appeared to be indicated in the document. Mike Levine said that this was just a starting point and that it was important to begin the process on a basis of broad agreement, allowing GAVI to operate in a context of trust in the vaccine research and development community. There was general agreement that it was necessary for the terms of reference to evolve and become more precise.

Roy Widdus suggested that there was a need for either a strategic review or a technical review or both. Research and development on vaccines went beyond product development: it implied basic research, covering economic and social issues. Dr Widdus felt that the notion of technology transfer was very difficult, almost utopian, especially when industry held intellectual property rights.

Alan Shaw thought that, in order to give itself a boost, GAVI should support a specific project that had a high chance of success. Carole Heilman agreed that a product might be chosen as a flag or model. Don Francis suggested selecting a project like that on meningitis A; Ariel Pablos-Mendez suggested dengue and meningitis A. Yahya Dowlati suggested that, whatever demonstration project was chosen, developing countries should play a prominent role.

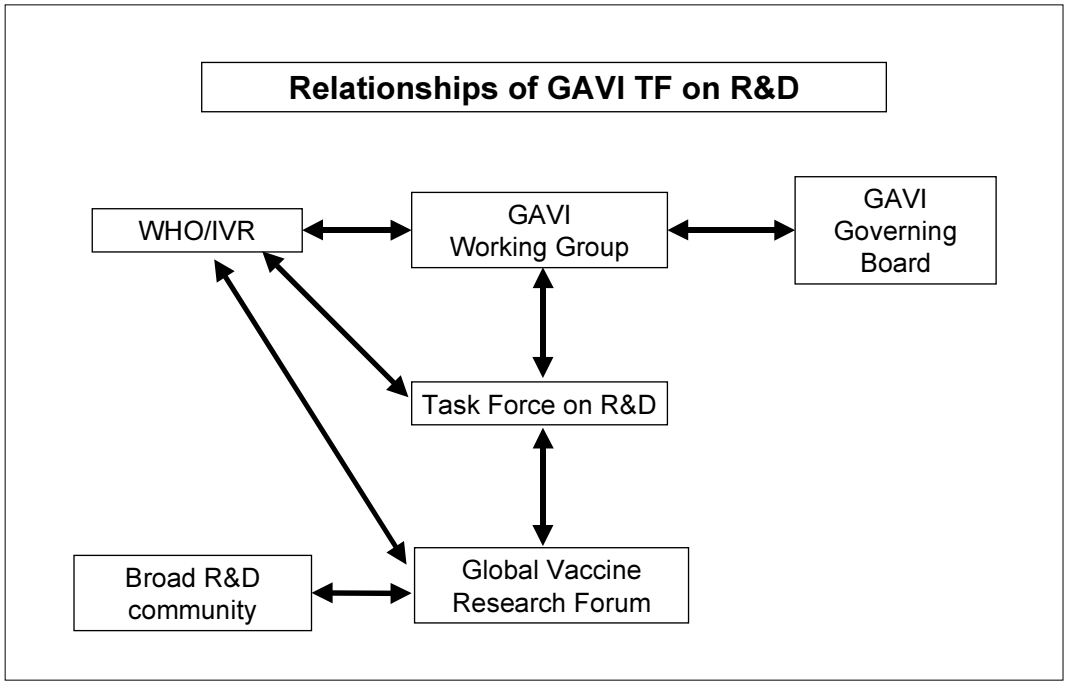
Bjorn Melgaard remarked that many inputs and comments had been delivered on the terms of reference and that they should now serve as strategic rather than operational guidelines, leaving the action to the partners. Claudio Lanata said that the Task Force on Research and Development should do whatever was necessary to make sure that GAVI objectives one (increased access to immunization services) and two (increased use of existing cost-effective vaccines) were achieved. Amie Batson supported this recommendation. Melinda Moree reminded the group that generic technologies for the improvement and simplification of immunization could also be part of the mandate of the Task Force. Kim Mulholland pointed out that despite their availability, some vaccines, such as Hib, hepatitis B and typhoid vaccines, were seriously underused. In part this was because of a lack of local epidemiological data demonstrating disease burdens. Epidemiological research was an important component of vaccine research but was frequently ignored.

By a show of hands the vast majority of those present indicated that they were in favour of the Task Force.

Relationships of the GAVI Task Force on Research and Development

The Task Force on Research and Development is one of several GAVI Task Forces. It has direct lines of communication with WHO/IVR and the GAVI Working Group (and through the Working Group with GAVI's Governing Board). It will collaborate with the annual Global Vaccine Research Forum, thus reaching the broader research and development community. WHO/IVR will serve as the Secretariat of the Task Force and will cosponsor the annual Global Vaccine Research Forum.

Relationship and lines of communication



Annex 1:
List of participants

Dr Pedro L. Alonso (Rapporteur), Hospital Clínic, Villarroel 170, E-08036 Barcelona, Spain
Tel: +34 93 227 57 96; Fax: +34 93 451 52 72
Email: alsonso@medicina.ub.es

Dr Francis André, Vice-President, Senior Medical Director, SmithKline Beecham Biologicals, Rue de l'Institut 89, B-1330 Rixensart, Belgium
Tel: +32 2 656 83 35; Fax: +32 2 656 90 58
Email: francis.andre@sbbio.be

Dr Luis Barreto, Director, International Public Health Affairs, Aventis Pasteur Limited, Connaught Campus, 1755 Steeles Avenue West, Toronto, Ontario M2R 3T4, Canada
Tel: +1 416 667 2738; Fax: +1 416 667 2865
Email: luis.barreto@aventis.com

Dr Mauricio L. Barreto, Universidade Federal de Bahia, Instituto de Saude Coletiva, rua Padre Feijo, 29 4°, Canela, 40 110-170 Salvador – Bahia, Brazil
Tel: +55 71 245 0544; Fax: +55 71 237 5856
Email: mauricio@ufba.br

Ms Amie Batson, Health Specialist, Health and Development Network, The World Bank, 1818 H Street, NW, Room G 3021, Washington DC 20433, USA
Tel: +1 202 458 8300; Fax: +1 202 522 3489
Email: abatson@worldbank.org

Dr Siné Bayo (Co-Chairperson), Institut National de Recherche en Santé Publique (INRSP), BP 1771, Bamako, Mali
Tel: +223 21 03 33; Fax: +223 21 19 99
Email: inrsp@spider.toolnet.org

Dr Seth F. Berkley, President, International AIDS Vaccine Initiative, 810 Seventh Avenue, New York, NY 10019-5818, USA
Tel: +1 212 655 0201; Fax: +1 212 843 0480
Email: sberkley@iavi.org

Dr Umberto Bertazzoni (Co-Chairperson), European Commission, DGXII-BII-1, SDME 8/49, Rue de la Loi 200, B-1049 Brussels, Belgium
Tel: +32 2 296 64 85; Fax: +32 2 295 53 65
Email: umberto.BERTAZZONI@cec.eu.int

Dr Natth Bhamarapravati, Centre for Vaccine Development, Mahidol University at Salaya, 23/25 Phutthamonthon 4, Nakhonpathom 73170, Thailand
Tel: +66 2 441 9744; Fax: +66 2 441 9744/9336
Email: stnbm@mucc.mahidol.ac.th

Dr Maharaj K. Bhan, Head, Division of Gastroenterology, Dept. of Paediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
Tel: +91 11 649 3883; Fax: +91 11 686 2663 or 652 1041
Email: bhanmk@medinst.ernet.in

Dr Kalifa Bojang, MRC Laboratories, Fajara, PO Box 273, Banjul, The Gambia
Tel: +220 494072/9 ext. 338; Fax: +220 496513
Email: kbojang@mrc.gm

Dr Gianluca Breghi, Head, Marketing, Chiron Vaccines, Via Fiorentina 1, I-53100 Siena, Italy
Tel: +39 577 243222; Fax: +39 577 243007
Email: breghi_gianluca@biocine.it

Dr Margaret Burgess (Rapporteur) (SAGE member), Centre for Immunization Research, The New Children's Hospital, P.O. Box 3515, Parramatta, NSW 2124, Australia
Tel: +61 2 9845 3069; Fax: +61 2 9845 3082
Email: margarb1@nch.edu.au

Dr John Clemens, Director, International Vaccine Institute, Seoul National University Campus, Shillim Dong, Kwanak-ku, P.O. Box 14, Seoul 151-600, Korea
Tel: +82 2 872 2801; Fax: +82 2 872 2803
Email: jclemens@ivi.org

Dr Joe Cohen, Smith Kline Beecham Biologicals, rue de l'Institut, 89, B-1330 Rixensart, Belgium
Tel: +32 2 656 8331; Fax: +32 2 656 8113
Email: Joe.Cohen@sbbio.be

Dr Gordon Dougan (Rapporteur), Imperial College of Science, Technology and Medecine, Department of Biochemistry, Exhibition Road, GB-London SW7 2AY, UK
Tel: +44 171 594 5256; Fax: +44 171 594 5255
Email: g.dougan@ic.ac.uk

Dr Yahya Dowlati, 8 Maysam avenue, 19518 Tehran, Islamic Republic of Iran
Tel: +98 21 877 2319; Fax: +98 21 888 1719
Email: dowlatiy@farabi.hbi.dmr.or.ir

Dr Lin Du, Lanzhou Institute of Biological Products, 118 Yanchang Road, Lanzhou Gansu, 730046 China
Tel: +86 931 836 8311; Fax: +86 931 834 3199
Email: ldfox@public.lz.gs.cn

Dr Maria da Luz Fernandes Leal, Oswaldo Cruz Foundation,
Av. Brasil 4365 - Manguinhos, 21045-900 Rio de Janeiro- RJ, Brazil
Tel: +55 21 564 2220; Fax: +55 21 260 4727
Email: malu@bio.fiocruz.br

Dr Donald P. Francis, President, VaxGen, Inc., 1000 Marina Blvd,
Second Floor, Brisbane, CA, USA
Tel: +1 650 624 1027; Fax: +1 650 624 1001
Email: dfrancis@vaxgen.com

Dr Ruth Frischer, Health Science Specialist, (USAID), G/PHN/CS,
Ronald Reagan Building, Room 3.07, 3rd floor, 1300 Pennsylvania Avenue,
Washington, D.C. 20523, USA
Tel: +1 202 712 0771; Fax: +1 202 216 3702
Email: rfrischer@usaid.gov

Dr Nirmal K. Ganguly, Director-General, Indian Council of Medical Research,
Ansari Nagar, Post Box 4911, New Delhi 110029, India
Tel: +91 11 65 17204; Fax: +91 11 6868662
Email: icmrhqds@sansad.nic.in

Dr Ann M. Ginsberg, NIAID, DMID, Respiratory Diseases Branch, Room 3131,
6700 Rockledge Drive, MSC 7630 Bethesda, MD 20892-7630, USA
Tel: +1 301 496 5305; Fax: +1 301 496 8030
Email: ag73i@nih.gov

Dr Reinhard Glück (Co-Chairperson), Head of Research and Development,
Swiss Serum and Vaccine Institute Berne, P.O. Box CH-3001 Berne, Switzerland
Tel: +41 31 888 5320; Fax: +41 31 888 5181
Email: reinhard.glueck@berna.org

Dr Tore Godal, Executive Secretary, Global Alliance for Vaccines and
Immunzation, UNICEF, Place des Nations, CH-1211 Geneva 10, Switzerland
Tel: +41 22 909 5020; Fax. 41 22 909 5900
Email: tgodal@unicef.ch

Dr Cesar Gonzalez Bonilla, Chair, Medical Research Unit in Immunology and
Infectious Diseases, Hospital de Infectologia "Dr Daniel Mendez Hernandez",
Delegacion 2 Noroeste del D.F., Centro Medico "La Raza",
Calzada Vallejo s/n esq. Jacarandas, Col. "La Raza" C. P. 02910, Mexico
Tel: +52 5 7245900; Fax: +52 5 583 06 26
Email: bonilla@mailer.main.conacyt.mx

Dr Jesse L. Goodman, Acting Medical Deputy Director,
Center for Biologics Evaluation and Research, Food and Drug Administration,
1401 Rockville Pike, Suite 200N, Rockville, MD 20852, USA
Tel: +1 301 435 5680; Fax: +1 301 827 0440
Email: goodmanj@cber.fda.gov

Dr Dan Granoff, Senior Research Scientist, Children's Hospital Oakland
Research Institute, 5700 Martin Luther King, Jr. Way. Oakland, CA 94609, USA
Tel: +1 510 450 7640; Fax: +1 510 450 7910
Email: dgranoff@chori.org

Dr Brian Greenwood (Rapporteur), London School of Hygiene and Tropical Medicine, Department of Infectious and Tropical Diseases, Keppel Street, GB-London WC1E 7HT, UK
Tel: +44 207 927 2348; Fax: +44 207 612 7882
Email: b.greenwood@lshtm.ac.uk

Dr George Edward Griffin (Rapporteur), Division of Infectious Diseases, St. George's Hospital Medical School, Cranmer Terrace, Tooting, GB-London SW17 ORE, UK
Tel: +44.181.725.5827/8/9; Fax: +44.181.725.3487
Email: ggriffin@sghms.ac.uk

Dr William Hausdorff (Co-Chairperson), Director, Scientific Affairs, Research and Strategy, Wyeth Lederle Vaccines, 211 Bailey Road, W. Henrietta, NY 14586, USA
Tel: +1 716 273 7713; Fax: +1 716 273 7677
Email: hausdowp@war.wyeth.com

Dr Carole Heilman (Co-Chairperson), Director, National Institute of Allergy & Infectious Disease, Division of Microbiology and Infectious Diseases, National Institutes for Health, 6700B Rockledge Drive, Room 3142-MSC 7630, Bethesda, MD 20892-7630, USA
Tel: +1 (301) 496 1884; Fax: +1 301 480 4528
Email: ch25v@nih.gov

Dr Donald Gray Heppner (Rapporteur), Walter Reed Army Institute of Research, Department of Immunology, Forest Glen, MD 20910, USA
Tel: +1 301 319 9414; Fax: +1 301 319 7358
Email:donald.heppner@na.amedd.army.mil

Dr Adrian Hill, University of Oxford, Molecular Immunology Group, Institute of Molecular Medicine, John Radcliffe Hospital, GB-Oxford OX3 9DS, UK
Tel: +44 1865 741166; Fax: +44 1865 221921
Email: adrian.hill@imm.ox.ac.uk

Dr Stephen Hoffman, Director, Malaria Programme (Code 42), Naval Medical Research Center, 503 Robert Grant Avenue, Silver Spring, MD 20910-7500, USA
Tel: +1 301319 7570; Fax: +1 301 319 7545
Email: hoffmans@nmripo.nmri.nnmc.navy.mil

Dr Soren Jepsen, Statens Seruminstitut, European Malaria Vaccine Initiative, Artillerivej 5, DK-2300-5 Denmark
Tel: +45 3268 3188; Fax: +45 3268 3228
Email: sje@ssi.dk

Dr David C. Kaslow (Co-Chairperson), Merck and Co. Inc., 770 Sumneytown Pike, West Point, PA 19486, USA
Tel: +1 215 652 8929; Fax: +1 215 652 2439
Email: david_kaslow@merck.com

Dr Stefan H.E. Kaufmann (Rapporteur), Director, Max-Planck-Institut for Infection Biology, Department of Immunology, Monbijoustr. 2, D-10117 Berlin, Germany
Tel: +49 30 384 60 500; Fax: +49 30 28460 501
Email:kaufmann@mpiib-berlin.mpg.de

Dr Wenceslaus Kilama, African Malaria Vaccine Testing Network, Tanzania Commission for Science & Technology, Building C26/27, Ali Hassan Mwinyi Road, P.O. Box 33207, Mali
Tel: +255 51 700018; Fax: +255 51 700380
Email: wkilama@africaonline.co.tz

Dr Keith P. Klugman, Director, South African Institute for Medical Research (SAIMR), Hospital Street, P.O. Box 1038, Johannesburg 2000, South Africa
Tel: +27 11 489 9010; Fax: +27 11 489 9012
Email: keithk@mail.saimr.wits.ac.za

Dr Simon C.W. Kwong, Hong Kong Institute of Biotechnology Ltd., 2 Biotechnology Avenue, 12 Miles, Tai Po Road, Shatin, N.T., Hong Kong
Tel: +852 29489250; Fax: +852 26035111
Email: simon-kwong@hkib.org.hk

Dr Rosanna Lagos, Hospital Roberto del Rio, Centro para Vacunas en Desarollo, Servicio de Salud Metropolitano Norte, Avenida Professor Zanartu 1085, Santiogo, Chile
Tel: +56 2 737 5022; Fax: +56 2 777 5766
Email: cvdchile@netup.cl

Dr Altaf Lal (Rapporteur), Centers for Disease Control and Prevention, Immunology Branch, Molecular Vaccine, Section, 4770 Buford Highway, Mail stop F12, Chamblee, GA 30341, USA
Tel: +1 770 488 4047; Fax: +1 770 488 4454
Email: aal1@ciddpd2.em.cdc.gov

Dr Paul-Henri Lambert, Professor, Center of Vaccinology, Centre Médical Universitaire, 1, rue Michel-Servet, CH-1211 Geneva 4, Switzerland
Tel: +41 22 702 5777; Fax: +41 22 702 5801
Email: Paul.Lambert@medecine.unige.ch

Dr John R. La Montagne (Co-Chairperson) (SAGE member), Deputy Director, National Institutes of Health, National Institute of Allergy & Infectious Diseases, 31 Centre Drive, Building 31, Room 7A03, Bethesda, MD 20892-2520, USA
Tel: +1 301 496 9677; Fax: +1 301 496 4409
Email: jm79q@nih.gov

Dr Claudio F. Lanata (Rapporteur), Instituto de Investigación Nutritional, La Molina, Apartado Postal 18 0191, Miraflores, Lima 18, Peru
Tel: +51.1349 6023; Fax: +51.1349 6025
Email: clanata@iin.sld.pe

Dr Myron M. Levine (Overall Meeting Chairperson), University of Maryland School of Medicine, 685, W. Baltimore Street, HSF 480, Baltimore, MD 21201, USA
Tel: +1 410 706 7588; Fax: +1 410 706 6205
Email: mlevine@medicine.umaryland.edu

Dr Orin S. Levine (Rapporteur), Respiratory Diseases Branch, DMID/NIAID, 6700-B Rockledge Drive, Room 3255, MSC 7630, Bethesda, MD 20892-7630, USA
Tel: +1 301 435 2865/7708; Fax: +1 301 496 8030
Email: olevine@niaid.nih.gov

Dr Alfred Lindberg, Senior Vice-President Research, Aventis Pasteur, 1841, avenue Marcel Mérieux, Campus Mérieux, F-69280 Marcy l'Etoile, France
Tel: +33 437 37 2078; Fax: +33 437 37 39 76
Email: alf.lindberg@aventis.com

Dr Margaret Liu (Rapporteur), 3656 Happy Valley Road, Lafayette, CA 94549, USA
Tel: +1 925 299 2959; Fax: +1 925 284 7201
Email: margaret_liu@yahoo.com

Dr Richard T. Mahoney, International Vaccine Institute, P.O Box Kwanak, Korea
Tel: +82 2 872 2801; Fax: +82 2.872.2803
Email: rmahoney@ivi.org

Dr William Makgoba (Co-Chairperson), President, Medical Research Council of South Africa, P.O. Box 19070, Tygerberg 7505, South Africa
Tel: +27 21 938 0211/0911; Fax: +27 21 938 0201
Email: malegapuru.makgoba@mvc.ac.za

Mr Jacques-Francois Martin, PARTEUROP S.A., 36, Quai Fulchiron, F-69005 Lyon, France
Tel: +33 478 42 63 89; Fax: +33 478 42 34 24
Email:parteurop@parteurop.fr

Dr Edward Mbidde, Director, Uganda-CWRU Research Collaboration, P.O. Box 663, Kampala, Uganda
Tel: +256 41 540 410 / 559 622; Fax: +256 41 530 188
Email:mbidde&uga.healthnet.org@uga.healthnet.o

Dr Mark Miller, Director of Research, Fogarty International Center, National Institute of Health, 31 Center Drive, Room B2C02, Bethesda, MD 20892-2220, USA
Tel: +1 301 496 1415; Fax: +1 301 402 2173
Email: millermark@nih.gov

Dr Tatsuo Miyamura, Director, Department of Virology II, National Institute for Infectious Diseases (NIID), 1-23-1 Toyama, Shinjuku-Ku, Tokyo 162-8640, Japan
Tel: +81 3 5285 1111 Ext. 2500; Fax: +81 3 5285 1161
Email: tmiyam@nih.go.jp

Dr Farrokh Modabber, Director, Infectious Disease Research Institute, 1124 Colombia Street, Suite 600, Seattle, WA 98104, USA
Fax: +1 206 381 3678
Email: modabber@idri.org

Dr Thomas P. Monath, Vice President, Research & Medical Affairs, OraVax Incorporated, 38 Sidney Street, Cambridge, MA 02139, USA
Tel: +1 617 494 1339; Fax: +1 617 494 1741
Email: thomas.monath@oravax.com at inet

Dr Melinda Moree, PATH, 4 Nickerson street, Seattle, WA 98109, USA
Tel: +1 206 285 3500; Fax: +1 206 285 6619
Email: mmoree@path.org

Dr Odette Morin-Carpentier, Director, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations (IFPMA), P.O. Box 9, 30 rue de St Jean, CH-1211 Geneva 18, Switzerland
Tel: +41 22 338 3200; Fax: +41 22 338 3299
Email: O.Morin@ifpma.org

Dr Carol Nacy, Sequella Global Tuberculosis Foundation, 9610 Medical Center Drive, P.O. Box 1067, Rockville, MD 20849-1067, USA
Tel: +1 301 762 7776; Fax: +1 301 762 7778
Email: carolnacy@sequella.com

Dr Neal Nathanson, Office of AIDS Research, 9000 Rockville Pike, Room 4E14, Bldg 2, Bethesda, MD 20892, USA
Tel: +1 301 496 0357; Fax: +1 301 496 2119
Email: nathansn@mail.med.upenn.edu

Dr Hanna Nohynek (Co-Chairperson), Senior Scientist, KTL National Public Health Institute, Department of Vaccines, Mannerheimintie 166, FIN-00300 Helsinki, Finland
Tel: +358 4744 8246; Fax: +358 9 474 48675
Email: hanna.nohynek@ktl.fi

Dr Steven Obaro, Medical Research Council Laboratories, P.O. Box 273, Fajara, The Gambia
Tel: +220 668 462; Fax: +220 668 626
Email: sobaro@gamtel.gm

Dr Ariel Pablos-Mendez, The Rockefeller Foundation, 420 Fifth Avenue, New York, N.Y. 10018, USA
Tel: +1 212-852 8322; Fax: +1 212-852 8279
Email: apablos-mendez@rockfound.org

Dr Regina Rabinovich, Director, Malaria Vaccine Initiative, 6290 Montrose Road, Rockville MD 20852, USA
Tel: +1 301 770 5377; Fax: +1 301 770 5322
Email: rrabinovich@malariavaccine.org

Dr Rino Rappuoli (Co-chairperson), Chiron SpA, Via Fiorentina 1, I-53100 Siena, Italy
Tel: +39 0577 243 414; Fax: +39 0577 243 564
Email: Rino-Rappuoli@biocine.it

Dr Gilles Riveau, Pasteur Institute of Lille, CIBP, Immunopharmacologie Vaccinale, 1 rue du Professeur A. Calmette, F-59019 Lille, France
Tel: +33 3 20 87 77 81; Fax: +33 3 20 87 78 88
Email: gilles.riveau@pasteur-lille.fr

Dr Nancy Rosenstein, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, N.E., Atlanta, GA 30333, USA
Tel: +1 404 639 7000; Fax: +1 404 639 7111
Email: nar5@cdc.goc

Dr Taraz Samandari, University of Maryland at Baltimore, Center for Vaccine Development, 685 W. Baltimore Street, Baltimore, MD 21201, USA
Tel: +1 410 706 7376; Fax: +1 410 706 6205
Email: tsamanda@medicine.umaryland.edu

Dr Philippe J. Sansonetti, Unité de P.M.M. Institut Pasteur, 28 rue du Docteur Roux, F-75724 Paris Cedex 15, France
Tel: +33 1 456 88 3425; Fax: +33 1 456 88 953
Email: psanson@pasteur.fr

Dr Geoffrey C. Schild (Rapporteur), Director, National Institute for Biological Standards & Control (NIBSC), Blanche Lane, South Mimms, GB-Potters Bar, EN6 3QG, UK
Tel: +44 1707 646 846; Fax: +44 1707 646854
Email: gschild@nibsc.ac.uk

Dr Anne Schuchat, Chief, Respiratory Diseases Branch, Centers for Disease Control and Prevention, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, 1600 Clifton Road, N.E., MS-C23, Atlanta, GA 30333, USA
Tel: +1 404 639 4720; Fax: +1 404 639 3970
Email: acs1@cdc.gov

Dr Alan Shaw, Executive Director, Virus and Cell Biology, Merck Research Laboratories, 770 Summertown Pike, Bldg 14, Room 100, West Point, PA 19486, USA
Tel: +1 215 652 7400; Fax: +1 215 652 2142
Email:alan-shaw@merck.com

Dr Rebecca Sheets, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, HFM-475, Rockville, MD 20852-1448, USA
Tel: +1 301 827 3070; Fax: +1 301 827 3532
Email: sheetsb@cber.fda.gov

Dr Gustavo Sierra Gonzalez, Finlay Institute, Centro de Investigación, Producción Vacunas y Sueros, Avenida 27 No. 19805, La Lisa, Ciudad Habana, Cuba
Tel: +53 7 21 75 97; Fax: +53 7 28 60 75
Email: gsierra@finlay.edu.cu

Dr Daniel B. Soland, Vice President and Director Marketing Operations, SmithKline Beecham, Rue de l'Institut 89, B-1330 Rixensart, Belgium
Tel: +32-2 656 9333; Fax: +32-2 656 90 30
Email: daniel.soland@sbbio.be

Dr Marti Vall Mayans, Directorate of Primary Health Care, "Ciutat Vella"/STD Unit, CAP Drassanes, Av de les Drassanes, 17-21, E-08001 Barcelona, Spain
Tel: +34 93 442 7763; Fax: +34 93 442 7763
Email: cvuts02@sapbcn.scs.es

Dr Roy Widdus, Director, Public-Private Partnership Project, Global Forum for Health Research, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland
Tel: +41 22 791 4369; Fax: +41 22 791 4888
Email: partnerships@globalforumhealth.org

Dr David Wood, Principal Scientist, National Institute for Biological Standards and Control, Division of Virology, Blanche Lane, South Mimms, GB-Potters Bar, EN6 3QG, UK
Tel: +44 1 707 654 753 ext. 305; Fax: +44 1 707 646 730
Email: dwood@nibsc.ac.uk

Dr Jianguo Xu, Director, Institute of Epidemiology and Microbiology, Chinese Academy of Preventive Medicine, P.O. Box 5, Changping, Beijing 102206, China
Tel: +56 86 617 39577; Fax: +56 86 617 30233
Email: xujg@public.bta.net.ch

Dr Douglas B. Young (Rapporteur), Imperial College School of Medicine, Department of Infectious Diseases and Microbiology, ICSM, St Mary's Campus, Norfolk Place, GB-London W2 1PG, UK
Tel: +44 20 7594 3956; Fax: +44 20 7262 6299
Email: d.young@ic.ac.uk

Dr Mohammad Yunus, International Centre for Diarrhoeal Disease Research, Bangladesh, ICDDDR,B, Center for Health and Population Research, GPO Box 128, Dhaka 1000, Bangladesh
Tel: +880 2 871 751; Fax: +880 2 9885657
Email: myunus@icddrb.org

Professor Dr B.A.M. van der Zeijst, Director, Vaccine Division, National Institute of Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, P.O. Box 1, NL-3720 BA Bilthoven, Netherlands
Tel: +31 30 274 41 64; Fax: +31 30 274 4439
Email: ben.van.der.zeijst@rivm.nl

WHO Secretariat*

Regional offices

Dr Ciro de Quadros, Director, Division of Vaccines and Immunization (HVP), WHO Regional Office for the Americas/Pan American Sanitary Bureau, 525, 23rd Street, N.W., Washington DC 20037, USA
Tel: +1 202 974 3247; Fax: +1 202 974 3635
Email: quadrosc@paho.org

Dr Mohammed Taky Gaafar, Regional Adviser, VPI, DCD, WHO Regional Office for the Eastern Mediterranean, P.O. Box 1517, Sultan Abdul Aziz Street, Mazarita, Alexandrie 21511, Egypt
Tel: +203 48 33 285 (direct); Fax: +203 48 32 285
Email: gaafart@who.sci.eg

WHO headquarters

Health Technology and Pharmaceuticals (HTP) cluster

Dr Yasuhiro Suzuki, Executive Director, HTP
Tel: +41 22 791 2511; Fax: +41 22 791 4889
Email: suzukiy@who.int

Dr José Esparza, Coordinator, UNAIDS/WHO HIV Vaccine Initiative (HVI), HTP
Tel: +41 22 7914392; Fax: +41 22 791 4865
Email: esparzaj@who.int

Dr Saladin Osmanov, Medical Officer, HVI/HTP
Tel: +41 22 791 4393; Fax: +41 22 791 4865
Email: osmanovs@who.int

Department of Vaccines and Biologicals (V&B), HTP

Dr M. Teresa Aguado, Coordinator, Vaccine Development (VAD), V&B
Tel: +41 22 791 2644; Fax: +41 22 791 4860
Email: aguadom@who.int

Dr Nora Dellepiane, Access to Technologies (ATT), V&B
Tel: +41 22 791 4788; Fax 41 22 791 43 84
Email: dellepianen@who.int

Ms Maria Dweggah, Secretary, VAD/V&B
Tel: +41 22 791 2350; Fax: +41 22 791 4860
Email: dweggahm@who.int

Dr Uli Fruth, Medical Officer, VAD/V&B
Tel: +41 22 791 2678; Fax: +41 22 791 4860
Email: fruthu@who.int

* Certain WHO staff participated in selected sessions only.

Dr Bernard Ivanoff, Medical Officer, VAD/V&B
Tel: +41 22 791 2698; Fax: +41 22 791 4860
Email: ivanoffb@who.int

Dr Luis Jódar, Scientist, VAD/V&B
Tel: +41 22 7913744; Fax: +41 22 791 4860
Email: lodarj@who.int

Dr Bjorn Melgaard, Director, V&B
Tel: +41 22 791 4408; Fax: +41 22 791 4227
Email: melgaardb@who.int

Dr Julie Milstien, Acting Coordinator, ATT/V&B
Tel: +41 22 791 3564; Fax: +41 22 791 4384
Email: milstienj@who.int

Dr Kim Mulholland, Medical Officer, VAD/V&B
Tel: +41 22 791 4760; Fax: +41 22 791 4860
Email: mulhollandk@who.int

Ms Karen O'Leary, Informatics, V&B
Tel: +41 22 791 4414; Fax: +41 22 791 4860
Email: olearyk@who.int

Dr Yuri Pervikov, Medical Officer, VAD/V&B
Tel: +41 22 791 2601; Fax: +41 22 791 4860
Email: pervikovy@who.int

Ms Claire Whitfield, Secretary, VAD/V&B
Tel: +41 22 791 3718; Fax: +41 22 791 4860
Email: whitfieldc@who.int

Mr Michel Zaffran, Programme Manager, V&B
Tel: +41 22 791 4373; Fax: +41 22 791 4227
Email: zaffranm@who.int

Communicable Diseases (CDS) cluster

Dr David Heymann, Executive Director, CDS
Tel: +41 22 791 2212; Fax: +41 22 791 4752
Email: heymannd@who.int

Dr Win Gutteridge, Chief, Product Research and Development, Communicable Disease Research and Development, Tropical Disease Research, CDS
Tel: +41 22 7913769; Fax: +41 22 7914854
Email: gutteridgew@who.int

Dr Howard Engers, Manager, Steering Committee on Vaccine Discovery Research, Tropical Disease Research, CDS
Tel: +41 22 7913736; Fax: +41 22 791 4854
Email: engersh@who.int

Dr Carlos Morel, Director, Tropical Disease Research, CDS
Tel: +41 22 791 3802; Fax: +41 22 791 4854
Email: morelc@who.int

Annex 2:
Updated prioritization questionnaire

Name: _____ Date: _____

Identify your area of expertise (e.g. pathogen of interest, clinical vaccine trials):

_____

Identify your affiliation (e.g. academia, industry, public health):

_____

Please indicate persons to whom this questionnaire should be distributed:

Name	Area of expertise	Address, email, fax

Instructions for completing this questionnaire

1) Identify the disease for which you will be completing the form. It is preferred that you choose the disease with which you are most familiar. If you wish to perform the exercise for more than this disease, please photocopy this form before completing it for the first disease.

2) You may choose HIV, tuberculosis or malaria if you feel only competent to complete the form for these diseases. However, since these are already part of the GAVI charter it is preferable that you complete the form for other diseases that are relevant to people living in developing countries. Please consult the enclosed list of infectious diseases on the next page.

3) In questions 1, 2 and 3 you do not have to give responses on regional issues. These questions should be answered for a specified region in a situation where the disease identified does not have a significant global impact but has a large disease burden in the region you identify. This would be the case for group A meningococcal meningitis in the Sahel region of Africa or Japanese B encephalitis in South-East Asia. If a disease has a global impact you need not identify a region.

4) In the fifth section on "Prioritization of vaccine development for developing market vaccines", please identify a very specific vaccine with which you are familiar for the disease you identified at the top of the form. Do not complete these questions (22-26) for a second candidate vaccine for the disease you have identified at the top of the form unless you are aware of a second candidate vaccine for your identified disease. Alternatively, if you are aware of a third candidate vaccine (or more), please photocopy this last set of questions and answer them for the additional vaccines.

5) You may leave any answer blank if you feel unable to respond to it for whatever reason, e.g. if the answer is unknown or if it is not relevant to the disease you have chosen.

6) If you feel that an issue (question) is not applicable to the topic, give it a score of 1. If you leave it blank it will not be counted towards the score for the issue.

7) If you have any concerns about the questionnaire - even if you wish to query its usefulness - please indicate this in your response. If you have any alternative suggestions they would be welcome.

Selected infectious diseases against which vaccines may be useful

1. *Non-negotiable priority vaccines*

Human immunodeficiency virus
Malaria
Mycobacterium tuberculosis

2. *Developing market vaccines (new/improved)*

a) New

Amoebiasis
American trypanosomiasis
Chikungunya virus
Dengue
EaggEC (enteroaggregative *Escherichia coli*)
EPEC (enteropathogeic *E. coli*)
ETEC (enterotoxigenic *E. coli*)
Hepatitis E
Hookworm
Lassa fever virus
Leishmaniasis
Mycobacterium leprae
Onchocerciasis
Rift Valley fever virus
Schistosomiasis
Shigellosis
Venezuelan equine encephalitis virus
West Nile virus

b) Improved

(Cholera)
Japanese B encephalitis
Neisseria meningitidis group A
Salmonella typhi

3. *Global market vaccines (new/improved)*
(i.e. useful to both developing and industrialized countries)

Adenovirus
Campylobacter jejuni
Chlamydia trachomatis
Group B streptococcus
Helicobacter pylori
Hepatitis C virus
Herpes simplex virus type 2
Human papilloma virus
Neiserria gonorrhoeae
Parainfluenza virus
Rotavirus
(*Salmonella enteritidis*)
Streptococcus pneumoniae
Treponema pallidum

4. Impeded vaccines
(i.e. potential for adverse consequences of a vaccine of which we are aware a priori)

Respiratory syncytial virus
Group A *Streptococcus pyogenes*
Cytomegalovirus
Group B meningococcus (polysaccharide)

5. Vaccines specific to industrialized countries
(i.e. not necessarily useful to developing countries)

Norwalk agent
Pseudomonas aeruginosa (for cystic fibrosis patients)

Prioritization of vaccine development

For developing market vaccines

The disease for which you are completing this form:

_____

Disease burden

1. The magnitude of the disease burden: short-term morbidity (questions on disease burden will be generated in conjunction with the Evidence and Information for Policy Group):

Global	Regional (identify region:_____)
1 = (small burden)	1 = (small burden)
2 =	2 =
3 =	3 =
4 =	4 =
5 = (large burden)	5 = (large burden)

2. The magnitude of the disease burden: long-term morbidity (questions on disease burden will be generated in conjunction with the Evidence and Information for Policy Group):

Global	Regional (identify region:_____)
1 = (small burden)	1 = (small burden)
2 =	2 =
3 =	3 =
4 =	4 =
5 = (large burden)	5 = (large burden)

3. The magnitude of the disease burden (mortality) (questions on disease burden will be generated in conjunction with the Evidence and Information for Policy Group):

Global	Regional (identify region:_____)
1 = (small burden)	1 = (small burden)
2 =	2 =
3 =	3 =
4 =	4 =
5 = (large burden)	5 = (large burden)

Other public health issues

4. The public perception of the disease and of the need for its control:

   1 = public little aware of existence of disease; government spends little of its resources on combating the disease

   2 =

   3 = public aware of the disease but it is not considered a serious problem in the community

   4 =

   5 = outbreaks receive extensive publicity (e.g. cholera, meningococcal meningitis); public outcry for government involvement; government spends a significant amount of its health budget to combat the disease

5. Whether alternative public health measures are available to prevent infection:

   1 = highly effective and simple measures available (e.g. water treatment)

   2 =

   3 = measures available but there are difficulties in implementation (e.g. condoms to prevent sexually transmitted HIV and other STDs)

   4 =

   5 = no alternatives to vaccination

6. Whether an effective treatment already exists:

   1 = cheap oral monotherapy available

   2 =

   3 = multiple antimicrobials needed, parenteral therapy only

   4 =

   5 = no or few effective and affordable antimicrobials

7. Whether there exists significant prevalence of antimicrobial resistance in the pathogen:

   1 = no resistance to existing antimicrobial agents

   2 =

   3 = moderate resistance, or multidrug resistance reported only in isolated locations

   4 =

   5 = widespread, multidrug resistance reported

8. Whether the disease has the potential to cause epidemics and pandemics (emerging/re-emerging disease):

   1 = little likelihood of geographical spread for various environmental and epidemiological reasons

   2 =

   3 = spread to other locations possible but vector or other factors make it unlikely

   4 =

   5 = highly contagious; prone to pandemics

9. Whether vaccination could regionally eliminate the disease:

   1 = human, animal or environmental reservoir makes elimination difficult

   2 =

   3 = disease so widespread that elimination from a given population may take generations

   4 =

   5 = no animal reservoir, regional elimination likely

10. Whether herd immunity would promote regional elimination of infection:

   1 = herd immunity unlikely since human to human transmission not an important route of infection (e.g. schistosomiasis)

   2 =

   3 = herd immunity possible but only if a specific immune response is generated by a vaccine (e.g. transmission-blocking malaria vaccine)

   4 =

   5 = herd immunity likely to be beneficial in reducing disease transmission (e.g. *Haemophilus influenzae* type b)

Travellers' vaccines

11. Whether travellers from industrialized countries could benefit from the vaccine:

   1 = rarely reported among travellers (e.g. Lassa fever)

   2 =

   3 = intermittent cause of disease among travellers (e.g. leishmaniasis)

   4 =

   5 = common cause of disease among travellers (e.g. ETEC, shigellosis)

Prioritization of vaccine development

For developing market vaccines

Development and evaluation issues

12. Whether the science is sufficiently mature to generate rational candidate vaccines (i.e. is enough known about the microorganism, the human immune response to the agent and correlates of immunity?):

    1 = little known about the microorganism or the human immune response to the pathogen

    2 =

    3 = substantial information about the microorganism but correlate of protective immunity or surrogate markers of immunity not elucidated

    4 =

    5 = genome has been sequenced; humoral and cellular immune responses to microbial agent are known; correlate of protective immunity or surrogate marker of protection is known

13. Complexity of microbe:

    1 = multiple serotypes or stages of a parasite or viral clades

    2 =

    3 = fewer than six serotypes cause approximately 90% of disease

    4 =

    5 = only one serotype, genetically stable microbe

14. Whether candidate vaccines are already in clinical trials, or whether transition to clinical trials is imminent:

    1 = only preclinical evaluations have been performed

    2 =

    3 = Phase I, II or IIB trials have been performed but safety, immunogenicity or efficacy profiles are marginal

    4 =

    5 = Phase I, II or IIB trials have been performed with adequate safety, immunogenicity and efficacy

15. Whether there exists the possibility of adverse consequences of which we are aware a priori:

    1 = potentiation of immunopathology in a vaccine (e.g. potential for dengue haemorrhagic fever if there is poor immunogenicity against all four serotypes, disease potentiation with formalin-inactivated RSV vaccine immunization)

    2 =

    3 = contains an antigen that theoretically may elicit an adverse effect (e.g. M protein of group A *Streptococcus*)

    4 =

    5 = no known reactogenicity or antigens leading to potentially autoimmune disorders with this pathogen

16. Ease of assessment of vaccine efficacy in Phase III trials:

    1 = trial would require decades of observation (e.g. tuberculosis); clinical end-points difficult to determine (e.g. malaria); correlate of protection unknown (e.g. HIV); incidence of disease is low, requiring large sample size

    2 =

    3 = trial duration extended but not over decades; clinical end-points clear but correlate of immunity unknown; moderate sample size;

    4 =

    5 = known correlate of immunity; Phase IIB trial can be performed ethically; degree of sophistication of microbiological laboratories in developing countries is adequate for diagnosing disease; incidence of disease is high, at least within certain subpopulations, such that with a relatively small sample size an efficacy trial can be conducted; a short duration is required for an efficacy trial

Prioritization of vaccine development

For developing market vaccines

Implementation issues for a specific vaccine

Please indicate candidate vaccine #1: _____

17. Ease of manufacture:

    1 = peptide, multivalent/multiantigen preparations

    2 =

    3 = live virus, polysaccharide conjugate, inactivated whole organism

    4 =

    5 = live bacterium, purified polysaccharide, DNA, toxoid

18. Concerns for deleterious non-target effects (e.g. survival in environment, hazard to unborn child of a pregnant individual or immunocompromised host, infection of non-human animals):

    1 = live microorganisms, non-auxotrophic, replicating, extended colonization

    2 =

    3 = live microorganism, auxotrophic, no shedding

    4 =

    5 = subunit, DNA, inactivated whole organism, toxoid, known carrier molecules

19. Whether the vaccine can be easily transported to the field (e.g. need for cold chain):

    1 = short shelf-life even under optimal conditions

    2 =

    3 = refrigeration necessary, cold chain required

    4 =

    5 = no cold chain necessary, vaccine has long shelf-life

20. Whether the vaccine can be combined or concomitantly delivered with other vaccines through existing immunization services:

    1 = does not integrate into EPI[1], national immunization days (NIDs)[2] or school-based immunization programmes

    2 =

    3 = easy integration into NID campaigns, school-based immunization programmes

    4 =

    5 = integrates easily into EPI

21. Whether the vaccine has characteristics that are particularly attractive for use in developing countries, such as non-parenteral administration (e.g. mucosal or transcutaneous), an immunization schedule that requires only one or two doses, and effectiveness in infants:

    1 = multiple doses, more than one parenteral dose

    2 =

    3 = multiple oral doses, one parenteral dose

    4 =

    5 = single dose, oral administration

[1] The Expanded Programme on Immunization (EPI) is the chief mechanism by which WHO can facilitate the vaccination of most of the world's children under the age of 5 years. It involves a minimum of three visits to a local vaccine clinic.

[2] National immunization days (NIDs) are a means by which large numbers of children are vaccinated in a short-term campaign. This has proved effective in the elimination of many diseases.

Prioritization of vaccine development

For developing market vaccines

Implementation issues for a specific vaccine

Please indicate candidate vaccine #2: _____

22. Ease of manufacture:

    1 = peptide, multivalent/multiantigen preparations

    2 =

    3 = live virus, polysaccharide conjugate, inactivated whole organism

    4 =

    5 = live bacterium, purified polysaccharide, DNA, toxoid

23. Concerns for deleterious non-target effects (e.g. survival in environment, hazard to unborn child of a pregnant individual or immunocompromised host, infection of non-human animals):

    1 = live microorganisms, non-auxotrophic, replicating, extended colonization

    2 =

    3 = live microorganism, auxotrophic, no shedding

    4 =

    5 = subunit, DNA, inactivated whole organism, toxoid, known carrier molecules

24. Whether the vaccine can be easily transported to the field (e.g. need for cold chain):

    1 = short shelf-life even under optimal conditions

    2 =

    3 = refrigeration necessary, cold chain required

    4 =

    5 = no cold chain necessary, vaccine has long shelf-life

25. Whether the vaccine can be combined or concomitantly delivered with other vaccines through existing immunization services:

    1 = does not integrate into EPI, NIDs or school-based immunization programmes

    2 =

    3 = easy integration into NID campaigns, school-based immunization programmes

    4 =

    5 = integrates easily into EPI

26. Whether the vaccine has characteristics that are particularly attractive for use in developing countries, such as non-parenteral administration (e.g. mucosal or transcutaneous), an immunization schedule that requires only one or two doses, and effectiveness in infants:

    1 = multiple doses, more than one parenteral dose

    2 =

    3 = multiple oral doses, one parenteral dose

    4 =

    5 = single dose, oral administration

Annex 3:

Preliminary results from responses to prioritization questionnaire

Thirty-one persons at the June 2000 Global Vaccine Research Forum completed the questionnaire. Some did not specify their field of expertise. Those who did described their expertise as: molecular biology, public health, vaccinology, microbiology, internal medicine, oncology, industry, vaccine supply and quality, enteric disease, or immunology.

The method of scoring involved totalling the raw scores from all sections of the questionnaire (i.e. without weighting). The scores with an asterisk relate to diseases for which too few responses were made to provide meaningful values.

Raw total scores (from highest to lowest)

1.	Tuberculosis	91.8	(5 respondents)
2.	HIV	91.3	(6 respondents)
3.	*Meningococcus* (A)	90.0	(3 respondents)
4.	*Pneumococcus*	89.2	(5 respondents)
5.	Leishmaniasis	87.0	(1 respondent)
6.	Malaria	86.2	(3 respondents)
7.	Shigellosis	80.8	(4 respondents)
8.	Typhoid fever	77.6	(2 respondents)
9.	RSV	76.7	(3 respondents)
10.	Rotavirus	73.4	(3 respondents)
11.	Schistosomiasis	65.0	(1 respondent)
	Japanese encephalitis	*	(2 respondents)
	Cryptosporidium	*	(1 respondent)
	ETEC	*	(1 respondent)
	Haemophilus influenzae b	*	(1 respondent)
	Hepatitis B	*	(1 respondent)