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

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# Abbreviations

AAVP	African AIDS Vaccination Programme
AD	auto-disable (syringes)
ADIP	Accelerated Development and Introduction Plan
AIDS	acquired immunodeficiency syndrome
APC	Antigen presenting cell
BCG	bacillus Calmette-Guérin (vaccine)
CD8	marker of cytotoxic T lymphocytes
CDC	Centers for Disease Control and Prevention (USA)
CDS	Communicable Diseases Cluster (WHO)
CIGB	Centro Ingeniería Genética y Biotecnología
CpG	oligonucleotides rich in CpG motifs
CRF	case report form
CSP	<i>P. falciparum</i> circumsporozoite protein
CTL	cytotoxic T lymphocytes
DOMI	Diseases of the most impoverished project
DOT	directly observed therapy
DT	diphtheria–tetanus (vaccine)
DTP	diphtheria–tetanus–pertussis (vaccine)
EDCTP	European and Developing Countries Clinical Trial Partnership
EGF	epidermal growth factor
ELISPOT	technique to evaluate cellular immune responses
EMA	European Medicines Evaluation Agency
PfEMP1	antigen of <i>Plasmodium falciparum</i>
EPI	Expanded Programme on Immunization
ETEC	enterotoxigenic <i>E. coli</i>
FACSscan	method to analyse cells surface molecule expression
FITC	labelled with fluorescein
GAVI	Global Alliance for Vaccines and Immunization

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GCP	good clinical practices
GMP	good manufacturing practices
GNP	gross national product
GVRF	Global Vaccine Research Forum
HbsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HepB	hepatitis B
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
HTP	Health Technology and Pharmaceuticals (WHO Cluster)
IAVI	International AIDS Vaccine Initiative
ICGEB	International Center for Genetic Engineering and Biotechnology
IgA	immunoglobulin A
IgG	immunoglobulin G
IOMAI	IOMAI Corporation, USA
IPR	intellectual property rights
IPV	injectable polio vaccine
IRB	institutional review board
IVI	International Vaccine Institute
IVR	Initiative for Vaccine Research
JE	Japanese encephalitis
LT	<i>E. coli</i> heat labile toxin
LT-B	B subunit of the <i>E. coli</i> heat labile toxin
MMR	measles-mumps-rubella (vaccine)
MMV	Medicine for Malaria Venture
MSP	<i>P. falciparum</i> merozoite surface protein
MVA	modified vaccinia Ankara (non replicative vaccinia virus strain)
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NK	natural killer lymphocytes
NRA	national regulatory authority
ODN	oligonucleotide
PATH	Program for Appropriate Technology in Health (USA)
PR	property rights
PS	polysaccharide

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RAPID	Rotavirus Action Programme for Introduction and Development
RTS,S	malaria vaccine candidate based on a fusion of CSP with hepatitis B surface antigen
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SIIL	Serum Institute of India
SIV	simian immunodeficiency virus
SOP	standard operating procedure
SPF	specific pathogen free
TB	tuberculosis
TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
Th1	Type 1 T helper lymphocyte
TLR9	Toll-like receptor 9
TT	tetanus toxoid (vaccine)
UN	United Nations
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
UPT	Universal Preservation Technology company
USNIH	United States National Institutes of Health
V&B	Department of Vaccines and Biologicals (WHO)
VDPV	vaccine-derived poliovirus
VERO	green monkey kidney derived cell line
WHO	World Health Organization



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# Introduction

Dr Yasuhiro Suzuki, Executive Director of WHO's Health Technology and Pharmaceuticals (HTP) cluster, warmly welcomed the participants and thanked them for attending this gathering of specialists in vaccine research and development. The Global Vaccine Research Forum (GVRF) was the seventh meeting in a series previously referred to as the "Montreux meetings" and the third joint WHO/GAVI meeting on global vaccine research.

Dr Suzuki outlined the broad objectives of the Forum:

- To provide an opportunity for GAVI partners to participate in shaping a global vaccine research and development agenda.
- To provide an overview of the activities of the GAVI Task Force on Research and Development.
- To analyse the current status of vaccine research and development against AIDS, malaria and tuberculosis.
- To identify opportunities for vaccine research and development within WHO/IVR.
- To review new vaccine technologies.
- To review opportunities and bottlenecks in vaccine research, development and introduction as perceived by the vaccine industry.

Dr Suzuki noted that 2002 was a critical year for GAVI research and development activities. The GAVI Accelerated Development and Introduction Plans (ADIPs) for pneumococcus and rotavirus vaccines would soon be finalized and the projects under way. Funding of the ADIPs by the Windows 3 mechanism of the Vaccine Fund had been authorized by the GAVI Board. Three new vaccine technology agendas had been selected as GAVI research and development priorities. Important changes in vaccine research and development were also occurring in WHO, Dr Marie-Paule Kieny having been appointed Director of the Initiative for Vaccine Research.

Dr Suzuki announced that, in future, GVRF would be held away from Geneva every second year. The 2003 meeting would be hosted by the International Vaccine Institute (IVI) in Seoul. Dr Suzuki expressed his regret that he would be leaving WHO at the end of June 2002, when Dr Arnafi Asamoah-Baah would succeed him as Executive Director of HTP. Dr Suzuki wished all participants an interesting and productive meeting.

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

## Malaria vaccines (Carter Diggs)

There is a pressing need for malaria vaccines. The number of persons at risk is increasing and each year the disease claims an enormous number of lives. During the last decades, technical difficulties facing the discovery of malaria vaccines have delayed progress in this domain. Impediments to vaccine development include the complex multistage life cycle of the malaria parasite, the heterogeneity of immune responses required for protection, interference from potentially disease-enhancing immune responses, a lack of adequate animal models for evaluating vaccine efficacy, as well as inadequate funding.

The first demonstration of the technical feasibility of a malaria vaccine involved immunization with irradiated sporozoites, which can give protection for months. Unfortunately, this approach is not practical except for the vaccination of a handful of volunteers.

Ideally, a vaccine should attempt to provide the same kind of immunity as is elicited by natural infection. Possible ways of intervening with a vaccine in the disease process include: i) avoiding retarding the release of merozoites from the liver; ii) avoiding retarding the development of blood-stage parasites; and iii) avoiding retarding the infection of the mosquito. Currently, attention is concentrated on the first two mechanisms. Prevention of systemic disease is likely to require the use of combination vaccines. In addition, immune responses required to prevent disease are likely to include antibodies that interfere with sporozoite entry into the liver, as well as CD8/CTL responses that attack intrahepatic parasites.

Many different antigens are under investigation as candidate vaccines, such as the CSP, MSP1 and PfEMP1 *P. falciparum* surface proteins. Early clinical trials with R32, a vaccine containing 32 repeats of the circumsporozoite protein CSP, have hinted at efficacy, i.e. one-third of volunteers in high-dose groups were protected against artificial challenge with infectious parasites. More complex vaccines containing CSP repeats fused with the hepatitis B surface antigen (RTS,S) are currently being tested. Artificial challenge studies, using prevention of blood-stage infection as the clinical end-point, have indicated an efficacy of 50%, but as yet only short-term protection has been demonstrated. In addition, the RTS,S vaccine shows promise in preventing disease among residents in areas of endemicity. Alternative vaccination strategies are also being pursued. They include: targeting the induction of both antibodies and CD8-mediated cytotoxicity with prime-boost protocols combining the use of live recombinant MVA or fowlpox vectors expressing *P. falciparum* antigens, as well as of peptides, DNA vaccines and subunit vaccines in various adjuvants.

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## HIV/AIDS vaccines (Marc Girard)

Since AIDS was first recognized in 1981 more than 60 million people have been infected by HIV and 20 million have died of the disease. HIV is now considered to be the leading infectious killer in the world. Research on HIV vaccine confronts many obstacles, one of which is the unavailability of completely predictive animal models. Chimpanzees, although they can be infected with HIV, do not develop AIDS, and simian AIDS in macaques is associated with infection with SIV, which is much more closely related to HIV-2 than to HIV-1.

Hardly anything is known about the immune correlates of protection against infection. The virus shows tremendous genetic variability, viral escape mutants readily emerge in the host, and primary virus isolates are resistant to neutralization by most antibodies. The recognition of viral subtypes (clades) and the identification of virus coreceptors on T-cells and macrophages have led to new approaches to vaccine development. There is some evidence that HIV strains possessing a tropism for different coreceptors, chemokine receptors CXCR4 for T-cells or CCR5 on macrophages, elicit different types of immune response. For example, HIV strains binding CXCR4 can easily be neutralized by antibodies whereas those entering target cells following attachment to CCR5 are extremely difficult to neutralize *in vitro*. There could therefore be a role for neutralizing antibodies directed against the viral envelope of glycoproteins gp 120 and gp140 in protecting against infection by CXCR4 tropic HIV viral strains, but these may not be effective against strains using CCR5 as a coreceptor. As yet it has not been possible to induce broadly effective neutralizing antibodies.

A recent development in AIDS vaccine research relies on measuring the viral load after infection with HIV and on assessing the role of the CTL response in controlling this load. It is important to understand why some HIV-infected individuals control viral replication and do not develop AIDS. This may be related to the strength of the initial CD8 response. The occurrence of specific cytotoxic T-lymphocytes in infected humans and monkeys and the rapid development of AIDS in CD8 T-cell-depleted macaques indicate the importance of the CD8 immune response. The current focus is therefore on the development of vaccines capable of inducing a strong CD8 response. As specific anti-HIV CD4 responses, and especially the associated cytokine and chemokine secretion, may also be important for protecting infected individuals against the development of the disease, much work is being done on the development of vaccines that induce a broad cellular immune response.

Various groups and companies are developing new-generation HIV/AIDS vaccines, including DNA vaccines, lipopeptides and live recombinant vectored vaccines, based on recombinant poxviruses (non-replicative MVA vaccinia virus, canarypox and fowlpox), adenoviruses, alphaviruses or BCG, and combinations of the above in various prime-boost immunization regimens. Approaches based on the utilization of attenuated HIV strains as live vaccine have been abandoned because a similar strategy induced AIDS in macaques. With regard to specific antigens for use as candidate vaccines, the focus is on the regulatory proteins *tat*, *rev* and *nef*, in addition to the structural HIV antigens *Gag* and *Env*. Recent vaccination studies with *tat* in macaques have provided very interesting preliminary results, the vaccinated animals presenting reduced viral loads. Clinical trials on the immunogenicity of HIV vaccines based on *tat* in humans have recently been initiated.

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As judged from results obtained in animal models, however, it seems unrealistic to expect these vaccines to provide sterilizing protection against HIV infection. It is hoped that they will induce potent and broad cellular immune responses resulting, in the event of infection, in clinically attenuated disease with lowered viral RNA loads, together with a decreased probability of viral transmission to uninfected persons. This would have a profound impact on the spread of the AIDS pandemic. The only way to validate these new concepts in vaccine design is to conduct phase III efficacy trials. Two efficacy trials of monomeric gp120 candidate vaccines are being conducted in North America and Thailand, and a new phase III trial of a prime-boost strategy (canarypox-HIV and gp120) is planned to start in Thailand in early 2003. In this context it is important to conduct more phase III trials as soon as possible with the most immunogenic candidate vaccines that are available.

### **Tuberculosis vaccines (Vijaya Satchidanandam)**

In 1998 it was estimated that 6.7 million new cases of tuberculosis and 2.4 million deaths from the disease occurred every year, exceeding those attributable to malaria, AIDS and all tropical diseases combined. Mathematical modelling suggests that the corresponding numbers in 2030 would be 225 million and 79 million (Murray and Salomon, *Proc. Natl. Acad. Sci. USA*, 1998;95:1481). This exponential increase is occurring despite the use of BCG and the implementation of directly observed therapy (DOT) in many high-burden countries. Consequently, very urgent countermeasures are needed and attempts are being made to identify new drugs and to develop vaccines that are more effective than BCG.

Disease develops in only 10% of individuals infected with *Mycobacterium tuberculosis*. It is therefore desirable to understand the immune mechanisms implicated in natural protection against progression to disease. In addition, new studies on environmental mycobacteria by Dockrell, Fine and Andersen suggest that an immune response to environmental mycobacteria interferes with BCG replication. This may explain why BCG fails to give effective protection against tuberculosis in areas of high endemicity, where these bacteria are prevalent.

A wide variety of novel TB vaccines is under development, including live attenuated *Mycobacteria*, subunit-adjuvanted proteins, DNA, and vectored vaccines. The first new TB vaccine recently entered clinical testing in the United Kingdom, under funding from the Wellcome Trust. This vaccine, developed by Hill and McShane, is based on Ag85A expressed in the modified vaccinia Ankara (MVA) highly attenuated vaccinia virus strain. While BCG is contraindicated in AIDS patients, attenuated BCG auxotrophs could be envisaged as TB vaccines, e.g. those developed by Jacobs and Bloom. Protection data obtained in the guinea pig model indicate that the recombinant BCG constructed by Horwitz and expressing Ag85B, is very promising as a candidate vaccine. Several other potential new vaccines will be entering clinical trials during 2002, and new methods are being developed to assess immune responses in humans. Dr Satchidanandam's own work on novel proteins present in Mtb strains from South India has shown that these proteins, expressed *in vivo* in vaccinated guinea pigs as DNA vaccines or as recombinant BCG vaccines, elicit both CD4 and CD8 responses.

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In the area of upstream research, the availability of the complete TB genomic and proteomic sequences has made it possible to discover new antigens. Large numbers of novel TB proteins can now be screened for their ability to stimulate the production of interferon gamma. Indeed, the production of this Th1 cytokine by antigen-specific T-cells, as well as the ability of these T-cells to inhibit intracellular growth of *M. tuberculosis*, are two widely accepted criteria for identifying potential TB vaccine antigens.

Several animal models are available for testing TB candidate vaccines, each with its own pros and cons. The WHO Task Force on Animal Models for TB Vaccine Evaluation has standardized the guinea pig model by using low-dose aerosol challenge. This model is now available in many laboratories. Nevertheless, there is a need for a validated primate model for testing promising TB vaccines.

Sizeable funding for TB vaccine research is coming from public sources spearheaded by the United States National Institutes of Health (USNIH), European governments, and the European Commission. In addition, large and medium-sized pharmaceutical companies, e.g. GlaxoSmithKline and Corixa, and numerous smaller biotechnology firms, are conducting research on TB vaccines. Overall, however, funding for the development of TB vaccines is insufficient. The USNIH blueprint for TB vaccine development states that US\$ 800 million should be spent on research and development in this field in order to develop a successful vaccine by 2020.

### **Recent achievements of the Malaria Vaccine Initiative (MVI)**

(Regina Rabinovich)

Some novel malaria vaccines have shown evidence of protection in clinical trials, and new cost-effectiveness models indicate that a reasonable profit can be made by marketing such vaccines. MVI was created, thanks to funding from the Bill and Melinda Gates Foundation, in order to address the issue of translational research focused on malaria.

In the recent past, MVI has entered into a number of important vaccine partnerships with both public research institutions and the private sector and much progress has been achieved during the last two years.. MVI currently supports projects pioneered by GlaxoSmithKline, the Walter Reed Army Institute of Research (USA), USNIH, Apovia (USA), ICGEB (India), Oxford University (United Kingdom) and Monash University (Australia), as well as other projects in Australia and Kenya. Both preclinical and clinical trial programmes are supported. The MVI approach is concerned with legal contracts and joint vaccine development rather than with the awarding of R&D grants.

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## Recent achievements of the International AIDS Vaccine Initiative (IAVI) (Wayne Koff)

The goal of IAVI is to accelerate work in the field of HIV/AIDS vaccines and to address the following issues:

- challenges in vaccine research;
- design of immunological assays – this is very important, especially for the evaluation of neutralizing antibodies. This issue will be addressed by a consortium of laboratories supported by IAVI;
- development – because the lack of capacity for production of candidate vaccines under good manufacturing practices (GMP) is a major obstacle, IAVI is concentrating on process development;
- clinical trials – the major impediment is the restricted number of suitable infrastructures in Africa and Asia;
- regulatory aspects – it is important to define what could be an efficacy end-point for licensing: could it be decreases in viral load in vaccinees as compared to not vaccinated infected subjects, and, if so, what size of decrease would be acceptable?

Significant progress has been made recently in the area of HIV vaccines. In animal models the best results have been obtained with live attenuated SIV, but the absence of safety in young macaques has discouraged commercial interest and has led to the abandonment of this approach. Immunization with certain vectored vaccines (e.g. recombinant adenoviruses) has been shown to retard HIV replication.

IAVI focuses on vaccines that can be used in the developing world. Contracts are therefore established with IAVI-sponsored investigators in order to assure tiered prices and access of countries where the disease is endemic to future HIV vaccines. As most HIV strains prevalent in developing countries belong to the A or C clades (whereas United States or European strains are usually of clade B), HIV vaccines must be designed to meet the specific needs of these countries.

A number of phase I and phase II clinical trials and immunogenicity studies are in progress. It is intended to initiate a phase III study by the end of 2004. The first IAVI-sponsored efficacy trial of an HIV vaccine will test a prime-boost strategy using both a DNA-based- and an MVA-based vaccine expressing various HIV antigens or peptides. This work is promoted by Andrew McMichael (University of Oxford, United Kingdom). IAVI also supports second-generation AIDS vaccines. Eight candidate vaccines are at the development stage and three vaccine strategies are entering into the early stages of testing. However, the feasibility of manufacturing some of these candidate vaccines, especially on a large scale, and their applicability for use in developing countries, is still questionable. It is therefore crucial to invest in scaling-up and process development. At present it is IAVI's view that any antigen demonstrating the capacity to elicit an effective neutralizing antibody response should be seriously considered for clinical evaluation.

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## Recent achievements of the Sequella Global Tuberculosis Foundation (Lewellys Barker)

TB remains a major public health problem in many parts of the world. The primary purpose of the Sequella Global Tuberculosis Foundation, founded in 1997, is to serve as a resource to the TB research community in the quest for new and better tools for diagnosis, treatment and prevention of the disease. The Foundation is particularly interested in supporting product-oriented translational research that can help to move basic research concepts and discoveries in immunology, microbiology, genomics and related fields to proof of principle by pursuing preclinical and early clinical testing. The Foundation's Tuberculosis Vaccine Collaboration, supported by the Bill and Melinda Gates Foundation, includes targeted research programmes on animal models for the preclinical assessment of TB candidate vaccines, on novel active and dormant TB detection techniques for evaluating vaccines, and on immunological response markers, which may correlate with vaccine-induced protection. Various other preclinical studies, including work on specific new TB candidate vaccines, are supported by the Tuberculosis Vaccine Collaboration. Special attention is given to clinical site development in Cape Town (South Africa), where Sequella supports work in epidemiology, human genetic studies and the engagement of country workers. The Foundation has recently initiated a phase IV comparative trial of BCG in infants, which will bank specimens for analysing potential immune correlates of protection against tuberculosis. Sequella also supports a vaccine innovation competitive grants programme and a training programme for clinical research site personnel, and provides assistance with the handling of intellectual property related to new TB vaccine technologies.

WHO recommends BCG for routine immunization of all infants at or close to birth, with a few exceptions related to HIV/AIDS. BCG is therefore widely used at the start of the EPI programme of childhood immunization. Accordingly, a new prophylactic TB vaccine development strategy may start by seeking to improve on the protection afforded by infant BCG immunization with a prime-boost or reimmunization approach, a new vaccine being used either before or after the administration of BCG to infants. Depending on the performance characteristics of new candidate vaccines, it may be possible to replace BCG. The characteristics of an ideal TB vaccine or immunization regimen differ in several ways from those of the BCG vaccination of neonates. The most important distinction would clearly be the consistent production of a high level of durable protection against clinical TB disease in immunized populations across a broad age spectrum, a feature that appears to be lacking with BCG.

There are many types of new TB candidate vaccines, including (1) live attenuated candidate vaccines, usually modified BCGs or attenuated Mtb; (2) subunit vaccines ranging from recombinant Mtb proteins to synthetic peptides, lipids or carbohydrates with appropriate adjuvants; and (3) DNA vaccines or live recombinant viral and bacterial vectors expressing Mtb antigens. Many issues relating to design, manufacture, quality control and safety need attention in connection with all of these strategies in order to bring candidate vaccines to the point of clinical trials. One particularly challenging issue in relation to the clinical development of TB vaccine is the lack of a correlate of protection which could be used for early evaluation of the potential of experimental vaccines to give protection against TB. There is considerable evidence indicating the importance of Th-1-type cell-mediated immunity as a correlate

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of TB immune protection, but the usefulness of measuring cell-mediated immune responses as a correlate of protection in human vaccine trials remains to be determined. Even further away is a truly validated immune response marker that could serve as a surrogate for predicting the efficacy of new TB vaccine products and eventually substitute for clinical outcomes in efficacy trials.

Several candidate TB vaccines are being studied by scientists participating in the Sequella Foundation's Tuberculosis Vaccine Collaboration. Three of these vaccines are at advanced stages of preclinical development which include the production and final testing of material suitable for phase I clinical trials.

### **Accelerating the rational introduction of new vaccines into developing countries: the importance of translational research (John Clemens)**

Although the Jordan Report has inventoried 386 candidate vaccines currently under development against 99 diseases, a number of new vaccines of proven efficacy are still underused. Two of the reasons for this are that: (1) the results on efficacy are not always concordant in phase III trials in industrialized countries with those obtained in the developing world, and it therefore seems very important to test new vaccines in parallel in various environments; (2) even after the completion of efficacy trials, some uncertainty remains as to the probability of uncommon side-effects, acceptability, affordability, ease of incorporation and impact when a new vaccine is introduced into public health systems of developing countries. Knowledge of such matters requires the implementation of translational research in order to generate practical evidence and provide a rational basis for policy decisions.

Translational research encompasses several areas and includes studies on disease burden, cost-effectiveness analysis, demonstration projects, behavioural studies, and policy research concerning the evaluation of potential channels for vaccine introduction and fair financing.

The example chosen to underline the importance of disease burden studies was that of *Haemophilus influenzae* type b (Hib). The annual incidence of Hib meningitidis at three IVI sites (China, Korea, and Viet Nam) was demonstrated to be low and variable between them. This has tremendous importance in relation to the opportunity of introducing an Hib vaccine in different Asian countries. There is therefore a need for the local assessment of disease burden. Likewise, economic studies are critical in connection with decisions to introduce new vaccines. This was illustrated by the example of Japanese encephalitis (JE), for which a study based on disease incidence and cost data in Shanghai showed that, from the societal perspective, the two JE vaccines now being used in China are achieving a net cost saving. The importance of demonstration projects was exemplified by the DOMI project, one of the activities of which consisted of mass immunization of half the population of Hue (Viet Nam) with a locally produced cholera vaccine. The success of this project was based in part on the low cost of the vaccine (\$0.89 per course of vaccination of two doses). It was underlined that experience in "early adopters" of vaccines can sometimes serve as a demonstration project to provide relevant evidence, such as the experience of using a Vi typhoid vaccine in China.

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Several approaches can be adopted in order to enhance the impact of translational research. Ideally, such research should meet the needs of policy-makers, and should therefore be designed on the basis of policy surveys. It is also enhanced by a collaborative, coordinated, multicountry approach, and by the deployment of coherent, multidisciplinary programmes of research.

**Policy development for post-certification polio immunization:  
the unfinished research agenda as eradication approaches completion**  
(Daniel Tarantola)

In 1988 the World Health Assembly adopted the goal of eradicating poliomyelitis by the year 2000. This aim was founded on the widely held perception that, as with the smallpox eradication programme, the containment of cases and the subsequent certification of eradication would allow the cessation of polio vaccination. It was estimated that the number of polio cases decreased from 350 000 in 1988 to fewer than 1000 in 2001, i.e. by over 99%.

Once the transmission of wild poliovirus has been interrupted globally, diagnostic and research laboratories and vaccine production facilities will be the only reservoirs of wild poliovirus. Laboratory containment aims at minimizing the risk of inadvertent or intentional reintroduction of wild poliovirus from laboratories or vaccine production sites into human circulation. Countries need to identify all laboratories storing wild poliovirus or materials potentially carrying wild virus in order to ensure the proper handling or disposal of such materials under appropriate conditions of biosafety. WHO has published an action plan for the laboratory containment of wild poliovirus and guidelines for implementing the pre-eradication phase of global containment. Ninety-nine countries are either conducting or have completed a national survey of biomedical laboratories and 74 of them are finalizing national inventories of laboratories confirmed to be storing wild poliovirus materials.

The certification of the absence of indigenous wild poliovirus is undertaken on a regional basis. Certification is granted when high-quality surveillance in all the countries of a WHO region indicates that there has been a period of three years free of wild virus. It is intended that global certification will be well advanced or completed by 2005. The certification of global polio eradication will be possible only when all WHO regions have been certified polio-free and all the tasks associated with the pre-eradication and post-eradication phases have been completed.

Overshadowed, perhaps, by the continuing transmission of the wild virus in areas of high endemicity, the recognition of circulating vaccine-derived polioviruses (VDPVs) has raised legitimate concerns about the continued use of OPV when transmission of the wild virus has been interrupted. After immunization with OPV, vaccinees excrete Sabin virus for a limited time. Very rarely, VDPVs may acquire the neurovirulence and transmission characteristics of wild-type poliovirus, as happened in Egypt (1988–1993), the Dominican Republic and Haiti (2000–2001), and the Philippines (2001).

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When polio eradication began in 1988 the assumption was made that the use of OPV would be discontinued after the wild virus was eradicated. This option now raises two questions: (1) How can a population be protected against the re-emergence of polio outbreaks which could result from circulating VDPVs if the oral polio vaccine continues to be used? (2) How is it possible to minimize and control the risk of reintroduction of polio virus associated with long-term excretors, laboratories or intentional release?

Post-certification policies will build on the evidence that is being accumulated through programme data, research and consultative processes. There are crucial gaps in knowledge, notable with respect to the frequency, nature and impact of VDPVs, optional policies on polio immunization, approaches to the stockpiling of vaccines, and the development of new ones that would minimize or eliminate the risk of emergence of cVDPVs (e.g. monovalent OPV or IPV derived from the Sabin strains). Research should be accelerated within a tight time frame: more time means more OPV, more risk of VDPVs and more resources. WHO has embarked on a challenging research agenda. It calls on institutions and researchers to revitalize work on poliovirus and help to bring the eradication campaign to its true end: the discontinuation of immunization against a virus that no longer exists.

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# GAVI's vaccine research and development projects

## **Update on GAVI activities (Tore Godal)**

There is a growing awareness of the link between health and development and of the need to improve health in order to reduce poverty. Soft loans and credits for health are now increasingly being recognized as important for poverty reduction strategies.

To date the Vaccine Fund (the financial arm of GAVI) has received 68 out of a possible 74 applications from eligible countries, and of those 60 have been approved. A viable market for sophisticated vaccines has been created in poor countries by vaccine procurement through the Vaccine Fund. Country plans for vaccinations indicate a substantial growth in coverage with DTP3 (third dose of diphtheria-tetanus-pertussis vaccine) and hepatitis B, but very limited increases in Hib vaccine coverage. It is also important to realize that, in addition to financing, satisfactory supply mechanisms are essential for the uptake of vaccines in developing countries.

GAVI is moving into an implementation phase. This has important implications for its operational mode, i.e. tighter management controls are needed in order to achieve the implementation goals. The strategy for 2006 to 2011 is being developed and questions of financial sustainability are central to the planning process.

## **Progress of the GAVI Task Force on Research and Development (Mike Levine)**

The Task Force on Research and Development helps to address several of GAVI's key objectives. It was asked to identify three key vaccine products (meningitis, pneumococcus and rotavirus vaccines) and three vaccine technology projects for support by GAVI and funding by the Vaccine Fund.

The GAVI research agendas for pneumococcal and rotavirus were initially developed through consultation with the research community and vaccine manufacturers, orchestrated by the Task Force. These agendas were then integrated with other priorities of the Task Force into a businesslike approach. In consultation with McKinsey & Company, the business plans were recently turned into target-driven plans (Accelerated Development and Introduction Plans; ADIPs). The meningitis vaccine project is currently developed by a WHO-PATH partnership funded by the Bill and Melinda Gates Foundation.

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Technology experts, in consultation with the Task Force, have identified the following top areas of priority in research on new technologies.

1. Innovative management and progressive elimination of the cold chain, and, in particular, the development of vaccine stabilization technologies (sugar glass).
2. Refined tools for measuring country progress and coverage, and, in particular, non-invasive field antibody tests.
3. The development and implementation of defanging syringes as a low-cost technology.

ADIPs have to be developed for these new technology areas. The funding of key targeted activities identified through the ADIPs is now possible thanks to the opening of Window 3 of the Vaccine Fund (authorized in June 2002 by the GAVI Board). ADIPs teams will be recruited and will coordinate the technical ADIPs operations and maximize the synergy of Window 3 funds with those of other donors or partners.

### **Meningococcal vaccines (Marc LaForce)**

Over the last 100 years, meningitis epidemics have caused enormous suffering in sub-Saharan Africa. The population at risk exceeds 250 million. The Meningitis Vaccine Project (MVP), a partnership between WHO and PATH funded by the Bill and Melinda Gates Foundation, has the goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, introduction and widespread use of conjugate meningococcal vaccines.

The currently available meningitis polysaccharide (PS) vaccines are far from ideal. Conjugate vaccines might overcome many of the key limitations of PS vaccines. MVP is involved in two projects, the first of which concerns a heptavalent EPI vaccine (DTPw, HepB, Hib, meningococcus A/C) with groups A/C glycoconjugate antigens, undergoing development by GlaxoSmithKline. MVP's role is to support clinical trials of this vaccine in Africa. The second project concerns a group A conjugate vaccine for use in mass immunization campaigns among persons aged 1-29 years; it is expected that 250 million people in 18 countries will be vaccinated over 10 years. The latter vaccine has no commercial market outside of Africa and would not be developed without the support of MVP.

Until this year, group A meningococci have accounted for about 85% of all cases of epidemic meningitis in Africa. In 2002, however, an outbreak of group W135 disease in Burkina Faso has complicated the situation. The development of a quadrivalent vaccine (including serogroups A/C/Y/W135) is therefore a possible strategy for dealing with the occurrence of serogroup W135 outbreaks besides the more classical serogroup A epidemics, but there are many problems in the way of successfully achieving this goal. Indeed, the cost of a quadrivalent vaccine is likely to exceed what is affordable for countries in the meningitis belt. Although it is not possible to predict what will happen to group W135 in 2003, a review of meningococcal isolates by WHO demonstrated that group A continued to be by far the principal cause of epidemic meningitis in sub-Saharan Africa with the exception of Burkina Faso. The development of a monovalent A conjugate was therefore chosen as the key focus for MVP. The advantages of this strategy are its simplicity, low cost and high potential impact, since most disease in Africa is still attributable to serogroup A *N. meningitidis*.

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When MVP was created it was thought that one of the large manufacturers in the industrialized world would produce this vaccine. This has not happened, mainly for economic reasons. MVP has therefore made a considerable effort to explore alternative strategies for the production of a monovalent A meningococcal vaccine. Three critical components were identified in this new model: (1) sources of high-quality serogroup A PS and tetanus toxoid (TT); (2) the development and transfer of a conjugation method; and (3) the identification of a commercial manufacturer capable of conjugation, blending, packaging and fill/finish/lyophilization.

A highly competent contract manufacturer has agreed to develop the technology for the production of group A PS, and several sources of highly purified TT have been identified. A discovery company was further chosen by MVP for the technological development and transfer of conjugation techniques. Importantly, an experienced vaccine manufacturer in a developing country was selected to be MVP's manufacturing partner. A cost of US\$ 0.40 per dose has been estimated for a market of 25 million doses per year. This is compatible with the sustainability of the use of the vaccine in Africa. It is now necessary to obtain support in local African structures for sustaining the achievements of the programme.

### **Rotavirus vaccines (Bernard Ivanoff)**

It is estimated that 600 000 infant deaths per year are attributable to rotavirus in developing countries, where the peak incidence of rotaviral disease occurs at 6-11 months of age. There is no variation in the percentage of hospitalized diarrhoea cases attributed to rotavirus between developed and developing countries. Vaccines are therefore extremely necessary, even more than improvements in sewage and water supplies. Strain surveillance in African and Asian networks has shown the G1 serotype to be the most important cause of disease.

Multiple vaccine approaches are in phase II and phase III testing with rotavirus strains derived from humans, cattle and sheep. Preclinical research on alternative strategies is also in progress, involving the use of DNA, non-structural proteins, and viral-like proteins. The work on three of the six candidates in advanced stages of development is being performed by manufacturers in developing countries. The RAPID group is supporting phase II studies in Bangladesh and South Africa. Phase III trials in developing countries are designed to assess the risk of intussusception. Indeed, an increased incidence of this adverse event led to discontinuation of the marketing of the first commercialized rotavirus vaccine (Rotashield).

### **Pneumococcal vaccines (Thomas Cherian)**

Pneumococcal pneumonia is a major cause of child mortality in developing countries. Currently available vaccines contain pneumococcal capsular polysaccharides. Antibodies raised against the polysaccharides are known to be protective against invasive pneumococcal disease but protection is serotype-specific. Vaccines with broad efficacy against *Pneumococcus* should therefore contain multiple polysaccharides. Vaccines based on protein antigens, which are not serotype-specific, are being developed.

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The efficacy of pneumococcal conjugate vaccines against invasive disease attributable to vaccine serotypes ranges from 75% to 95%. Efficacy against pneumonia is the outcome of public health interest in developing countries. However, estimation of such efficacy is complicated because of the lack of adequate methods for identifying cases of pneumococcal pneumonia. Preliminary data from two recent trials show 20% protection against radiographic pneumonia attributable to any cause, but these point estimates have wide confidence limits and further data are required in order to clearly define efficacy against *Pneumococcus* pneumonia.

Efficacy against otitis media is important in industrialized countries and may have important implications in connection with the interpretation of data on pneumonia. In otitis, reduced disease attributable to vaccine types in conjugate vaccine is offset by increased disease resulting from non-vaccine types of *Pneumococcus* (a phenomenon called strain replacement). It is not known whether, nor to what extent, this may occur in relation to pneumonia but the phenomenon may lead to underestimation of the efficacy of vaccines against vaccine types of *Pneumococcus*. Furthermore, efficacy against otitis media shows that the effect is greater on recurrent or more severe diseases. A similar effect may be seen with pneumonia. Both aspects need to be investigated.

The value of the vaccine extends beyond the immunized age group. Data from California Kaiser Permanente and CDC show significant decreases in invasive pneumococcal disease among adults aged 20–39 and 60+ years, following vaccination of children.

Analytical work by McKinsey & Company – a management consulting firm - indicates that the principal factor causing high prices for new vaccines and which the public sector can influence relates to the issue of demand uncertainty. Accelerated Development and Introduction Plans (ADIPs) represent a strategy for assuring adequate supplies of vaccine at affordable prices to developing countries by reducing such uncertainty. The strategy is focusing initially on large vaccine manufacturers in the industrialized world and on advanced products. Later it will also support technology transfer and new approaches, e.g. the use of protein vaccines. The pneumococcal vaccine ADIP, like the rotavirus vaccine ADIP, is organized around three basic objectives: establishing, communicating and delivering the value of the vaccine. Establishing the value of the vaccine ultimately depends on accurate determination of the burden of disease and on showing the impact of the vaccine on pneumonia mortality, a challenge for the pneumococcal research and development community.

### **New technologies (John Lloyd)**

In November 2000 the GAVI Board requested the Task Force on Research and Development to recommend up to three non-vaccine-specific research projects that would lead to improved immunization systems and technologies. These projects were to be additional to the three GAVI vaccine-related research and development priorities. It was understood that these projects would be focused on selected technologies that could be introduced into services within a time frame of 5–10 years.

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The Task Force undertook extensive information-gathering, evaluation, rationalization and prioritization in order to identify key technologies and improved management or operational strategies which could have a favourable impact on immunization services in developing countries. Three teams were formed to look at different potential research areas: 1) hardware solutions, with particular emphasis on administration safety and waste management; 2) software solutions and operational research focusing on management and outreach strategies; and 3) formulation and process solutions. Using the criteria of potential programmatic impact, technical feasibility, probability of successful introduction, and cost-benefit ratio, the recommendations of the teams were merged into a short list of three prioritized vaccine technology agendas. Specific promising technologies were identified and prioritized in order to address each of these agendas, which were then described.

It is well recognized that current cold chain systems are inadequate and sometimes cause vaccines to freeze. There are various strategies and technologies for streamlining the cold chain and progressively removing vaccines from it. In particular, liquid bacterial vaccines that are currently sensitive both to heat and freezing may be stabilized to the extent that they no longer need to be kept in the cold chain. Such stabilization would allow new vaccines to be integrated into vaccine distribution systems at the lowest possible cost, eliminating wastage, maximizing potency and permitting access to immunization services for more children. The identification of sugar glass preservation as the highest priority for reducing dependence on the cold chain is the first item on the GAVI agenda for new technologies. Vaccines preserved in this way could be delivered by reconstitution, non-aqueous suspension, sugar needle, or powder injection. In addition to this very promising technology, other strategies for reducing the risk of freezing and extending immunization outreach were also identified as GAVI targets.

The second item on the technologies agenda is the development of oral fluid assays for objective assessment of coverage. GAVI's focus on performance requires more accurate and less expensive methods for tracking the number of children immunized than the current Data Quality Audit and National Cluster Coverage Surveys. In the absence of effective surveillance, antibody tests provide an indisputable outcome measure for the success or failure of an immunization service. Saliva tests that can be used in the field are desirable for tetanus and also for meningococcal meningitis A, measles and hepatitis B. Finger-prick tests may be available as a short-term surrogate by 2004. Oral assays will take longer to reach the market.

The third priority focuses on reducing infectious waste and the ultimate elimination of sharps. The widespread introduction of auto-disable (AD) syringes is addressing the problem of needle safety, but ADs increase the volume of infectious sharps waste. Current options for waste disposal (burning in open pits, incineration, burying and disposal with community garbage) are inadequate, particularly in urban areas, and the casual discarding of used syringes and needles outside health facilities is all too common. Simple and inexpensive field tools are thus needed for removing needles from syringes and depositing them in safe boxes. Such tools are already being field-tested and it may be possible to introduce them relatively soon, e.g. the device designed to defang needles, one of the priority technologies chosen for GAVI support. Other technologies, e.g. aerosol measles administration, could be available by 2009.

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# Update on new technology improvements

## Transcutaneous immunization (Richard Kenney)

Transcutaneous immunization is a strategy for delivering vaccine antigen into the skin directly to Langerhans cells, which are the local dendritic antigen-presenting cells. The IOMAI Corporation's mission consists of improving vaccine efficacy and safety using patch technology. IOMAI has established commercial links with several other pharmaceutical and biotechnology companies, some of which have developed modified patch technologies (e.g. dry patches). IOMAI uses LT as an adjuvant in several of its projects. It has an ETEC project entering phase II, a project on tetanus, as well as a few other programmes that are progressing towards clinical evaluation, including one on influenza.

Delivery of vaccines using patches does not result in direct targeting of proteins into the bloodstream. Indeed, antigens reach Langerhans cells in the epidermis which, when activated, move towards local lymph nodes. These cells are phagocytic before activation and become migratory APC upon activation. With FITC as a marker of delivery, monitored using FACScan analysis, it has been demonstrated that Langerhans cells reach the lymph nodes within 24-48 hours. Interestingly, patches placed in different locations will target different lymph nodes. IOMAI uses *E. coli* LT from Berna Biotech as its adjuvant, which is safely used on the skin. LT is essential for optimizing the anti-antigen response. It is also possible to stimulate a mucosal response following transcutaneous immunization. Clinical studies were first undertaken with LT alone as an adjuvant, using the original patch which was a simple gauze wet-patch system. A sustained and boostable immune response (IgA and IgG) was obtained. A further clinical study evaluated the immune response elicited by transcutaneous immunization with the CS6 antigen combined with LT. CS6 is an adherence factor for ETEC and both LT and CS6 responses were obtained in the clinical study. Unfortunately, a contact dermatitis developed in two-thirds of the people in the trial. However, this may have been associated with LPS contamination, and the adverse event was not observed in a later trial in which cleaner CS6 material was employed.

Antibodies persist for a long time following transdermal immunization. IOMAI used ELISPOT in order to look at the induction of specific antibody secreting cells, and detected good levels of Ig-producing lymphocytes in a significant percentage of vaccinees for both LT and CS6. Immunity to ETEC challenge correlated with the magnitude of anti-LT and anti-CS6 responses. IOMAI is investigating the possibility of using lower levels of LT by modifying the mode of delivery with tape stripping or by using an abrasive in order to improve responses to LT. Indeed, it has been shown that 10 µg of LT are effective with modifications of the application of the antigen to

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the skin. The aim is to couple this improvement with better patch technology (using a dry patch the size of a one-euro coin). The Corporation is about to move into clinical trials with a patch technology involving the use of a printing process for adhering the antigen-adjuvant formulation to the patch. The stability of these materials and the optimal time for wearing the patch are being analysed.

### **Plant-derived vaccines (Charles Arntzen)**

The concept of using plant-derived vaccines involves expressing the genes encoding protective antigens from pathogens in transgenic plants. The plants are then processed to allow for the distribution of a uniform dose of vaccine. The potential advantages of this technology could include heat stability, low capital investment, multivalency and oral activity. The feasibility of the approach has been amply demonstrated. At present the aims are to improve plant technology, management and process technology and to evaluate the new vaccines in clinical trials. Work on improving plant technology includes the use of synthetic genes, of cellular targeting signals and of improved promoters sequences in order to increase expression levels. Some success has been obtained with HBsAg. In early experiments the overexpression of some antigens, e.g. LT-B, had a detrimental effect on plant growth, so the focus is now on the use of tissue-specific promoters, e.g. endosperm-specific promoters in maize seed. Fruit-specific promoters, such as those active in tomatoes, have been used successfully to express antigens such as LT-B. As antigen overexpression in the tomato fruit did not adversely affect the growth of the plant, it was possible to produce high yields of tomatoes in glasshouses. The group headed by Dr Arntzen is currently developing a GMP facility for transgenic plants.

Studies are in progress on process technology for the improvement of product consistency. Dehydration and blending can be used for this purpose. The harvesting of tomatoes at different stages of development is being examined with a view to determine optimal harvest and processing times. One dose of oral hepatitis B vaccine is projected to contain 2 mg HBsAg. With the current productivity of transgenic tomatoes and a dehydrated vaccine formulation, 120 doses could be obtained per plant per season, and a million doses could be produced in a glasshouse of only 55 x 60 metres. Approximately 40 acres of glasshouses would allow the production of sufficient hepB vaccine to immunize the children born annually in China. The cost of producing tomatoes containing antigen is less than \$0.01 per dose. The costs of processing, formulation and packaging have not been determined yet. Lower costs of production might be attainable with alternative crops, e.g. alfalfa.

For proof of concept, phase I human clinical trials have been performed with raw potatoes and LT-B and Norwalk-like virus (calicivirus) antigens. Good humoral and local antibody responses were obtained with LT-B, but very modest immune responses were seen with the calicivirus vaccine. New single and multivalent formulations of this antigen should therefore be engineered. In a study with HbsAg delivered in uncooked potatoes, strong evidence of boosting of pre-existing immunity by the plant-derived antigen was obtained.

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## New adjuvants including CpG oligonucleotides (Risini Weeratna)

Traditional vaccines consist of whole killed or live attenuated pathogens, or of inactivated toxins. These vaccines are often very efficacious in limiting the spread of disease but have sometimes drawbacks with respect to safety. Moreover, they often lack the ability to induce simultaneously potent humoral and cell-mediated immunity. A more recent approach to vaccine development has involved the use of subunit vaccines. These have a better safety profile but are often less immunogenic. This has led to work on the use of adjuvants, i.e. substances that, when coadministered with an antigen, can modulate the antigen-specific immune response. Alum is the only adjuvant licensed for human use globally. However, various compounds that may function as vaccine adjuvants have been evaluated. The most promising candidates in this category are the saponin derivative QS-21, synthetic oligonucleotides containing CpG motifs (CpG ODN), bacterial toxins and their derivatives, the lipopolysaccharide derivative monophosphoryl lipid A, muramyl dipeptide derivatives, detox, cytokines and hormones. Coley Pharmaceutical is deeply involved in the development of CpGs as vaccine adjuvants.

The concept of using CpG ODN as adjuvants is based on the observation that bacterial DNA can act as an adjuvant and targets Toll-like receptors, thus activating the innate immune response (TLR-9 is the receptor targeted by bacterial DNA). The cellular mechanisms underlying the adjuvant activity of CpGs were recently investigated. It was shown that CpG enters the endosomal compartment, binds TLR-9 and activates a signal transduction pathway which can stimulate B-cells, plasmacytoid dendritic cells and NK cells. In addition, unlike conventional adjuvants, synthetic CpG molecules can very effectively stimulate a cellular immune response and, in particular, are a potent stimulator of Th1 responses. The coadministration of antigen with CpG ODN induces strong humoral and cell-mediated immunity, and CpG motifs can be optimized to provide maximal immunostimulation of the immune system for a particular mammalian species. CpG-induced immune stimulation is synergistic with that induced by some of the classical adjuvants. For example, it can drive Th1 responses in the presence of alum and minimizes the amount of antigen (such as HBsAg) needed in vaccine formulations. It can also overcome hyporesponsiveness to hepatitis B vaccine in orang-utans. Moreover, CpGs can provide help for the induction of an immune response to hepatitis B vaccine in neonates, but these preparations also need alum to drive the production of specific antibodies. It has recently been shown that CpG ODN are also effective adjuvants for transcutaneous and mucosal delivered vaccines. These routes are of particular interest since they may lead to the development of needle-free vaccines, which would help to make delivery easier and reduce cross-contaminations of vaccine recipients through the use of contaminated needles.

Several clinical trials have been conducted in humans where oligonucleotides were added to Energix-B (hepatitis B vaccine formulation). An improved or rapid onset of hepatitis B protective titres after primary and boosting immunizations was obtained with 0.5 mg CpG. This approach also improved the avidity of antibodies. Likewise, CpG coadministration with influenza vaccines seems to improve interferon gamma production.

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# Vaccines for the developing world against infectious agents that could be used deliberately to cause harm

## Smallpox vaccines (Akira Homma)

The discovery made by Jenner in 1796 eventually led to the global eradication of smallpox, a disease that used to cause devastating epidemics with hundreds of deaths and terrible disabilities in survivors.

In the 1960s a concerted international effort was launched under the leadership of WHO to handle the key issues related to smallpox eradication, including financing, training, standardizing procedures, improving vaccine quality, ensuring vaccine supply, strengthening epidemiology and surveillance, and streamlining political will. In May 1980, more than ten years after the establishment of the Intensified Smallpox Eradication Programme, the Thirty-third World Health Assembly declared that the world was free of smallpox. Unfortunately, the events of 11 September 2001 have revived the possibility of the use of smallpox virus as a biological weapon. If smallpox vaccine were needed today there would be a global shortage, as only a few countries have maintained their stocks and these would be insufficient to vaccinate the large numbers of susceptible people.

Several WHO Member States have recently reactivated their production of smallpox vaccine. WHO's Communicable Diseases Cluster (CDS) has prepared an emergency plan and the Department of Vaccines & Biologicals is revising the minimum requirements for the production and quality control of smallpox vaccines. The question arises as to which seed virus should be used. Should it be the Lister strain, as previously selected and adopted by WHO for smallpox eradication, or should more recent vaccinia virus strains be used, such as:

- ACAM 1000, derived for the New York City Health Board by plaque purification and cloning on human diploid cells;
- LC16m8, derived from the Lister strain after 36 passages in primary rabbit kidney cells;
- MVA, derived after 570 passages in chicken embryo fibroblast cell culture;
- Elstree-BN and MVA-BN strains, derived from Lister-Elstree and MVA by the Bavarian Nordic biotechnology company.

Although LC16m8 and MVA were tested in humans before smallpox eradication was achieved, the efficacy of these more attenuated strains remains to be demonstrated. The Lister strain therefore appears to be the viable choice as a seed strain.

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It is also necessary to consider the choice of a substrate for vaccine production, which can be performed *in vivo* on calf skin, on SPF chicken chorioallantoic membrane or in cell culture (human diploid MRC-5 cells, VERO cells, SPF chicken fibroblast cells, rabbit primary kidney cells). With each production system there are specific quality control issues. In all cases, however, the minimum requirements include bacterial sterility and GMP.

Several other questions need to be addressed, relating to preclinical testing, neurovirulence, reproductive toxicity, potency testing, local tolerance and clinical trials, before these new smallpox vaccines can be used in humans .

### **Anthrax prevention (Peter Turnbull)**

The vaccination of humans in developing countries in order to protect them against the bioaggressive use of anthrax is not a practical proposition. Alternative approaches to minimizing the adverse effects of the deliberate malevolent release of anthrax spores in developing countries are therefore necessary.

It is important to assess the risk of the occurrence of bioaggressive events involving anthrax. Various forms of bioaggression scenarios can be defined, ranging from state-sponsored biowarfare to terrorism sponsored by states or ideological groups and to petty biocrime committed by individuals. The number of bioaggressive events of this kind has been small, the number involving the genuine use of anthrax has been even smaller, and developing countries have barely featured in the statistics. The principal reason for this probably lies in the practical difficulties facing would-be perpetrators, relating to the acquisition of cultures, facilities, skills and finance, the delivery of effective doses, hazards affecting perpetrators, and so on. It is unlikely that the situation will change greatly. In the context of the many urgent problems of developing countries, therefore, bioaggression and potential bioaggression can be considered as low on the priority scale.

Even if this assessment were wrong the vaccination of humans against anthrax is not the way forward in the foreseeable future. There appear to be only four or five fairly small-scale manufacturers of human anthrax vaccines, all concerned with meeting local needs. The United Kingdom and the USA produce non-living human anthrax vaccines, ostensibly for persons in at-risk occupations but, in reality, mostly for these countries' defence communities. Several initial doses are needed in order to induce protection, followed by annual booster doses. The American vaccine has been beset by numerous production and political difficulties in recent years and can probably be regarded as unavailable outside the USA. The British vaccine is more available outside the United Kingdom but supplies would probably be limited. In both cases, a single dose would cost at least \$15-20. In China and the Russian Federation, live spore vaccines analogous to vaccines for livestock are produced for use in humans. There is one producer in China and one, or possibly two, in the Russian Federation. One or two doses are administered initially and annual boosters are given. The Chinese operation can only meet domestic needs but the Russian vaccine could be made available outside the Russian Federation at relatively low cost.

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Given that vaccination is not a viable approach to minimizing the effects the deliberate release of anthrax, the best alternative is to ensure that there is an alertness and response system based on surveillance, reporting and control programmes, which should already be in place for the natural disease. The surveillance and reporting mechanisms should enable immediate awareness of new unexpected cases of anthrax, whether in humans or animals. Response plans should make it possible to identify exposed populations rapidly, evacuate them if necessary, supply appropriate postexposure antibiotic prophylaxis, identify and eliminate the vehicle of exposure, and carry out clean-up, disinfection and livestock vaccination. In developing countries, of course, many factors would hinder alertness and response programmes, e.g. inadequate resources, roads, transport and trained personnel. These countries might establish on-call agreements with developed countries in order to cope with any aggressive misuse of anthrax.

### **Public health implications of vaccine control of agents that could be deliberately used to cause harm (Giuseppe Ippolito)**

During the past century the richer countries have lived under the protective umbrella of vaccination programmes. Vaccination has been the single most cost-effective public health intervention. However, in the least developed countries, where the leading causes of death are almost all preventable and where life expectancy at birth does not exceed 50 years, the use of vaccines against infectious agents that could be used deliberately to cause harm is probably an unjustified option. In the more industrialized countries a global surveillance network for detecting the production and/or use of a bioterrorism infectious agent is urgently needed so that early and effective responses become possible.

Vaccines against biological agents are already either available or licensed i.e. anthrax, plague and smallpox vaccines, or are still being studied, i.e. for botulism, certain encephalitis viruses, haemorrhagic fevers, tularaemia and Q fever. New candidate vaccines for anthrax and smallpox, which have higher immunization rates and fewer adverse events, are also under investigation.

A debate is developing on different types of vaccination campaigns:

- compulsory, voluntary or recommended;
- pre-exposure or postexposure;
- directed at high-risk persons or exposed persons or entire unexposed populations.

Decisions will depend on the agent involved, the epidemiological patterns of the infectious agent, the risk assessment of the exposure, the target population, the adverse events associated with the vaccine, and vaccine safety data. The pros and cons of the ring vaccination strategy are also been discussed. In all cases, the strategic plans implemented by health authorities urgently need answers to all the questions raised above.

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In conclusion, the value of vaccines in protecting populations against the deliberate release of infectious organisms is not altogether clear. Further prospective epidemiological, clinical and laboratory studies are needed in order to better clarify the level of preparation and response of national and international public health systems, the basic translational and behavioural research for new vaccines, the re-evaluation of existing vaccines, models, simulations and demonstration projects of vaccination campaigns, operational and organizational research for target definition and vaccine management. Moreover, the evaluation of public health implications and integration with intelligence agencies, decision-makers, and policy and political analysts need careful analysis.

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# Clinical trials in developing countries

## **Regulatory pathways for developing market vaccines (Julie Milstien)**

It used to be that vaccines were developed and used first in industrialized countries and then gradually trickled down to the developing world, on the basis of regulatory decisions taken in the industrialized world. Today, however, there is a need for new vaccines that may never be used in the industrialized countries and that are targeted against diseases in developing countries

WHO advises UN procurement agencies on the acceptability in principle of products proposed for purchase. This process is called prequalification. The list of prequalified products is also used by many countries that buy vaccines directly and by procurement agencies not affiliated to the UN. The prequalification procedure depends on the provision of consistent and continuing regulatory oversight by national regulatory authorities (NRAs). WHO has identified six essential functions to be undertaken by an effective vaccine regulatory system: a published set of requirements for licensing; surveillance of vaccine field performance; a system of lot release; the use of a laboratory when needed; regular inspections for GMP; and evaluation of clinical performance. This definition is the basis for the designation of vaccines of assured quality and for WHO activities concerned with strengthening vaccine regulation.

NRAs have differing activities with regard to the exportation and importation of vaccines. The United States Food and Drug Administration was established to function only for the domestic market. The European Medicines Evaluation Agency (EMA) operates similarly for the countries of the European Union but has expressed an interest in providing additional regulatory functions for vaccines made in Europe and targeted at developing markets. There are many competent NRAs in both the developing and the industrialized world which could make decisions on the licensing of new products but would need a new regulatory framework to do so for products intended only for use in developing countries. Some countries import vaccines only from assured sources and lack the basic infrastructure necessary for making regulatory decisions on their own.

WHO envisages the following approaches to ensuring regulatory functions for vaccines in the developing country market.

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### *1. Licensing in the country of manufacture*

For many countries the lack of a marketing authorization for a developing market vaccine in the USA or Europe would render a licensing decision difficult. Actions by the American and European regulatory agencies to expand their mandates could thus be helpful. Stronger advocacy messages from the public health community to the governments of these countries would be needed in order to bring this about.

### *2. Proposal to the European Commission*

The European Commission has determined that products may be considered for licensing only if they have a market in Europe. Currently licensed products that would no longer be used in Europe will eventually have their authorizations withdrawn. However, an innovative compromise is proposed for the scientific assessment of product files by EMEA at the request of WHO, with continuing regulatory oversight in the countries of manufacture. Marketing authorization would not be granted, but scientific opinions on files could be given for products if the applicants were located in Europe, registered as manufacturers in Member States, and responsible for final batch release. This amendment is expected to be approved and in force by 2004.

### *3. Export provisions*

The receiving country would perform regulatory functions under export provisions. The burden would be on the exporter to determine compliance with regulatory requirements. However, the product would have to be manufactured, processed and packaged “in substantial conformity” with current GMP. Since the use of export provisions shifts responsibility for regulatory oversight to the receiving country, NRAs in potential receiving countries would have to be strengthened.

### *4. Shared manufacturing, and licensing in the country of final manufacture*

This approach proposes shared manufacturing, with licensing and regulatory oversight in the country where the finished product is released. Until very recently the feasibility of this approach was limited by the credibility of the quality of manufacturing and regulatory institutions in developing countries. Steady improvement in the NRAs of developing countries has occurred. Vaccine production and NRAs have been assessed by WHO as fully functional in 16 countries classed as developing or as having economies in transition. Manufacturers in seven of these countries already produce certain products that are prequalified for sale to UN agencies

NRA assessment procedures hold everyone to the same standards. The establishment of an NRA network, similar to the Developing Country Vaccine Manufacturers Network and including a few well-functioning regulatory agencies, will promote the sharing of information on regulatory decisions, dissemination on the rational underlining their decisions, and the sharing of expertise between NRAs.

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## Strengthening capacity for clinical trial monitoring (Juntra Karbwang)

Well-conducted clinical trials are essential in biomedical research. In order to ensure the quality of the clinical studies undertaken under its guidance or funding, WHO/TDR promotes GCP, international ethical and scientific quality standards and accordingly advocates for a quality framework for clinical trials. For each trial this framework involves a clinical coordinator, the Data Safety Monitoring Board, a clinical monitor, the investigator and an ethics committee.

In order to increase the quality of trials, all players need training and guidance. TDR has established a training curriculum for investigators, ethical committees and monitors. Specific training for investigators and study teams include general GCP training, specific GCP training for particular trials, and training in clinical research ethics. Training assures that investigators are aware of their responsibilities and that sufficient time is devoted to the conduct of trials.

Quality support for laboratories participating in clinical trials consists of conducting laboratory assessments, establishing quality assurance and quality control networks, providing assistance for writing SOP, and establishing normal laboratory values for the populations concerned.

Several documents have been pioneered by TDR for the establishment, training and monitoring of ethics committees. TDR operational guidelines for these committees have been translated into 19 languages, always on the initiative of the countries concerned. The guidelines can be instrumental in the establishment of ethics committees. In addition, *Guidelines for Surveying and Evaluating Ethics Committees* was published in 2002. This document facilitates and supports procedures for ethics committees that already exist. *Guidelines to Practice for Ethics Committees*, dealing with local variations, standards and international studies, will soon be issued.

With regard to individual training, ethics workshops and ethics training courses are regularly held in the various regions. An inventory of ethics committees is being carried out. The recently established SIDCER network of regional forums will be of critical importance in consolidating all these activities.

Clinical trials have to be monitored because patients' welfare and safety is paramount and because data of high quality are needed in order to ensure that products reach the market without delay. The main objective of monitors is to prevent careless error, neglect, misconduct or violations of protocol in the conduct of trials. Their main responsibilities involve liaising with sponsors and investigators, helping investigators in every possible way, checking data for accuracy and completeness, and discussing study plans with investigators.

Training sessions for clinical monitors were initiated by TDR in 1998-1999. The *Workbook for Clinical Monitors* has been published by WHO and a clinical monitor network has been established. The monitors recruited to this network are all highly experienced physicians and scientists. They attend a GCP refresher course annually and, if necessary, receive specific GCP training for particular trials. They also receive training on ethics in clinical research.

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In addition, it is vital to assure quality in data management. For this reason, TDR is now evaluating software for data management, and producing and evaluating CRF templates.

### **Vaccine clinical trials in paediatric populations: ethical considerations**

(Mary Ann Lansang)

Because infectious diseases are leading causes of premature deaths and disability it is of utmost importance that vaccines against infectious pathogens be developed and tested in children.

In connection with the health of children and their involvement in biomedical research it should be noted that the Convention on the Rights of Children, approved by the UN General Assembly in 1989, included the following declarations:

- All human rights apply to all children without exception.
- In all actions, children's interests have priority so as to ensure the protection and care necessary for their well-being.
- Children have the right to the highest possible level of health.
- Children have the right to obtain information, and their opinions have to be taken into account.

There are various ethical considerations relating to the participation of children in medical research. What is their degree of autonomy? Can they provide informed consent or assent? What is their mental competence? Have they received sufficient information? Are there enough opportunities for the provision of information? Have adequate time and opportunities been given to their parents for decision-making? Although informed consent is provided by parents or legal guardians, it is particularly important to take all necessary steps whereby children can provide their assent. Children who can already understand what is involved should be given the chance to assent to their participation in clinical trials. It is the right of children to be the main deciders. The age at which children are asked for assent differs from country to country. The American Pediatric Association considers that children can give assent at the age of 7 years. For other countries the age of assent is 12 years. It is also important to consider who really makes the decision to consent to participate in a trial. In a paediatric vaccine trial in the Philippines a survey on informed consent showed that in 50% of cases both parents took the decision. However, it also happens that only one parent or even a grandmother provides consent. In addition, relatives or professionals, e.g. grandmothers, aunts, neighbours, health workers and paediatricians may be asked for their opinions.

The principles of beneficence and non-maleficence are very important in paediatric trials. It has been proposed that it should be acceptable to recruit healthy children for biomedical research that is considered not to present more than minimal risk. This should mean risk that is no greater than what is experienced in ordinary life. Children can be involved in research involving more than minimal risk only when there is a potential direct benefit or when the research is likely to yield important generalizable knowledge about the children's own disorders.

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Additional common concerns when children are included in clinical trials include the potential need for multiple blood sampling and multiple injections, the fear of testing novel or unlicensed vaccines in children (in particular, DNA vaccines), and the fear of potential adverse events. In view of these concerns it is very important to understand both the potential benefit that children might obtain by participating in a clinical trial and the reasons for their participation. These may depend on the nature of the disease in question, the availability of other interventions, and the definition and understanding of the risk-benefit ratio among IRB members in developing countries.

The timing of the initiation of studies among children in developing countries needs careful review. It is generally accepted that no clinical trial should be started in infants or children unless the results of phase I and phase II trials in older populations have been obtained. This suggests a stepwise approach for diseases affecting both adults and children, and for children from both developed and developing countries. On the other hand, a stepwise accelerated approach is recommended for diseases mainly or only affecting children. Indeed, although a more stringent ethical review of trials in children is warranted, the refusal of trials in infants or the overcautious exclusion of infants because their cries are interpreted as refusal to participate, may deprive them from potential benefit. Thus harm may come to children as a result of overprotection.

Many other public health, medical, scientific, ethical and financial factors should be considered. For example, controversy surrounded a vaccine trial of acellular pertussis: in Italy and Sweden, children in the placebo arm received only DT antigens, whereas in the USA there was no placebo arm. The investigators provided the justification that the standard pertussis vaccine used in Sweden was not highly immunogenic. Furthermore, the high cost and relative lack of access to new vaccines in developing countries should not be used as a justification for the use of placebo arms.

Ethics is also concerned with the principles of justice and equity. Ethical reviews of clinical trials in children should consider the post-trial availability of vaccines, the access and affordability of products to vaccine recipients, and comparable matters.

Whose ultimate responsibility is it to protect children involved in biomedical research? Better regulatory policies on paediatric vaccine trials are needed, as well as functioning and trained ethics review boards. Experts in child health and child health research should be called upon as resource persons in the ethical review of paediatric vaccine trials. The views of community members should also be obtained. Investigators should also be trained on the technical and ethical issues that arise in connection with such trials

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## The European and Developing Countries Clinical Trial Partnership (EDCTP) (Arnd Hoever)

The overall goal of EDCTP is to develop new clinical interventions against the global problems of HIV/AIDS, TB and malaria through a long-term partnership between Europe and developing countries. In order to fulfil this mission the global features of EDCTP should allow the development of long-term sustainability, i.e. lasting 10-20 years, and the ownership of this initiative to be shared by European and developing countries. The structure should be dynamic and flexible, with balanced involvement of different stakeholders (developing countries, the European Commission, industry, WHO and other international organizations). EDCTP is distinguished from many other initiatives against HIV/AIDS, TB, malaria and diseases of poverty by its long-term relationship with the developing countries and by the proposal for it to be a North-South partnership.

The basis for developing the EDCTP strategic plan has been established by a committee of five European and five African representatives in consultation with the stakeholders. This plan forms the basis for the operational functions of EDCTP and guides the development of appropriate governance structures and of the Partnership's business plan. As a legal entity, EDCTP has been established as a European Economic Interest Grouping. Its governance structures include the following.

- A governing board that meets regularly to review, discuss and approve performance and strategy. It includes one representative from each participating Member State of the European Union or associated state, one EC representative and one developing country representative.
- A strategic committee that makes decisions on operational strategic priorities. In order to reflect the equal partnership between the European and developing country participants and organizations, it comprises equal numbers of representatives from Europe and developing countries.
- A secretariat.

The scope of EDCTP activities includes clinical intervention for HIV/AIDS, malaria and TB, drugs, vaccines, and non-pharmaceutical interventions such as those involving the use of bednets or other commodities. Priority has been placed on phase II clinical trials (proof of principle) and on some phase III trials (efficacy). Most EDCTP-supported trials will be conducted in Africa. Only a few phase I safety trials will take place in Europe.

The main objectives of the programme are to:

- improve networking and cooperation between European national programmes so as to increase efficiency;
- accelerate the development of new interventions by supporting and/or funding clinical trials;
- strengthen clinical research capability in developing countries through sustained partnerships between these countries and Europe and through South-South networking.

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## **The African AIDS Vaccine Programme (AAVP) (José Esparza)**

African scientists, multilateral and donor organizations, research agencies and industry met in Cape Town on 3 and 4 June 2002 to discuss how to accelerate research and testing for the development of an AIDS vaccine for Africa. The meeting aimed to define a plan of action for the next seven years, and to raise \$233 million for AAVP.

Only 21 years after AIDS was initially discovered, 40 million people in the world are living with the Human Immunodeficiency Virus (HIV), and 70% of them are Africans. AIDS is the leading cause of death in Africa and the fourth most important cause of death worldwide. African vaccine research currently receives only a very small proportion of the funds globally used for HIV research, estimated at \$2.5 billion. Although more than 60 HIV vaccine trials have been conducted globally since 1987, only one study using canarypox-HIV clade B in Uganda (1999) and one trial testing a clade A DNA vaccine in Kenya (2001) have been carried out in Africa. HIV strains present in Africa are different from those in other parts of the world. Vaccines that are being tested in Asia or the USA may not be appropriate for African patients.

Part of the strategy of AAVP is the proactive participation of African scientists and institutions. One of the major obstacles to HIV vaccine research on the continent is the inadequacy of research infrastructures. Some of the \$233 million required will contribute to building up regional facilities and strengthening local expertise.

Five thematic working groups have been established, each with a work plan. These groups concentrate on: biomedical sciences; population studies; ethics, law and human rights; national strategic planning and advocacy; education and resource mobilization. Strategic milestones have been based on the progress of HIV vaccine clinical trials in Africa as follows: 2004 – appropriate candidate vaccines to have been developed for Africa; 2005 – at least four phase I/II trials to be initiated in Africa; 2006 – at least one phase III efficacy trial to be initiated.

The following main activities and functions are foreseen for AAVP: 1) serving as the voice of Africa; 2) surveying vaccine-testing facilities; 3) supporting preparatory research; 4) developing national AIDS vaccine plans; 5) contributing to policy definition and protocol review, and 6) funding product development and vaccine trials.

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# Industrial development of new vaccines and private initiatives

## **Renewed interest of the private sector in vaccine development**

(Christian Schirvel)

Although it is often stated that the private sector is progressively leaving the field of vaccines because opportunity costs are too high, vaccine development has attracted much new interest from the private sector in recent years. Indeed, the competitive environment for vaccines has changed from that of active and passive immunization for acute infectious diseases to include immunotherapies, the targeting of chronic diseases (infectious and non-infectious diseases and cancer) and the use of therapeutic monoclonal antibodies. The potential exists for this new development to increase both sales and benefits.

After centuries of empirical development leading to the development of a limited number of vaccines, the last 20 years have seen a rapid increase of the number in new vaccines registered. Moreover, significantly more prophylactic vaccines have been under development recently than was the case only a few years ago, although the number of candidate vaccines in phase III trials has increased less markedly. These products encompass innovative prophylactic infectious disease vaccines with blockbuster potential, and much research and development is progressing on new prophylactic and therapeutic vaccines for multiple chronic diseases. On the other hand, a number of vaccines have failed during the research and development process, sometimes after heavy financial investment. Outside factors have had an important influence on the field of vaccines, including the emergence of HIV/AIDS, the establishment of the Bill and Melinda Gates Foundation and of GAVI, increased drug resistance in a few pathogens, and, more recently, bioterrorism.

The number of potential players in the vaccine field is increasing. Besides the traditional vaccine manufacturers in the industrialized world, manufacturers in developing countries have emerged as developers of new vaccines. The number of biotechnology companies dedicated to vaccines rose from around 10 in 1990 to nearly 150 in 2001. The products under development by these companies are evenly split between prophylactic and therapeutic vaccines; cancer vaccines account for 25% of the total. A number of the companies are technology platforms. It is worth noting that certain companies have been forced to merge and it is predicted that few of the new small companies will survive. The high cost of vaccine development, estimated as around \$500 million per product, is clearly an issue for both biotechnology companies and major vaccine companies.

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## **The experience of the Medicine for Malaria Venture and its relevance to vaccines (Chris Hentschel)**

Africa carries 90% of the malaria disease burden. It has been suggested that the increase in drug resistance explains the deterioration in the malaria control situation. The Medicine for Malaria Venture (MMV) is a public-private partnership created with the sole mission of developing new drugs active against malaria. Organizations of this type have certain theoretical advantages when faced with the lack of commercial incentives to drive innovation for new therapeutic interventions targeted at the neglected diseases, whether drugs or vaccines are concerned.

The drugs versus vaccines divide could be considered as mostly irrelevant. Many modern drugs alter or support immune responses or contain components of such responses, while vaccines often require adjuvants, i.e. drugs, in order to work. Both can be used therapeutically and prophylactically, and both can be designed for public health rather than private wealth. Could for example a drug, such as one currently being developed by MMV and effective in curing infection after one single dose be considered as a vaccine surrogate, given that it kills a massive number of infected cells that would help to stimulate an immune response? This convergence indeed should not occult the fact that much more is spent on malaria drugs for public health (\$58 587 000) than on malaria vaccines (\$15 000 000).

The experience of MMV suggests that careful attention should be given to two fundamental concepts. Firstly, the individual partnership agreements that govern partnered research and development need very careful crafting. All partners should benefit if the research and development are to be successful. Otherwise the partnerships are unsustainable. Additionally, individual partnership agreements should be treated as part of a portfolio with professional portfolio management concepts defining the management style of the organization. One of MMV's main achievements has been to show that public-private partnerships can work. The size of the antimalarial portfolio now managed by MMV is the largest that has been co-ordinately managed since the Second World War. The contractual arrangements put into place have been described as leading to "win-win" situations. Indeed, MMV retains rights in developing countries and IPR in the "field", as well as return on non-developing countries' sales, whereas pharmaceutical companies own rights in non-developing countries, as well as IPR outside of the field.

## **Research, development, production and applications of vaccines in Cuba (Gustavo Sierra)**

Health care and scientific research have been given high priority in Cuba during the last four decades. There are about 1.8 researchers per 1000 inhabitants and the number of children surviving up to 5 years of age per 1000 live births is the same as in the most advanced industrialized countries, although the GNP per capita is that of a developing country. Various infectious diseases have been eliminated, including polio (1962), neonatal tetanus (1972), diphtheria (1979), measles (1993), rubella (1995), parotiditis (1995), whooping cough (1997), congenital rubella (1989) and postparotiditis meningoencephalitis (1989). The incidence of tetanus and *Haemophilus influenzae* type b in children under 5 years of age has been drastically reduced.

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There have been reductions in the morbidity and mortality rates attributable to meningococcal disease of 95% and 99% respectively. The incidence of acute hepatitis B in children under 5 years of age has been reduced to zero during the last two years, and there has been only one case among children aged under 15 years during this time.

The Cuban scientific system consists of more than 210 centres with more than 30 000 scientific staff and over 12 000 scientists. A major part of its work is dedicated to the Programme for Research, Development and Production of Vaccines, coordinated by the Finlay Institute.

Nine important vaccines are being produced industrially under the Cuban Vaccine Programme: meningococcal meningitis serogroups B and C, hepatitis B (recombinant), trivalent anti-leptospirosis, typhoid fever (poly Vi), tetanus and DTPw/DT vaccines. The Finlay Institute has produced and distributed more than 45 million doses of meningococcal meningitis B + C vaccine for the control of outbreaks of meningococcal disease, mainly in Latin America. The vaccine is registered and currently distributed in 15 countries. The Finlay Institute and GlaxoSmithKline have signed a license agreement on this meningitis B vaccine. CIGB is prequalified by WHO to sell HepB vaccine to international agencies.

A second group of vaccine projects concerns nearly 20 new products now in the development phase (clinical trials or registration). These are in particular meningococcal meningitis serogroups A and C vaccines, combined vaccines (DTPw-HepB, DTPw-HepB-Hib, DT-Poli Vi, HepB-Hib, DTPw-MenBC and Poly Vi-Men AC), eight candidate anticancer vaccines of which three are undergoing advanced clinical trials: an EGF-vaccine, a ganglioside vaccine and an anti-idiotypic vaccine.

A third group comprises vaccines in the research phase, including: oral cholera vaccine, conjugate Hib vaccine, dengue vaccine, hepatitis A or C vaccines, multivalent pneumococcal vaccine, new-generation meningitis B vaccine, several candidate HIV/AIDS vaccines, a tuberculosis vaccine, cancer vaccines, an *Amoeba* vaccine (in collaboration with Mexico) and a Chagas disease vaccine (in partnership with Brazil). In addition, very promising results have been obtained with nasal formulations containing hepatitis B core and surface antigens and a new potential candidate therapeutic vaccine based on partially delipidated HBsAg.

In addition, some results obtained with new adjuvants may be of interest for international collaboration in the fight against infectious diseases.

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## **The experience of Indonesia with UniJect™ (Abdallah Marzuki)**

Almost a billion injections are administered each year globally by immunization services. In 1994 a WHO survey revealed that about one-third of them were not sterile.

The UniJect™ device consists of a small single-use plastic container with a dose of liquid vaccine and an attached needle. The UniJect™ project in Indonesia was carried out in collaboration with PATH and UNICEF. The production of vaccines formulated in UniJect™ was initiated on 3 November 2000. Current vaccines used with UniJect™ include tetanus vaccine, which is prequalified by WHO and hepatitis B vaccine for which the prequalification process is ongoing.

The wastage of vaccines formulated in UniJect™ devices was evaluated in detail. Likewise, the cost of UniJect™ -formulated vaccines was analysed and assessed vis-à-vis a theoretical price limit of \$1. The cost of UniJect™ was found to be similar to that of the classical vaccine vial and syringe. It is worth noting that for new vaccines the main costs are those of the active ingredients rather than those of injection devices. For example, the cost of the UniJect™ device is \$0.11, whereas the price of one dose of hepatitis B vaccine is slightly under \$1. UniJect™ also has the advantage of increased facility of administration as the vaccine is already distributed into the syringe.

## **Research and development at the Serum Institute of India (Cyrus Poonawalla)**

One of every two neonates in the world receives a vaccine made by the Serum Institute of India (SIIL), which aims to produce vaccines of international quality in large quantities and at affordable prices. SIIL has made a strategic decision not to protect its intellectual property rights, and no patents have been filed by the company. Furthermore, the Institute has chosen to concentrate on vaccines that are urgently needed to save human lives and are not readily available in the developing world. Achieving this goal requires process innovation, equipment and engineering innovation, as well as personnel development.

With regard to a new liquid adsorbed rabies vaccine the challenge was to produce a virus grown on the most acceptable cell strain, with the highest safety, the smallest possible reactogenicity, high stability and in sufficient quantities. SIIL has produced this vaccine in substantial quantities on human diploid cells, using the Pitman Moore rabies virus strain as seed. The vaccine is thus available at affordable prices. This has been possible through close collaboration between SIIL's internal research and development group and its production teams.

Another challenge faced by SIIL was that of the large-scale production of measles-mumps-rubella (MMR) vaccine. The major hurdle was that of growing rubella virus on human diploid cells. An innovative technology made it possible to increase the production of rubella vaccine by a factor of 10-20 in the available laboratory space. This has helped to make the vaccine available in large quantities and at an affordable price.

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SIIL is now placing much emphasis on *Haemophilus influenzae* type B conjugate vaccine and other combination vaccines like DTP-hepatitis B and DTP-Hib, again with the objective of making them available in substantial quantities at affordable prices. In collaboration with WHO/IVR, SIIL has recently embarked on a project for the development of an aerosol formulation of a measles vaccine. This project, established under a WHO/CDC/American Red Cross partnership, is funded by the Bill and Melinda Gates Foundation. In collaboration with UPT and PATH the Institute is also at an advanced stage of research and development on a thermostable MMR vaccine, with a view to dispensing with cold chain requirements.

## **Impact of new technologies on the vaccine industry**

(Marie-José Quentin-Millet)

Four new technologies can be expected to have a great impact on the vaccine industry:

- the digital revolution;
- automation;
- high throughput screening;
- miniaturization.

In order to determine the needs for these technologies it is important to understand the environment and the trends within it. Where is the impact of these technologies in the value chain of vaccine development? What is still lacking?

Human and microbial genome sequencing can be expected to lead to the discovery of many more antigens. Likewise, new technologies will lead to increased productivity in the upstream phases of vaccine development. However, they will not necessarily lead to new vaccines because the downstream steps will be limiting. Nevertheless, they will have an impact throughout the value chain of vaccine development. Indeed, these new technologies are being or will be implemented to do better and more thoroughly what is already being done. This process will be largely driven by increasing safety concerns.

New technologies have not yet brought about predictable animal models and knowledge on surrogate markers of protection. However, some new cellular immunology assays may provide read-outs that are more indicative of the type of immune response needed for protection against infection, and these may become in the future acceptable markers of protective immunity. Some examples of such technologies are those based on tetramer assays, intracellular cytokine measurements and ELISPOT.

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# Discussion and summary of the 2002 Global Vaccine Research Forum

(Guss Nossal and Puneet Pitisuttithum)

The Global Vaccine Research Forum continues to be the premier vehicle for the exchange of views on research progress and implementation plans for all the cooperating stakeholders in global immunization. As such it constitutes an important forum for consensus-building and the presentation of research plans. On the present occasion, for example, a major new initiative of the European Union was announced and it was explained that GAVI would open a third window of funding that could be accessed for research and development in priority areas.

The meeting revealed that global vaccine research has expanded considerably in recent years. Only a decade ago a similar meeting would have noted a small and very fragmented research and development effort for vaccines destined chiefly for developing countries. It would also have noted that the donor community was tired and dispirited and that there was difficulty in bringing even the six standard EPI vaccines to all children. Today there is a vibrant, optimistic and strongly collaborative vaccine community. There is vigorous North-South and South-South collaboration and there are significant public-private partnerships.

The research effort is aimed at both vaccines reasonably close to availability and vaccines that are much more distant. In the former situation, the term “translational research” has been introduced for an area distinct from and complementary to prelicensing research. It deals with practical matters such as disease burden, cost-effectiveness, demonstration projects, behavioural studies and policy research, including mechanisms for sustainable funding. In relation to more distant vaccines, significant progress is being made in difficult areas such as those of HIV/AIDS, malaria and tuberculosis.

For the first time, GVRF received a briefing on bioterrorism and on vaccines that may be required, the need for extra research and the substantial plans of some Member countries in connection with this phenomenon.

A strengthened vaccine manufacturing sector in developing countries is making its presence felt and has great potential to help the world. Vaccine manufacturers in Cuba, India, and Indonesia, for example, deserve particular notice. One very significant new experiment involves the meningitis vaccine project, a collaboration between WHO and PATH funded by the Bill and Melinda Gates Foundation. This envisages a public-private partnership and a developing country manufacturer doing much of the research towards a meningococcus A serotype vaccine, aided by scientists of industrialized countries. It is believed that this will be considerably less expensive than reliance on manufacturers in industrialized countries.

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Developing countries are becoming increasingly involved in clinical trials as local capacity in this area is strengthened. Significant ethical problems arise in this field, including those of obtaining informed consent in less developed communities and guaranteeing the availability of vaccine supplies in areas where trials have been conducted.

Emphasis has been placed on new technologies for vaccine deployment. These include: streamlining the cold chain or progressively removing vaccines from it; the use of less expensive methods for auditing vaccination coverage; the reduction of infectious wastes and the ultimate elimination of sharps; transcutaneous immunization strategies; the use of plant-derived edible vaccines; and the use of new adjuvants, including CpG oligonucleotides.

The meeting received an update on the eradication of poliomyelitis, noting that in 2001 there were fewer than 1000 cases globally, of which 480 were confirmed. Wild poliomyelitis type 2 has not been seen since October 1999. In 2001 nearly two billion doses of Sabin oral poliomyelitis vaccine were distributed among 570 million children, a truly amazing effort. There is concern over three mini-epidemics involving vaccine-derived polio viruses that may have reassorted with other enteroviruses. One was in Egypt between 1988 and 1993, involving the type 2 virus; one in Hispaniola during 2000-2001 comprised 21 cases of type 1 virus; and one in the Philippines in 2001 involved 3 cases of type 1. Low immunization coverage predisposes to such mini-epidemics, which complicate the polio "endgame". Immunization will probably have to continue for a number of years: a consensus will have to be built among experts on this question.

After the events of 11 September 2001 the urgency of achieving greater social justice has become clear to the richer countries, as witnessed by the proliferation of funds measured in billions, rather than millions, of dollars. This new climate imposes great challenges on the global vaccine research and development community. It is necessary to continue and extend the coordination process. We must strengthen still further the advocacy effort and redouble work in capacity-strengthening and training. We must work closely with new large initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, using them as the fruits of research reach maturity. And the Global Vaccine Research Forum must continue: the next meeting is planned for Seoul in mid-2003.

WHO established the Initiative for Vaccine Research in response to the need to identify a single locus within WHO where vaccine research efforts could be consolidated. IVR's mission is to provide overall guidance and vision to vaccine research and development efforts and to enable and support the development of new vaccines. The meeting recognized that IVR should focus simultaneously on global targets, e.g. HIV/AIDS, malaria and tuberculosis, GAVI-selected diseases (meningitis, rotaviral diarrhoea and streptococcal pneumonia), and more regional or neglected diseases e.g. dengue, leishmaniasis and HPV.

Finally, the meeting wished to thank Dr Teresa Aguado for her work throughout 2001 as Acting Coordinator of the IVR, and to welcome Dr Marie-Paule Kieny as the new Head of the WHO Initiative for Vaccine Research and as the meeting Secretariat. We wish her well in her important endeavors.

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# List of participants

**Dr Remon Abu-Elyazeed**, US Naval Medical Research Unit No. 3,  
PSC 452 Box 5000, FPO AE 09835 0007  
*Tel.:* +20 2 684 1375/6/8; *Fax:* +20 2 684 1382/9625  
*Email:* +AbuELYazeedR@namru3.med.navy.mil

**Dr Francis André**, Rue du Moulin 23, B-1330 Rixensart, Belgium  
*Tel.:* +32 2 653 7976; *Fax:* +32 2 653 7976  
*Email:* feandre@yahoo.com

**Dr Charles Arntzen**, 7686 E. Wilderness Trail, Superstition Mountain,  
AZ 85218-1806, USA  
*Tel.:* +1 480 282-1402; *Fax:* +1 480 288-1406  
*Email:* charles.arntzen@asu.edu

**Dr Abraham Aseffa**, Armauer Hansen Research Institute, POB 1005,  
Addis Ababa, Ethiopia  
*Tel.:* +251 1 710 288; *Fax:* +251 1 711 390  
*Email:* aseffaa@yahoo.com

**Prof. Roberto Jose da Silva Badaro**, Federal University of Bahia,  
Rua Joao das Botas, s/n – Canela, Salvador, BA 40110-160, Brazil  
*Tel.:* +55 71 235 4901; *Fax:* +55 71 245 2756  
*Email:* badaro@ufba.br

**Dr Zhi-Sheng Bai**, Lanzhou Institute of Biological Products, 118 Yanchang Road,  
Lanzhou, Gansu Province 730046, People's Republic of China  
*Tel.:* +86 931 836 8311; *Fax:* +86 10 6431 2692  
*Email:* baizs@public.lz.gs.cn

**Dr Lewellys F. Barker**, Chief Medical Officer, Sequella Global Tuberculosis  
Foundation, 9610 Medical Center Drive, Suite 200, Rockville, MD 20850, USA  
*Tel.:* +1 301 762 3100; *Fax:* +1 301 762 2122  
*Email:* lewbarker@sequellafoundation.org

**Dr Jacques Berger**, Senior Vice President, Corporate Public Policy,  
Aventis Pasteur SA, 2 Avenue Pont Pasteur, F-69367 Lyon Cedex 07, France  
*Tel.:* +33 4 3737 7010; *Fax:* +33 4 3737 7830  
*Email:* jacques.berger@aventis.com

**Dr Sujit Bhattacharya**, Director, National Institute of Cholera and Enteric  
Diseases, P-33 CIT Road, Scheme XM, Beliaghata, P.O. Box 177,  
Calcutta 700 010, India  
*Tel.:* +91 33.350 1176; *Fax:* +91 33.350 5066  
*Email:* bsandip@cal3.vsnl.net.in/bsujit@vsnl.net

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**Dr Sophie Biernaux**, Director Business Programme for Paediatric Vaccines, Paediatric Vaccines Development Unit, GlaxoSmithKline Biologicals, Rue de l'Institut 89, B-1330 Rixensart, Belgium  
*Tel.: +32 2 656 8291; Fax: +32 2 656 8044*  
*Email: sophie.biernaux@gskbio.com*

**Dr John Breen**, Permanent Mission of the United States to the United Nations in Geneva, Geneva, Switzerland  
*Tel.: +41 22 749 4619*  
*Email: breenjx@state.gov*

**Dr Robert F. Breiman**, Head, Programme on Infectious Diseases and Vaccine Sciences, ICDDR,B Centre for Health and Population Research, Mohakhali, Dhaka 1212, Bangladesh  
*Tel.: +880-2-988-1761; Fax: +880 2 882 3963*  
*Email: rfbreiman@yahoo.com*

**Dr Michael Brennan**, Chief, Laboratory for Microbacteria, Center for Biologics, Evaluation & Research, Food and Drug Administration 29 Lincoln Drive, Bldg 29, Room 505, Bethesda, MD 20906, USA  
*Tel.: +1 301 496 9559; Fax: +1 301 435 5675*  
*Email: brennan@cber.fda.gov*

**Dr Claire V. Broome**, Deputy Director, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, N.E., MS D14, Atlanta, GA 30333, USA  
*Tel.: +1 404 639 7860; Fax: +1 404 639 7770*  
*Email: cvb1@cdc.gov*

**Dr Margaret Burgess**, Director, National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Locked Bag 4001, Westmead NSW 2145, Australia  
*Tel.: +61 2 98 45 30 69; Fax: +61 2 9845 30 82*  
*Email: margarb1@chw.edu.au*

**Dr Concepcion Campa-Juergo**, President, Center for Research-Production of Vaccines and Sera, Finlay Institute, Avenue 27, No. 19805, La Lisa, A.P. 16017, CP 11600, La Habana, Cuba  
*Tel.: +53 721 1454; Fax: +53 733 6075*  
*Email: ccampa@finlay.edu.cu*

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

**Ms Diana Cotran**, Medicines for Malaria Venture (MMV), International Center Cointrin, Block G, 3rd Floor, 20 route de Pré-Bois, PO Box 1826, CH-1215 Geneva 15, Switzerland  
*Tel.: +41 22 799 4068; Fax: +41 22 799 4061*

---

**Dr George T. Curlin**, Acting Director, National Institute of Allergy and Infectious Diseases (NIAID/NIH), Division of Microbiology and Infectious Diseases, National Institutes of Health, 6700-B Rockledge Drive – Room 3116, Bethesda, MD 20892 (or MD 20817 for express mail), USA  
*Tel.: +1 301 496 5893; Fax: +1 301 480 8030*  
*Email: gc24a@nih.gov*

**Dr Ron Dagan**, Director, Soroko Medical Center, Pediatric Infectious Disease Unit, P.O. Box 151, Beer Sheva, 84101, Israel  
*Tel.: +972 8640 0547; Fax: +972 8623 2334*  
*Email: rdagan@bgumail.bgu.ac.il*

**Dr Jose Da Rocha Carvalheiro**, Research and Development Coordinator, Coordenacai dos Institutos de Pesquisa, CIP/SES-SP, State of Sao Paulo Health Department, Av. Dr Arnaldo 351, 1 andar, 01246-000 Sao Paulo, SP, Brazil  
*Tel.: +55 11 3062 0441; Fax: +55 11 3081 9161*  
*Email: jrcarval@usp.br*

**Dr Mahima Datla**, Vice President, Strategic Business Development, Biological E. Ltd., 18/ 3 Azamabad, Hyderabad, Andra Pradesh 500 020, India  
*Tel.: +91 40 761 7831; Fax: +91 40 767 5003*  
*Email: mdatla@biologicale.com*

**Dr Giuseppe del Giudice**, Chiron, Divisione Biologici et Farmaceutici, via Fiorentina 1, I-53100 Siena, Italy  
*Tel.: +39 5 7724 3261; Fax: +39 5 7724 3564*  
*Email: giuseppe\_del\_giudice@chiron.it*

**Dr Francis Delpeyroux**, Epidémiologie Moléculaire des Entérovirus, Institut Pasteur, 25-28 rue du Docteur Roux, F-75724 Paris Cedex 15, France  
*Tel.: +33 1 40 61 33 22; Fax: +33 1 40 61 33 22*  
*Email: delpeyro@pasteur.fr*

**Dr Carter Diggs**, Senior Technical Advisor, USAID, Room 3.07-013, 1300 Pennsylvania Avenue, Washington, D.C. 20523-3700, USA  
*Tel.: +1 202 712 5728; Fax: +1 202 216 3702*  
*Email: cdiggs@usaid.gov*

**Prof. Gordon Dougan**, Imperial College of Science, Technology and Medicine, Department of Biochemistry, Exhibition Road, GB-London SW7 2AZ, United Kingdom  
*Tel.: +44 207 594 5256; Fax: +44 207 594 5255*  
*Email: g.dougan@ic.ac.uk*

**Dr Filip Dubovsky**, Malaria Vaccine Initiative at PATH, 6290 Montrose Road, First Floor, Rockville, MD 20852 USA  
*Tel.: +1 301 770 5377; Fax: +1 301 770 8784*  
*Email: fdubovsky@malariavaccine.org*

**Dr Mohamed A. El-Abaddi**, Chief Executive Officer, Vacsera Egyptian Organization for Biological Products and Vaccines, 51 Wezaret El Zeraa Street, Agouza, Giza, Egypt  
*Tel.: +20 2 336 9872; Fax: +20 2 748 3187*  
*Email: ceo@vacsera.com*

---

**Dr Elaine Esber**, Executive Director, International Medical Affairs,  
Merck Vaccine Division, WP 97A-325, P.O. Box 4, West Point, PA 19486, USA  
*Tel.: +1 215 652 8828; Fax: +1 215 652 8918*  
*Email: elaine\_esber@merck.com*

**Dr Jean-Louis Excler**, Regional Office for South East Asia, World Health House,  
Indraprastha Estate, Mahatma Gandhi Road, New Delhi 110002, India  
*Tel.: +91 11 3317804; Fax: +91 11 3378412*  
*Email: jlexcler@yahoo.com*

**Dr Mark A. Fletcher**, Director Adjoint, International Scientific Affairs,  
Wyeth Lederle Vaccines, Le Wilson II, 80 avenue du Général de Gaulle,  
F-75181 Puteaux Paris la Défense, France  
*Tel.: +33 1 41 02 79 57; Fax: +33 1 41 02 75 34*  
*Email: FletcherM@eu.wyeth.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 Bernard Fritzell**, Vice-President, International Scientific and Clinical  
Affairs, Wyeth Lederle Vaccines, Le Wilson II, 80 avenue du Général de Gaulle,  
F-75181 Puteaux Paris la Défense, France  
*Tel.: +33 1 41 02 75 11; Fax: +33 1 41 02 76 66*  
*Email: FritzellB@eu.wyeth.com*

**Prof. Marc Girard**, Fondation Merieux, 17 rue Bourgelat, F-69002 Lyon, France  
*Tel.: +33 4 72407956; Fax: +33 4 72407934*  
*Email: marc.girard@fond-merieux.org*

**Dr Roger Glass**, Center for Disease Control and Prevention, Viral Gastroenteritis  
Unit (G04), 1600 Clifton Road, Mailstop G04, Atlanta, GA 30333, USA  
*Tel.: +1 404 639 3577; Fax: +1 404 639 3645*  
*Email: rglass@cdc.gov*

**Dr Reinhard Glück**, Head of Research and Development, Swiss Serum and  
Vaccine Institute Berne, P.O. Box 3001, CH-3001 Berne, Switzerland  
*Tel.: +41 31 980 6500; Fax: +41 31 980 6785*  
*Email: reinhard.glueck@bernabiotech.com*

**Dr Tore Godal**, Executive Secretary, GAVI Secretariat, c/o UNICEF,  
Palais des Nations, 5-7 avenue de la Paix, CH-1211 Geneva, Switzerland  
*Tel.: +41 22 909 5020; Fax: +41 22 909 5900*  
*Email: tgodal@unicef.org*

**Dr Jesse Goodman**, Deputy Director, Medicine, Food and Drug Administration,  
Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 2000,  
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 7915  
Email: [dgranoff@chori.org](mailto:dgranoff@chori.org)

**Dr Haleh Hamedifar**, Pasteur Institute of Iran, Pasteur St, 13164, Tehran, Iran  
Tel.: +98 913 215 3342; Fax: +98 21 466 4991  
Email: [halehfar@yahoo.com](mailto:halehfar@yahoo.com)

**Dr G.V.J.A. Harshavardhan**, Adviser – Quality Assurance, Bharat Biotech International Limited, 726 Road 3, Banjara Hills, Hyderabad 500 078, India  
Tel.: +91 40 348 0567; Fax: +91 403 348 0560  
Email: [bbiladvisor@yahoo.com](mailto:bbiladvisor@yahoo.com)

**Dr Chris Hentschel**, CEO, New Medicines for Malaria Venture, 3rd floor, ICC Building, 20 route de Pré-Bois, CH-1215 Geneva 15, Switzerland  
Tel.: +41 22 799 40 62; Fax: +41 22 799 40 61  
Email: [hentschelc@mmv.org](mailto:hentschelc@mmv.org)

**Dr Socrates Herrera**, Universidad del Valle, Instituto de Immunologia, Calle 4B, No. 36-00, San Ferndando, Cali, Columbia  
Tel.: +572 558 1931; Fax: +57 2 55 70 449  
Email: [soheva@inmuno.univalle.edu.co](mailto:soheva@inmuno.univalle.edu.co)

**Dr Arnd Hoeveler**, Head of Unit, office SDME 7/31, European Commission, DG Research, Rue de la Loi 200, B-1049 Bruxelles, Belgium  
Tel.: +32 2 295 68 01; Fax: +32 2 295 53 65  
Email: [arnd.hoeveler@cec.eu.int](mailto:arnd.hoeveler@cec.eu.int)

**Dr Joachim Hombach**, GlaxoSmithKline Biologicals, Rue de l'Institut, 89, B-1330 Rixensart, Belgium  
Tel.: +32 2 656 7080; Fax: +32 2 656 8145  
Email: [joachim.hombach@gskbio.com](mailto:joachim.hombach@gskbio.com)

**Dr Akira Homma (DCVMN)**, Director, Fiocruz/BioManguinhos, Av. Brasil 4.365 - Manguinhos, Rio de Janeiro, Cx. Postal 926 – CEP 21045-900, Brazil  
Tel.: +55 21 2564 2220; Fax: +55 21 2260 4727  
Email: [Akira@bio.fiocruz.br](mailto:Akira@bio.fiocruz.br)

**Dr Jose Ignacio dos Santos**, Director General, Centro Nacional para la Salud de la Infancia y Adolescencia, Fco de P Miranda 177, 2 piso, Col. Merced Gomez, 01600 Mexico DF, Mexico  
Tel.: +525 593 1122; Fax: +525 593 1144  
Email: [jisantos@supernet.com.mx](mailto:jisantos@supernet.com.mx)

**Prof. Asma Ismail**, Director, Universiti Sains Malaysia, Centre for Medical Innovations & Technology Development, Kubang Kerian, 16150 Kelantan, Malaysia  
Tel: +60 9 7642286; Fax: +60 9 764 8673  
Email: [asma@kb.usm.my](mailto:asma@kb.usm.my)

---

**Dr Giuseppe Ippolito**, Scientific Director, Istituto Nazionale per le Malattie Infettive, Lazzaro Spallanzani- IRCCS, Via Portuense, 292 - 00149 Rome, Italy  
*Tel.: +39 6 5594 223; Fax: 39 6 5594 224*  
*Email: ippolito@inmi.it*

**Dr Bernard Ivanoff**, 36B route de Saint Cergue, Nyon 1260, Switzerland  
*Tel.: +41 22 361 41 61*  
*Email: bivan@bluewin.ch*

**Dr Suresh S. Jadhav**, Executive Director, (Quality Assurance & Regulatory Affairs), Serum Institute of India, Regd. Office and Laboratories, 212/2 Hadapsar, Pune Solapur Road, Pune 411 028, India  
*Tel.: +91 20 699 3900; Fax: +91 20 699 3945*  
*Email: ssj@vsnl.com*

**Dr Mark Kane**, Director, Bill and Melinda Gates Children's Vaccine Program, c/o PATH, 4 Nickerson Street, Seattle, WA 98109, USA  
*Tel.: +1 206 285 3500; Fax: +1 206 285 6619*  
*Email: mkane@path.org*

**Dr Anders Kärnell**, Medical Director, SBL Vaccin AB, SE-105 21 Stockholm, Sweden  
*Tel.: +46 8 7351172; Fax: +46 8 834174*  
*Email: anders.karnell@powderject.com*

**Dr Richard Kenney**, VP, Clinical Development, IOMAI Corporation, 20 Firstfield Road, Suite 250, Gaithersburg, MD 20878, USA  
*Tel.: +1 301 556 4521; Fax: +1 301 556 4501*  
*Email: rkenney@iomai.com*

**Dr Scott Kitchener**, Acambis Inc., Research and Medical Affairs, 100 Fulbourne Road, GB-Cambridge CB1 9PT, United Kingdom  
*Tel.: +44 1223 275300; Fax: +44 1223 416300*  
*Email: scott.kitchener@acambis.com*

**Dr Andrew Yona Kitua**, Director General, National Institute for Medical Research, P.O. Box 9653, Ocean Road, Dar es Salaam, Tanzania  
*Tel.: +255 22 2130770; Fax: +255 22 2130660*  
*Email: akitua@twiga.com*

**Dr Wayne Koff**, Senior Vice President for Research & Development, International AIDS Vaccine Initiative (IAVI), 110 William Street, Floor 27, New York, NY 10038-3901, USA  
*Tel.: +1 212 847 1061; Fax: +1 212 847 1111*  
*Email: wkoff@iavi.org*

**Prof. Karen L. Kotloff**, Chief, Domestic Epidemiological Studies Section, University of Maryland School of Medicine, Center for Vaccine Development, 685 West Baltimore Street, Baltimore, MD 21201, USA  
*Tel.: +1 410 706 5328; Fax: +1 410 706 6205*  
*Email: kkotloff@medicine.umaryland.edu*

**Prof. Simon Wain-Hobson**, Unité de Rétrovirologie Moléculaire, Institut Pasteur, 28 rue du Dr Roux, F-75724 Paris, Cedex 15, France  
*Tel.: +33 1 45 68 88 21; Fax: +33 1 45 68 88 74*  
*Email: simon@pasteur.fr*

---

**Dr Ryoko Krause**, IFPMA, 30 rue de St Jean, PO Box 758,  
CH-1211 Geneva 13, Switzerland  
*Tel.: +41 22 338 3212; Fax: 41 22 338 3299*  
*Email: r.krause@ifpma.org*

**Dr Marc Laforce**, Director of the Meningitis Vaccine Project (MVP),  
Program for Appropriate Technology in Health (PATH), Centre d'Aumard,  
55 avenue Voltaire, F-01210 Ferney-Voltaire, France  
*Tel.: +33 450 282563; Fax: +33 450 280407*  
*Email: fmlaforce@path.org*

**Dr Rosanna Lagos**, Coordinator, Centro para Vacunas en Desarrollo,  
Hospital de Niños Roberto del Rio, Avenida Zanartu, 1085 (4 Piso),  
Independencia Santiago, Chile  
*Tel.: +56 2 735 7263; Fax: +56 2 777 5766*  
*Email: rlagos@adsl.tie.cl*

**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@medicine.unige.ch*

**Dr John La Montagne**, 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 Lanata**, Instituto de Investigación Nutricional,  
Av. La Molina 865, Lima 12, Peru  
*Tel.: +51 1349 6023; Fax: +51 1349 6025*  
*Email: clanata@iin.sld.pe*

**Dr Mary Ann Lansang**, Executive Director, INCLLEN Trust, Section E,  
5/F Ramon Magsaysay Center, 1680 Roxas Boulevard, Malate, Manila 1004,  
Philippines  
*Tel.: +632 400 4374; Fax: +632 400 4374*  
*Email: mlansang@inclentrust.org*

**Dr Dagna Laufer**, Associate Medical Director, Vaccines, Wyeth Ayerst  
International, 120 N. Radnon-Chester Road, St Davids, CA 19087, USA  
*Tel.: +1 610 902 4928; Fax: 1 610 964 5670*  
*Email: lauferd@labs.wyeth.com*

**Dr Myron M. Levine**, 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*

**M. Yves Leurquin** Dipl.-Ing., B.Sc., Associate Marketing Director,  
GlakoSmithKline Biologicals, Berna Biotech, Rehhagstrasse 79,  
CH-3018 Bern, Switzerland  
*Tel.: +41 31 980 68 21; Fax: +41 31 980 67 75*  
*Email: yves.leurquin@bernabiotech.com*

---

**Dr Orin S. Levine**, Epidemiologist, Centers for Disease Control and Prevention,  
1600 Clifton Road N.E., Atlanta, GA 30333, USA  
*Tel.: +1 301 435 7708; Fax: +1 301 496 8030*  
*Email: olevine@niaid.nih.gov*

**Dr Margaret Liu**, Vice-Chairman, Transgene, 11 rue de Molsheim,  
F-67082 Strasbourg Cedex, France  
*Tel.: +33 3 88 27 91 22; Fax: +33 3 88 27 91 11*  
*Email: liu@transgene.fr*

**Mr John Lloyd**, Resident Adviser, Program for Appropriate Technology in  
Health (PATH) Centre d'Aumard, 55 Avenue Voltaire, F-01210 Ferney-Voltaire,  
France  
*Tel.: +33 450 280049; Fax: +33 450 280407*  
*Email: jlloyd@path.org*

**Dr Hermilo Lopez Coello**, Director General, Laboratorios de Biologicos y  
Reactivos de Mexico (Birmex), Amores 1240, Col. Del Valle, C.P. 03100, Mexico  
*Tel.: +525 54 22 28 41; Fax: +525 54 22 28 80*  
*Email: blopezc@yahoo.com*

**Dr Christian Loucq**, Business Director, Vaccines, Rhein Biotech,  
Gaetano Martinolaan 95, NL-6229 GS Maastricht, Netherlands  
*Tel.: +31 43 356 7821; Fax: +31 43 356 7830*  
*Email: c.loucq@rheinbiotech.com*

**Dr Shabir Madhi**, Deputy Director, Respiratory and Meningeal Pathogens  
Research Unit, South Africa Institute for Medical Research (SAIMR),  
Chris Hani-Bara Hospital, Room 11, Old Potch Road, Johannesburg 1813,  
South Africa  
*Tel.: +27 11 489 8723 ; Fax: +27 11 489 8692*  
*Email: shabirm@mail.saimr.wits.ac.za*

**Prof. Richard Mahoney**, Arizona Biomedical Institute,  
School of Health Administration and Policy, Arizona State University,  
53 Gambel Lane, Sedona, AZ 86336, USA  
*Tel.: +1 928 2030172; Fax: +1 928 2220074*  
*Email: Richardmahoney@earthlink.net*

**Dr William Makgoba**, President, Medical Research Council of South Africa,  
P.O. Box 19070, Tygerberg 7505, South Africa  
*Tel.: +27 21 938 0211/0240; Fax: +27 21 938 0201*  
*Email: malegapuru.makgoba@mrc.ac.za*

**Dr Abdullah Marzuki**, President Director, PT. BIO FARMA (Persero),  
Jl. Pasteur 28, P.O. Box 1136, Bandung 40161, Indonesia  
*Tel.: +62 22 2033 755 ; Fax: +62 22 204 1306*  
*Email: marzuki@biofarma.co.id*

**Dr Yair Quinones Maya**, Deputy Director for Vaccine Productions,  
Ave 31, 158 y 190, Cubanacan, Playa P.O. Box 6162, La Havana 10600, Cuba  
*Tel.: +53 7 271 8675; Fax: +53 7 271 8675*  
*Email: yair.quinones@cigb.edu.cu*

---

**Dr Harriet Mayanja-Kizza**, Senior Lecturer, Makerere University Department of Medicine , P.O. Box 7072, Kampala, Uganda  
*Tel.: +256 77 593482; Fax: +256 41 533531*  
*Email: bmk@afsat.com*

**Dr Mark Miller**, Director of Research, Fogarty International Center, National Institute of Health, 16 Center Drive, Building 16, Room 217, Bethesda, MD 20892, USA  
*Tel.: +1 301 496 0815; Fax: +1 301 496 8496*  
*Email: millermark@nih.gov*

**Dr Mary Elizabeth Miranda**, Rabies Research Program Leader and Head, Veterinary Research Department, Research Institute for Tropical Medicine, Alabang, Muntinlupa City, 1770, Philippines  
*Tel.: +63 28072628 ext 233; Fax: +63 28422245*  
*Email: bmiranda@laguna.net*

**Dr Farrokh Moddaber**, Director, Infectious Disease Research Institute (IDRI), 1124 Columbia Street, Suite 600, Seattle, WA 98104, USA  
*Tel.: +1 206 381 0883; Fax: +1 206 381 3678*  
*Email: fmodabber@idri.org*

**Dr Melinda Moree**, Program for Appropriate Technology in Health (PATH), 1455 NW Leary Way, Seattle, WA 98107-5136, USA  
*Tel.: +1 206 285 3500; Fax: +1 206 285 6619*  
*Email: mmoree@path.org*

**Dr Odette Morin Carpentier**, Director, Regulatory and Scientific Affairs, IFPMA, P.O. Box 753, 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 Trudy Murphy**, Chief, Infant Immunization Activity, National Immunization Programme, Childhood & Vaccine Preventable Diseases Epidemiology Section, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Mail Stop E-61, Atlanta, GA 30333, USA  
*Tel.: +1 404 639 8845; Fax: +1 404 639 8665*  
*Email: tkm4@cdc.gov*

**Prof. Francis K. Nkrumah**, Noguchi Memorial Institute for Medical Research, University of Ghana, P.O. Box LG 581, Legon, Ghana  
*Tel.: +233 21 50 11 78; Fax: 233 21 50 21 82*  
*Email: Fnkrumah@noguchi.mimcom.net*

**Sir Gustav J.V. Nossal**, Professor Emeritus, Department of Pathology, University of Melbourne, Melbourne 3010, Australia  
*Tel.: +61 3 8344 6946; Fax: +61 3 8347 5242*  
*Email: gnossal@weptime.com.au*

**Dr Solomon Nwaka**, Medicines for Malaria Venture (MMV), International Center Cointrin, Block G, 3rd Floor, 20 route de Pré-Bois, PO Box 1826, CH-1215 Geneva 15, Switzerland  
*Tel.: +41 22 799 4068; Fax: +41 22 799 4061*

---

**Dr Weiqing Pan**, Department of Parasitology, Second Military Medical University, Institute of Medical Biotechnology and Molecular Genetics, 800 Xiang Yin Road, Shanghai 200433, People's Republic of China  
*Tel.: +86 21 2507 0250; Fax: +86 21 2507 0250*  
*Email: malaria@guomai.sh.cn*

**Dr Punnee Pitisuttithum**, Chief of Clinical Infectious Diseases Research Unit, Mahidol University, Faculty of Tropical Medicine, 420/6 Rajvithi Road, Rajthavee, Thailand  
*Tel.: +66 2 245599; Fax: +66 2 6435598*  
*Email: punneep@dmc.inet.co.th*

**Dr Cyrus Poonawalla**, Chairman, Serum Institute of India Research Foundation, 212/2 Hadapsar, Pune 411028, Maharashtra, India  
*Tel.: +91 20 699 3939; Fax: +91 20 699 3921*  
*Email: cspoonawalla@hotmail.com*

**Dr Adar C. Poonawalla**, Member of Board of Governing Council of Serum Institute of India Research Foundation, 212/2 Hadapsar, Pune 411028, Maharashtra, India  
*Tel.: +91 20 699 3939; Fax: +91 20 699 3921*  
*Email: cspoonawalla@hotmail.com*

**Dr Peter Potter-Lesage**, Chief Financial Officer, Medicines for Malaria Venture (MMV), International Center Cointrin, Block G, 3rd Floor, 20 route de Pré-Bois, PO Box 1826, CH-1215 Geneva 15, Switzerland  
*Tel.: +41 22 799 4068; Fax: +41 22 799 4061*  
*Email: potter-lesagep@mmv.org*

**Dr Marie-José Quentin-Millet**, Vice-President R&D, Aventis Pasteur Site France, 1541 avenue Marcel Mérieux, F-69280 Marcy l'Etoile, France  
*Tel.: +33 4 37 373577; Fax: +33 4 37 37 3976*  
*Email: marie-jose.quentin-millet@aventis.com*

**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**, Head of Research, Chiron SpA, Via Fiorentina 1, I-53100 Siena, Italy  
*Tel.: +39 0577 243 414; Fax: +39 0577 243 564*  
*Email: rino\_rappuoli@chiron.it*

**Prof. Isaias Raw**, Director, Instituto Butantan, Av. Vital Brazil 1500, São Paulo 05503-900, Brazil  
*Tel.: +55 11 813 56 94; Fax: +55 11 815 1505*  
*Email: iraw@butantan.gov.br*

**Dr K.I. Varaprasad Reddy**, Managing Director, Shantha Biotechnics Private. Ltd., Serene Chambers, 3rd Floor, Road No. 7, Banjara Hills, Hyderabad 500 034, India  
*Tel.: +91 40 678 8880; Fax: +91 40 354 1713*  
*Email: varaprasad@shanthabiotech.com*

---

**Dr Lise Riopel** Medicines for Malaria Venture (MMV),  
International Center Cointrin, Block G, 3rd Floor, 20 route de Pré-Bois,  
PO Box 1826, CH-1215 Geneva 15, Switzerland  
*Tel.: +41 22 799 4068 ; Fax: +41 22 799 4061*

**Dr Polly Sager**, Assistant Director for International Research in Infectious  
Diseases, DMID, NIAID, NIH 6700 B Rockledge Drive, Bethesda,  
MD 20892-7630, USA  
*Tel.: +1 301 496 1884*  
*Email: psager@niaid.nih.gov*

**Dr Christian Schirvel**, Parteurop Développement S.A., 36, quai Fulchiron,  
69005 Lyon, France  
*Tel.: +33 4 72 56 38 60; Fax: +33 4 78 42 34 24*  
*Email: christian.schirvel@parteurop.com*

**Dr Anne Schuchat**, Chief, Respiratory Diseases Branch, Centers for Disease  
Control and Prevention, Division of Bacterial and Mycotic Diseases,  
National Center for Infectious Diseases, Mailstop C23, Atlanta, GA 30333, USA  
*Tel.: +1 404 639 4720; Fax: +1 404 639 3970*  
*Email: aschuchat@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\_r\_shaw@merck.com*

**Dr Claire-Ann Siegrist**, Head, WHO Collaborating Centre for Neonatal  
Vaccinology, Centre Médical Universitaire, 1 rue Michel Servet,  
CH-1211 Geneva 4, Switzerland  
*Tel.: +41 22 702 5778; Fax: +41 22 702 58 01*  
*Email: siegrist@cmu.unige.ch*

**Dr Gustavo Sierra Gonzalez**, Vice President, Investigaciones and President,  
Experts Committee for the Cuban Vaccine Programme, Finlay Institute, Centro  
de Investigacion, Produccion Vacunas y Sueros, Ave 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 Sodiomon Bienvenu Sirima**, Head, Public Health Unit, Centre National de  
Lutte Contre le Paludisme (CNLP), B.P. 2208 Ouagadougou 01, Burkina Faso  
*Tel.: +226 324695/96; Fax: +226 310477*  
*Email: s.sirima.cnlp@fasonet.bf*

**Dr Duncan Steele**, Medical University of South Africa (MEDUNSA),  
Diarrhoeal Pathogens Research Unit, Department of Virology, PO Box 173,  
MEDUNSA 0204, Pretoria, South Africa  
*Tel.: +27 12 521 5938; Fax: +27 12 521 5794*  
*Email: adsteele@medunsa.ac.za*

---

**Dr Yoksan Sutee**, Director, Center for Vaccine Development,  
Inst. of Science & Technology for Research & Dev., 25/25 Phutthamonthon 4,  
Nakhonpathom 73170, Thailand  
*Tel.:* +66 2 441 0190; *Fax:* +66 2 441 9336  
*Email:* [grsys@mucc.mahidol.ac.th](mailto:grsys@mucc.mahidol.ac.th)

**Dr Aldo Tagliabu**, Deputy Director for Laboratory Research, International  
Vaccine Institute, Kwanak-ku, P.O. Box 14, Seoul 151-600, Republic of Korea  
*Tel.:* +82 2 872 2801; *Fax:* +82 2 872 2803  
*Email:* [atagliabue@ivi.int](mailto:atagliabue@ivi.int)

**Dr Keiko Taya**, 1-23-1 Toyoma, Shinjuku-ku, 162-8640 Tokyo, Japan  
*Tel.:* +81 3 5285 1111; *Fax:* +81 3 5285 1129  
*Email:* [ktaya@nih.go.jp](mailto:ktaya@nih.go.jp)

**Dr Alan Thomas**, Chairman, Parasitology Department, Biomedical Primate  
Research Centre, P.O. Box 3306, 139 Lange Kielweg, NL-2280 GJ Rijswijk,  
Netherlands  
*Tel.:* +31 15 284 2640; *Fax:* +31 15 284 39 86  
*Email:* [thomas@bprc.nl](mailto:thomas@bprc.nl)

**Dr Nadia Tornieporth**, Research and Development, GlaxoSmithKline  
Biologicals, 89 rue de l'Institut, B-1330 Rixensart, Belgium  
*Tel.:* +32 2 656 8974; *Fax:* +32 2 656 6160  
*Email:* [nadia.tornieporth@gskbio.com](mailto:nadia.tornieporth@gskbio.com)

**Dr Peter Turnbull**, Artemis Technology Ltd, 86 St Mark's Avenue,  
GB-Salisbury SP1 3DW, United Kingdom  
*Tel.:* +44 1722 331472; *Fax:* +44 1722 331472  
*Email:* [peterturnbull@tesco.net](mailto:peterturnbull@tesco.net)

**Dr Satchidanandam Vijaya**, Associate Professor, Dpt. of Microbiology and Cell  
Biology, Indian Institute of Science, Bangalore 560012, Karnataka, India  
*Tel.:* +91 80 3092685; *Fax:* +91 80 3602697  
*Email:* [vijaya@mcbl.iisc.ernet.in](mailto:vijaya@mcbl.iisc.ernet.in)

**Dr Risini Weeratna**, Senior Scientist, Coley Pharmaceutical Canada,  
725 Parkdale Avenue, Ottawa (Ontario) K1Y 4E9, Canada  
*Tel.:* +1 613 761 94 54 x 3120; *Fax:* +1 613 761 86 61  
*Email:* [rweeratna@coleypharma.com](mailto:rweeratna@coleypharma.com)

**Dr Roy Widdus**, Manager, Initiative on Public-Private Partnerships for Health,  
Global Forum for Health Research, International Centre Cointrin (ICC),  
Block G, Third Floor, C. P. 1826, CH-1215 Geneva 15, Switzerland  
*Tel.:* +41 22 799 4086/4088; *Fax:* +41 22 799 4089  
*Email:* [roy.widdus@ippph.org](mailto:roy.widdus@ippph.org)

**Dr Peter Wilson**, Hillcrest, Guilford Road, GB-Ottershaw KT16 0QL,  
United Kingdom  
*Tel.:* +44 1932 872 358; *Fax:* +44 1932 874501  
*Email:* [wilsonprb@compuserve.com](mailto:wilsonprb@compuserve.com)

**Dr Riccardo Wittek**, Institut de Biologie Animale, Bâtiment de Biologie,  
Université de Lausanne, CH-1015 Lausanne, Switzerland  
*Tel.:* +41 21692 4112; *Fax:* +41 21 692 4115  
*Email:* [riccardo.wittek@iba.unil.ch](mailto:riccardo.wittek@iba.unil.ch)

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## WHO Secretariat

### *Regional offices*

#### *Regional Office for Africa (AFRO)*

Parirenyatwa Hospital, Mazoe Street, PO Box, BE 773, Belvedere Harare, Zimbabwe

**Dr O. Babaniyi**, Regional Adviser, EPI, AUSAID (Australia)

*Tel.:* +1 321 733 9384; *Fax:* +263 49 0146

*Email:* babaniyio@whoafro.org

#### *Regional Office for the Americas (AMRO)*

WHO Regional Office for the Americas/Pan American Sanitary Bureau, 525 23rd Street, N.W., Washington, D.C. 20037, USA

**Dr Ciro de Quadros**, Director, Division of Vaccines and Immunization (HVP),

*Tel.:* +1 202 974 3247; *Fax:* +1 202 974 3635

*Email:* quadrosc@paho.org

**Dr Jose Luis di Fabio**, Coordinator, Vaccine Technology Access, Division of Vaccines and Immunizations

*Tel.:* +1 202 974 3788; *Fax:* +1 202 974 3635

*Email:* difabioj@paho.org

#### *Regional Office for the Eastern Mediterranean (EMRO)*

WHO Post Office, Abdul Razzak Al Sanhoury Street, Nasr City, PO Box 7608, Cairo 11371, Egypt

**Dr Peter Graaf**, Regional Adviser for Essential Drugs and Biologicals

*Tel.:* +202 276 5301; *Fax:* +202 670 24 92

*Email:* graaffp@emro.who.int

#### *Regional Office for Europe (EURO)*

8 Scherfigsvej, Copenhagen, Denmark

**Dr Bernardus Ganter**, Regional Adviser for Communicable Disease Surveillance and Response

*Tel.:* +45 39 17 17 17; *Fax:* +45 39 17 18 51

*Email:* bga@who.dk

#### *Regional Office for South East Asia (SEARO)*

**Dr W. Harjotanojo**, Senior Adviser to Regional Director, Health Technology and Pharmaceuticals, G.P.O. Box 250, House N° 12, Road N° 7, Dhanmondi Residential Area, Dhaka 1000, Bangladesh, India

*Tel.:* +880 2 86 46 53; *Fax:* +880 2 86 32 47

*Email:* hardjotanojow@whosea.org

### *WHO headquarters*

21 avenue Appia, CH-1211 Geneva 27, Switzerland

**Dr M. Teresa Aguado**, Coordinator, Research on Bacterial Vaccines (BAC), Initiative for Vaccine Research (IVR), Vaccines and Biologicals (V&B)

*Tel.:* +41 22 791 2644; *Fax:* +41 22 791 4860

*Email:* aguadom@who.int

---

**Mr David Alnwick**, Project Manager, Roll Back Malaria (RBM),  
Communicable Diseases (CDS) cluster  
*Tel.: +41 22 791 2769*  
*Email: alnwickd@who.int*

**Dr Claire-Lise Chaignat**, Coordinator, Global Task Force on Cholera Control,  
Department of Communicable Disease Surveillance and Response (CSR), CDS  
*Tel.: +41 22 7913914; Fax: +41 22 7914667*  
*Email:chaignatc@who.int*

**Dr Thomas Cherian**, Medical Officer, BAC/IVR/V&B  
*Tel.: +41 22 791 4460; Fax: +41 22 791 4860*  
*Email: cheriant@who.int*

**Dr John Clements**, Medical Officer, Expanded Programme on Immunization  
(EPI), V&B  
*Tel.: +41 22 791 4402; Fax: +41 22 791 4193*  
*Email: clementscj@who.int*

**Dr Ottorino Cosivi**, Emerging Public Health Risks including Drug Resistance  
(EPH), CSR/CDS, WHO  
*Tel.: +41 22 791 2531*  
*Email: cosivio@who.int*

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

**Dr Howard Engers**, Manager, Steering Committee on Vaccine Discovery  
Research, Special Programme for Research and Training in Tropical Diseases  
(TDR), CDS  
*Tel.: +41 22 791 3736; Fax: +41 22 791 4854*  
*Email: engersh@who.int*

**Dr Jose Esparza**, Coordinator, Research on Viral Vaccines (VIR), IVR/V&B  
*Tel.: +41 22 7914392; Fax: +41 22 791 4865*  
*Email: esparzaj@who.int*

**Ms Nadia Fisher**, Secretary, IVR/V&B  
*Tel.: +41 22 791 4395; Fax: +41 22 791 4860*  
*Email: fishern@who.int*

**Dr Ana-Maria Henao-Restrepo**, EPI/V&B  
*Tel.: +41 22 791 34502; Fax: +41 22 791 4193*  
*Email: henaorestrepa@who.int*

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

**Dr Juntra Karbwang**, Clinical Coordinator, Product Research and Development,  
TDR/CDS  
*Tel.: +41 22 791 3868; Fax: +41 22 791 4854*  
*Email: karbwangj@who.int*

---

**Dr Ulla Kou**, Associate Professional Officer, Vaccine Assessment and Monitoring (VAM), V&B

*Tel.: +41 22 791 4289; Fax: +41 22 791 4210*

*Email: kouu@who.int*

**Dr Marie-Paule Kieny**, Director, IVR/V&B

*Tel.: +41 22 791 4289; Fax: +41 22 791 4210*

*Email: kienym@who.int*

**Dr Julie Milstien**, Coordinator, Access to Technologies (ATT), V&B

*Tel.: +41 22 791 4471; Fax: +41 22 791 4384*

*Email: milstienj@who.int*

**Dr Carlos Morel**, Director, TDR/CDS

*Tel.: +41 22 791 3802; Fax: +41 22 791 14854*

*Email: morelc@who.int*

**Dr Sonia Pagliusi**, Scientist, BAC/IVR/V&B

*Tel.: +41 22 791 3718; Fax: +41 22 791 4860*

*Email: pagliusis@who.int*

**Dr William Perea**, Global Alert and Response (GAR), CSR/CDS

*Tel.: +41 22 791*

*Email: pereaw@who.int*

**Dr Robert Ridley**, Coordinator, Product Research and Development (PRD), TDR/CDS

*Tel.: +41 22 791 3767*

*Email: ridleyr@who.int*

**Dr Cathy Roth**, GAR/CSR/CDS

*Tel.: +41 22 7913896*

*Email: rothc@who.int*

**Dr Yasuhiro Suzuki**, Executive Director, Health Technology and Pharmaceuticals (HTP) cluster, WHO

*Tel.: +41 22 791 2511; Fax: +41 22 791 4889*

*Email: suzukiy@who.int*

**Dr Daniel Tarantola**, Director, V&B

*Tel.: +41 22 791 2779; Fax: 41 22 791 4860*

*Email: tarantolad@who.int*

**Ms Emma Uramis**, Scientist/Global Training Network (GTN) Coordinator, ATT/V&B

*Tel.: +41 22 791 3579; Fax: +41 22 791 4384*

*Email: uramise@who.int*

**Ms Claire Whitfield**, Secretary, BAC/IVR/V&B

*Tel.: +41 22 791 3718; Fax: +41 22 791 4860*

*Email: whitfieldc@who.int*

**Dr Chris Wolff**, VAM/V&B

*Tel.: +41 22 791 4524*

*Email: wolffc@who.int*