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Proceedings of the fourth Global Vaccine Research Forum

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Abbreviations and acronyms

ADIP	accelerated development and introduction plan
AIDS	acquired immunodeficiency syndrome
CBER	Center for Biologics Evaluation and Research
CD8	marker of cytotoxic T lymphocytes
CDC	Centers for Disease Control and Prevention (USA)
CpG	oligonucleotides rich in CpG motifs
CHO	Chinese Hamster Ovary cells
CPMP	Committee for Proprietary Medicinal Products
CSP	*P. falciparum* circumsporozoite protein
CTL	cytotoxic T lymphocytes
DC	developing country
DEN	dengue
DOMI	diseases of the most impoverished project
DTP	diphtheria–tetanus–pertussis (vaccine)
DTP3	three doses of DTP
DTwP	diphtheria–tetanus–wholecell pertussis (vaccine)
EDCTP	European and Developing Countries Clinical Trial Partnership
EMEA	European Medicines Evaluation Agency
EPI	Expanded Programme on Immunization
EU	European Union
FDA	Food and Drug Administration
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	good manufacturing practice
GSK	GlaxoSmithKline Biologicals
GVRF	Global Vaccine Research Forum
Hib	*Haemophilus influenzae* type b

HIV	human immunodeficiency virus
HPV	human papillomavirus
HTP	Health Technology and Pharmaceuticals (WHO Cluster)
IgA	immunoglobulin A
IgG	immunoglobulin G
IVB	Department of Immunization, Vaccines and Biologicals (WHO)
IVI	International Vaccine Institute
IVR	Initiative for Vaccine Research
JE	Japanese encephalitis
KFDA	Korean Food and Drug Administration
MCH	major histocompatibility complex
MMV	Medicine for Malaria Venture
MVA	Modified Vaccinia Ankara (non replicative vaccinia virus strain)
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NRA	national regulatory authority
OPV	oral polio vaccine
PATH	Program for Appropriate Technology in Health (USA)
IPR	intellectual property rights
PS	polysaccharide
RTS,S	malaria vaccine candidate based on a fusion of CSP with hepatitis B surface antigen
TC	countries in transition
TB	tuberculosis
TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TT	tetanus toxoid (vaccine)
UN	United Nations
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USNIH	United States National Institutes of Health
Vero	green monkey kidney-derived cell line

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and the World Health Organization**

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Preface

Dr Daniel Tarantola, Director of WHO's Department of Vaccines and Biologicals (now renamed Department of Immunization, Vaccines and Biologicals (IVB)), and Dr Marie-Paule Kieny, Director of WHO's Initiative for Vaccine Research (IVR),warmly welcomed the participants and thanked them for attending this gathering of specialists in vaccine research and development. The third Global Vaccine Research Forum (GVRF) is the eighth meeting in a series previously referred to as the Montreux meetings, as well as the third joint WHO/GAVI (Global Alliance for Vaccines and Immunization) meeting on global vaccine research.

The broad objectives of the Forum were reviewed. These are:

- to provide an opportunity for GAVI partners to participate in shaping a global 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.

It was noted that 2003 constituted a very important year for GAVI research and development activities. Indeed, the GAVI accelerated development and introduction plans (ADIPs) for pneumococcus and rotavirus vaccines had been finalized during the first half of the year, and the vaccine research and development (R&D) community greeted Drs Orin Levine and John Wecker as the newly appointed directors of these new and promising enterprises. In addition, a comprehensive review of the three new potential GAVI vaccine technology agendas had been completed under the auspices of the Research and Development Task Force. As these two critical milestones had been reached, it was explained that the GAVI R&D Task Force had fulfilled its mission and would therefore cease to exist after the July 2003 GAVI Board meeting. The GAVI R&D Task Force co-chairs heartily thanked their colleagues on the Task Force for outstanding contributions and the vaccine R&D community at large for their support.

Important developments in vaccine research and development had also occurred in WHO. Following the appointment of Dr J.W. Lee as the new Director-General of WHO, it was decided to move the Department of Vaccines and Biologicals and IVR to the Family and Community Health (FCH) cluster, under the leadership of Joy Phumaphi, previously Minister of Health in Botswana. In addition, the Initiative for Vaccine Research under the direction of Dr Marie-Paule Kieny had recently completed the review of its programme, disease priorities and *modus operandi* in order to optimize WHO activities in the field of vaccine R&D.

The 2003 GVRF also constituted a milestone as it was the first of this series of meetings to be held outside of the Geneva area. The meeting co-chairs thanked Dr John Clemens and the staff of the International Vaccine Institute (IVI) in Seoul for their participation in the organization of the conference and for allowing meeting participants to visit their newly inaugurated IVI facility.

Finally, the meeting co-chairs and secretariat wished all participants an interesting and productive meeting.

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

1.1 Will blood-stage malaria vaccines be developed using current strategies? *(Michael Good)*

The current approaches to the development of malaria vaccines are largely based on the use of "subunit" or recombinant proteins, the production of which is facilitated by availability of data on cloning and sequence of malaria genes, which has been generated over the past 20 years. However, the overall success to date has been quite modest.

Most of the current malaria vaccine strategies aim to duplicate natural immunity, which is known to be incomplete. A number of challenges and scientific unknowns have to be addressed to enable the rational design of candidate vaccines, including the following.

- Natural immunity against malaria infection is very slow to develop, if ever. Natural history studies clearly demonstrate that there is lack of naturally acquired sporozoite immunity in adult endemic populations.
- A number of immune mechanisms that could be implicated in interference or suppression of protective immune responses, e.g. inhibition of primary immune responses mediated by dendritic cells (DC), depletion of parasite-specific T-cells, interference of pre-existing antibodies with fine specificity of immune response to malaria antigens, as is the case with maternal antibody response that interferes with the immune response of a neonate.
- Additional challenges for vaccine development are also posed by extensive antigenic polymorphism in principal epitopes of the parasite, as well as poor immunogenicity of subunit proteins used as immunogens.

To address these challenges, it was proposed to promote a multi-stage approach, focusing on induction of immune responses to cryptic, more conserved determinants of potentially protective immune responses. One such approach was presented, which is based on the use of inactivated wholecell ("killed") vaccine. It has recently been shown that IL-12 or CpG (an IL-12-inducing adjuvant) could enhance immunogenicity of a whole inactivated preparation of the mouse parasite *P. chabaudi*. However, a large dose of an antigen was used in these experiments, making it highly impractical for human use. Further on, it was shown that naive human volunteers could be immunized with a low dose of parasite-infected red blood cells containing approximately 30 parasites. The ultra-low dose is probably critical to prevent the occurrence of apoptosis of parasite-specific T-cells. The low-dose infection in the volunteers was treated after one week. Following three such immunizing infections, three out of four volunteers were completely protected against challenge with infectious

parasites. Immune responses in vaccinees were characterized by a strong cell-mediated immune response and the absence of any antibody response. The results from these two studies initiated a proposal to develop a human malaria vaccine by using an ultra-low dose of killed *P. falciparum* (~10^3 parasites equivalent), grown *in vitro* in human blood cells, and using adjuvants CpG and alum. Also, based on the evidence that live ultra-low dose infection can give rise to heterologous protection in a rodent model, it is anticipated that similar heterologous protection could be achieved in humans by targeting antigens that activate cell-mediated immunity and which are likely to be highly conserved.

1.2 Tuberculosis vaccines *(Sang-Nae Cho)*

The epidemiological data available to date demonstrate that the spread of tuberculosis (TB) is a global health emergency. By the year 2003, it is estimated that more than 30% of the global population will be infected with TB. The tuberculosis pandemic continues its spread at a rate of 8 million annual infections resulting in approximately 2.7 million deaths per year. In Korea, the TB epidemic follows similar global trends, where TB prevalence is maintained at a 30% level with an annual incidence of approximately 40 000 (or 80 cases per 100 000) and more than 3000 TB-related deaths every year. This continuous spread of the TB pandemic justifies a need for the accelerated development of safe, more effective and affordable vaccines and new therapeutic strategies.

The only currently available vaccine against tuberculosis was developed more than 100 years ago. Several variants of this vaccine based on different attenuated stains of *M. bovis* (BCG-Pasteur, Tokyo, GlaxoSmithKline Biologicals, Tice, etc.) are being used as part of childhood immunization programmes in many parts of the world, supported by WHO and UNICEF. Over the past years, BCG has been shown to be safe and inexpensive. However, it has been established that BCG vaccines are not able to prevent infection with wild type *M. tuberculosis* in children, although they are still effective in preventing meningitis and miliary TB in up to 80% of vaccinated children. Importantly, this protective efficacy can vary significantly in different geographical locations and different populations. There are additional safety concerns related to the use of BCG vaccines in populations with high prevalence of HIV.

A new generation of TB vaccines is presently under development, mostly targeting the induction of cell-mediated immunity by stimulation of CD4+/CD8+ T-cells. All the modern vaccination strategies are being explored, including recombinant BCG vaccines, recombinant subunit vaccines, DNA vaccines, attenuated *M. tuberculosis*, viral vectors and saprophytes, as well as combined vaccine approaches.

Several vaccine candidates have been shown to be effective in preventing virulent TB infection in animal models. Immunization using a recombinant BCG expressing Ag85B, as well as its combination with recombinant Ag85B protein, produced promising results by preventing infection in lungs and spleen, and increasing the survival time of vaccinated animals *(1, 2, 3).* Other vaccine approaches, based on DNA expression of Ag85, alone and in combination with a Modified Vaccinia Ankara (MVA) vector's expression of the same antigen, have also produced encouraging results in preventing TB infection in animal models *(4, 5).* Additional research is under way to modulate immunogenicity of candidate vaccines by addition of cytokines. Among these studies, evaluating adjuvant effects of granulocyte macrophage-colony stimulating factor (GM-

CSF) on BCG-based vaccines and IL-12 on DNA vaccines are showing promising results *(6, 7)*.

At least seven candidate TB vaccines and their combinations have entered human clinical trials and are aimed at replacing or improving existing vaccination and treatment strategies for TB. Attenuated *M. tuberculosis* and a combination of BCG+rAg85A have been proposed to replace BCG for vaccination in children. Several vaccine strategies, using either a live vaccinia vector expressing Ag85A, heat inactivated *M. vaccae* or fusion TB protein, are currently being evaluated for their capacity to prevent TB infection. Other vaccine approaches are aiming at boosting BCG efficacy in adults or enhancing TB chemotherapy efficacy *(8)*.

The Korean TB vaccine research programme, under the responsibility of five national clinical research centres, is pursuing various types of vaccine approaches, including: recombinant BCG (Korean Institute of Tuberculosis); CFP & Triton-X soluble proteins (Choongnam University), DNA vaccines, adenovirus vector and IL-12 (Pohang University); DNA vaccines and cytokines (Seoul National University); gene "knock out" in mycobacteria (Youngnam University), peptides, recombinant proteins and recombinant BCG (Yonsei University).

1.3 AIDS: The Asian epidemiological situation *(Swarup Sarkar)*

The HIV/AIDS pandemic continues its accelerated spread. By the end of the year 2002, there were more than 42 million people living with HIV/AIDS. In 2002 alone there were 5 million new HIV infections and 3.1 million deaths due to HIV/AIDS. Despite well documented and successful HIV prevention programmes in a few countries, the epidemic in Asian and Pacific countries continues to steadily spread in the region and has contributed up to 7.2 million cases to the global number of HIV/AIDS cases. Over the past two years the situation has changed rapidly in several parts of the region, with annual incidence reaching close to one million new infections every year. The world's highest populated countries, such as China and India, are experiencing serious, localized epidemics affecting many millions of people, although the prevalence rate data look relatively small (approximately less than 1%) and do not provide a realistic picture of the situation.

The HIV/AIDS epidemic in the region is fuelled by high-risk factors and vulnerability of large populations with regard to HIV infection. Throughout the region, drug injection has become a leading cause of HIV transmission, resulting in high HIV prevalence. In some parts of India, Myanmar, Nepal, and Thailand, the HIV prevalence among injecting drug users is as high as 50%. High rates of needle sharing have been documented in Bangladesh and Viet Nam, which is also linked with commercial sex trade. Increasing prevalence rates have been documented among sex workers in China, Indonesia and Viet Nam.

Despite the sweeping epidemics in the region, the populations at large have minimum access to services provided by prevention and treatment programmes. In order to sustain and further strengthen national AIDS control programmes there is an increasing need for sustainable sources of high-level investment. The development of a safe, effective and affordable vaccine suitable for use in Asia and the Pacific will undoubtedly contribute to a solution of this health crisis in the region.

1.4 Results of the first AIDS vaccine efficacy trial *(Don Francis)*

The results from the first HIV vaccine efficacy trial with rgp120BB' (VaxGen) candidate vaccine in Canada, the Netherlands and the United States of America have recently been published. Prior to this efficacy trial, the rgp120-based candidate vaccines underwent intensive evaluation in all phases of preclinical studies, as well as in phase I and II human trials conducted mostly in the USA and Thailand. These studies demonstrated that the rgp120B candidate vaccines were able to protect chimpanzees from HIV infection. The subsequent phase I and II trials using a bivalent form (AIDSVAX B/B) of the candidate vaccine have also demonstrated its safety and immunogenicity.

The first HIV vaccine efficacy phase III trial was initiated in June 1998, using a bivalent rgp120BB'[MN+GNE8] candidate vaccine conjugated with alum. The trial had a multicentre, placebo-controlled, double-blind randomized (vaccine : placebo, 2 : 1) design. The trial enrolled 5417 volunteers from 61 sites in Canada, the Netherlands and the USA, including 5109 non drug-injecting men who have sex with men (MSM) and 308 women at heterosexual risk. The majority of men participating in the trial were white (86.3%) and women belonged mostly to the non-white population (70.5%). Immunization included seven doses given at 0, 1, 6, 12, 18, 24 and 30 months.

The results of this trial showed that the vaccine was well tolerated and induced specific humoral responses. It was demonstrated that the trial was well controlled and randomized and well conducted. No evidence was found for enhanced susceptibility to infection or increased progression to disease in vaccinees with concurrent HIV infections. Self-reported baseline risk behaviour correlated with infection rate: HIV infection occurred in 9.3% of 3006 volunteers with high-risk behaviour versus 3.7% of 2397 with lower risk.

The primary end-point for vaccine efficacy (VE) was defined as risk of HIV infection in vaccine recipients compared to risk in placebo recipients expressed as ([1-relative risk] x 100%). The secondary end-point in this trial was defined by reduction of viraemia in vaccinees or time to starting antiretroviral treatment in vaccinees as compared to the placebo group. The overall results of this trial did not demonstrate significant vaccine efficacy, which was calculated at 3.2% level. However, further subset analysis discovered that vaccine efficacy varied significantly in different race and gender groups, increasing to 50.6% in a "non-white" group, 77.6% in Afro-Americans and up to 86.5% in women. Also, estimates of vaccine efficacy, overall and within subgroups, were significantly higher in the higher risk group compared to lower risk. Multivariate analysis, controlling age, education, geographic region and risk behaviour, showed similar VE estimates.

A detailed analysis of data generated by this trial is under way, which aims to explain differences between different treatment arms, and examines both host and virus-related factors (levels of neutralizing antibodies, sieve analysis, etc.). Final analysis of these data may justify further research and clinical trials to confirm or clarify the indicative vaccine efficacy detected in this trial.

1.5 EDCTP: A new partnership to develop vaccines against AIDS, TB and malaria *(Fred Binka)*

HIV/AIDS, malaria and tuberculosis represent a major threat to global health. These 3 diseases are causing more than 5 million deaths every year, with 95% of this mortality occurring in the developing world. No vaccines have been successfully developed for HIV/AIDS and malaria, while BCG-based vaccines are far from being perfect for prevention and control purposes. The development of these much needed vaccines for marketing mostly in less developed countries is not perceived as high priority by the pharmaceutical industry, and there is an urgent need to establish public funds for investment in this neglected area. In response to this emergency, the European Commission (EC) is committed to providing a broad and comprehensive support in a wide range of policy areas, including trade, development and research.

In the area of vaccines, the EC has identified and addressed two challenges, including:

1) support of research projects for the development of new promising vaccine approaches and candidate vaccines, and their accelerated progress through preclinical development and human testing in early phase I trials; and
2) development of a programme to support phase II and III clinical trials in Africa.

The latter challenge is being addressed by a newly created European and Developing Countries Clinical Trials Partnership (EDCTP) by the EC Directorate of Research, Health Directorate, F3 unit: Poverty-related Diseases.

The EDCTP is being developed as a long-term initiative (10–20 years), with shared ownership of European and developing countries, and a dynamic structure with balanced involvement of different stakeholders, including European and developing countries, the European Commission, industry and international organizations.

The overall aims of the EDCTP are to:

- increase the effectiveness of Europe's investment in clinical trials for interventions against poverty-related diseases;
- attract more resources for the development of these interventions;
- accelerate the development of candidate products and their processing through the developmental pipeline;
- accelerate the development of capacity and capability of developing countries in testing efficacy of these interventions.

The interventions to be tested against HIV/AIDS, TB and malaria include the following:

- new drugs and combination therapies;
- vaccines;
- diagnostics;
- microbicides against HIV; and
- other commodities for malaria prevention, such as insecticide-treated bed nets.

It has been stated that EDCTP should focus only on research needs, and that it should not use its funds for other purposes, such as alleviating poverty, improving health care systems and providing treatment, funds for which should be sought from other relevant programmes.

An overall budget in the region of 600 million for five years will be supported by EU countries, the 6th Framework Programme for Research and the private sector (foundations and industry). The activities will be supervised by an EDCTP partnership board where the EC, European States, developing-country scientists and private industry will be represented.

In 10 years from now the success of EDCTP will be assessed on the basis of:

- the development of a package of interventions to control poverty-related diseases which can be deployed effectively;
- a number of independent African scientists or a team of scientists competing successfully within the EU and other international grant programmes to conduct clinical trials in Africa; and
- a number of African institutions capable of initiating phase I and phase II clinical trials on poverty-related diseases with African scientists as principal investigators.

2. The GAVI vaccine R&D projects

2.1 Update on GAVI activities *(Abdallah Bchir)*

The GAVI goals focus on three areas: (1) reversing the downward trend in immunization coverage that has been seen in recent years, (2) reducing the delay in the introduction of new vaccines, such as hepatitis B vaccine and *Haemophilus influenzae* type b (Hib) conjugate, and (3) saving lives by accelerating the development and introduction of the newest vaccines that are currently in late-stage development, such as multivalent pneumococcal conjugate and rotavirus vaccines.

Progress has been made with the Vaccine Fund, which has to date approved immunization support for 68 of the 75 eligible countries. Two additional countries are in the submission/review process and five countries have yet to apply. Achievements at the country level have also progressed with an additional three million children receiving full DTP3 coverage in 2001. An analysis of the disbursement of funds and resources has shown that 77% of the funds have reached the districts and regions.

This success is driven by performance-based grants from the Vaccine Fund, which allow countries to set their own targets to increase immunization coverage, and to decide on how to utilize the funds donated. In addition, countries are rewarded for the number of additional children immunized, this system being subject to an external audit and verification process. Eight countries are eligible for these reward incentives in 2003.

Despite the inroads made, some major challenges remain. These include:

- financial sustainability after the five-year support period;
- vaccine availability; and
- barriers to vaccine coverage.

Twelve countries have had to review their financial sustainability plans, with eight requiring minor revision and four major revisions. However, of extreme concern is the reduced availability of vaccine. Indeed the availability of DTP has dropped dramatically over the last few years. Finally, there remain many barriers to increased vaccine coverage, which include lack of political will and commitment by countries, the absence of physical infrastructures and equipment to deliver the vaccines, the lack of monitoring systems to evaluate disease burden, poor immunization performance and planning, and the gap in human resources for improved immunization delivery and social mobilization.

GAVI is working closely with WHO to help countries that have not yet applied for support, or that require assistance with their financial sustainability plans.

2.2 Meningococcal vaccines *(Luis Jodar)*

Epidemic meningitis is associated with great morbidity and mortality in sub-Saharan Africa, and across the "meningitis belt", with an estimated 250 million people at risk. Children and young adults up to 29 years of age constitute the target-age group at risk. The Meningitis Vaccine Project (MVP) is a partnership between WHO and the Program for Appropriate Technology in Health (PATH), funded by the Bill and Melinda Gates Foundation, and developed after all the major manufacturers had suspended their development projects of group A meningococcal conjugate vaccines. Although the primary objective of the MVP is to develop a safe and efficacious vaccine against meningitis, three guiding principles have been defined: (1) the project is about public health impact and not simply about making a vaccine available, and thus (2) decisions about the future candidate vaccine are linked to introduction strategies and likely financial constraints, and (3) African public health officials are closely involved with the MVP.

Discussions with African public health officials have highlighted that the most important factor in the introduction of the vaccine is cost. The meningitis-belt countries are amongst the poorest in the world and the vaccine price should therefore not exceed US$ 0.50 per dose.

Despite the outbreak in 2001–2002 of a serogroup W135 *N. meningitidis* strain in Burkina Faso, it was decided to move ahead with the development of a monovalent A vaccine candidate, with a backup strategy allowing the development of an A/W vaccine. Careful monitoring of epidemic meningitis will help to determine if W135 will become a major strain in the region. The main reason for the development of a monovalent A vaccine is that the vast majority of meningococcal isolates in Africa are still type A and that the lower price of a monovalent vaccine will allow the greatest public health impact.

An ambitious timetable of clinical trials has been developed which anticipates the production of clinical lots of the vaccine in 2004, with phase I and II trials starting by 2005. It is hoped the vaccine could be licensed for use by 2008.

The MVP faces both challenges and opportunities. Challenges include the high risk of the project, technical and managerial complexities and currently a lack of mechanisms to ensure long-term large-scale and sustainable production of the vaccine. Opportunities certainly include the low cost of the vaccine, the acceptable although ambitious timelines and the possibility of developing a tailor-made vaccine for Africa.

2.3 Rotavirus vaccines *(Irene Perez-Schael)*

The global burden of morbidity and mortality of rotavirus infection is well recognized and an estimated 480 000–600 000 deaths in young children <5 years of age are attributable to rotavirus annually. In addition, rotavirus is responsible for approximately 3–5% of all paediatric hospital admissions and 40–75% of hospitalized diarrhoeal episodes. The dehydrating nature of rotavirus infection occurs predominately in infants under 12 months of age. Due to these factors, the development of a rotavirus vaccine has been prioritized for the past two decades.

Two rotavirus vaccines are currently licensed – the reassortant rhesus rotavirus (RotaShield) in the USA, and a lamb rotavirus strain in China, which is used only in this country. However, the reported association of the RotaShield vaccine with intussusception has resulted in the company withdrawing this vaccine from the market. Two other live, oral-attenuated vaccines are in late stage clinical development. These include the bovine reassortant vaccine developed by Merck and the human monovalent vaccine being developed by GSK.

The human monovalent rotavirus strain is currently under clinical evaluation in three Latin-American countries and in Europe. Recent results of these clinical trials have indicated good immunogenicity of the vaccine as well as good protective efficacy against severe rotavirus disease, comparable with those achieved with RotaShield. Large phase III safety and efficacy trials have started in 12 Latin American countries.

The bovine reassortant vaccine of Merck is a pentavalent vaccine containing the human rotavirus VP7 genes for serotypes G1–G4 and the VP4 P1a[8] gene. This vaccine candidate has also shown good immunogenicity and protective efficacy in a clinical trial carried out in Finland. A large phase III safety and efficacy trial is currently under way in the USA and Europe.

Finally, there are several other rotavirus vaccine candidates under development including other bovine reassortant strains, neonatal human strains and virus-like particles.

2.4 Rotavirus Accelerated Development and Introduction Plan (ADIP) *(John Wecker)*

The GAVI Rotavirus ADIP has recently been established at PATH in Seattle under the directorship of Dr John Wecker. The primary objective of the ADIP is to reduce the long delay between development and licensure of a new vaccine and its implementation in countries where it is most needed. Two main contributors to this delay are believed to be uncertain supply of vaccine by vaccine producers and uncertain demand for the vaccine by countries. The Rotavirus ADIP is intended to break this "vicious circle".

To address the issue of vaccine supply, multiple vaccine candidates should be developed. A potential objective of the Rotavirus ADIP might therefore be to engage the big pharmaceutical companies (such as GSK and Merck, who are both developing vaccine candidates), to encourage the efforts of local manufacturers such as Bharat or BioFarma, and to consider new partnerships with other candidate vaccine strains.

To address the issue of demand, it is necessary for the Rotavirus ADIP to establish the value of the vaccine and to communicate that value to policy and decision-makers. Thus the Rotavirus ADIP will engage, with strategic partners, in burden of disease surveillance to demonstrate the need and create an awareness of and demand for the vaccine. Secondly, the Rotavirus ADIP will support clinical evaluation of the vaccine candidates in developing countries to demonstrate the effectiveness of the vaccine. In addition, the Rotavirus ADIP will undertake demand forecasting in collaboration with the private and the public sectors.

Finally, Rotavirus ADIP intends to complement activities already in place with other public sector partners. The ADIP will not make policy, but enable policy decision-making; it will not perform research and development *per se*, but engage with other partners to support R&D efforts; it will not procure vaccine for countries but invest in the process whereby these vaccines can become available. Importantly, the Rotavirus ADIP is not there to replace other funds and donors, but to complement these activities.

2.5 Pneumococcal vaccines *(Rosanna Lagos)*

Streptococcus pneumoniae disease remains a major cause of childhood mortality in developing countries, and is associated with 3.5 million deaths annually. Over half of these occur in young children <5 years of age. The expectations of paediatric vaccination against *S. pneumoniae* are, therefore, to prevent life-threatening pneumococcal diseases (invasive disease and pneumonia), to reduce highly prevalent but less severe diseases, such as acute otitis media, and to reduce carriage and transmission of *S. pneumoniae* and the spread of antibiotic resistant strains of *S. pneumoniae.*

For the development of pneumococcal conjugate vaccines, the capsular polysaccharide is considered a critical virulence factor and antibodies against this antigen have been shown to be protective. However, there are more than 90 capsular polysaccharide serotypes and the protection is serotype specific, which means that the vaccines should contain multiple polysaccharides. Fortunately 7–12 serotypes account for most paediatric invasive infections worldwide; this has led to the development of polyvalent conjugate vaccines.

The efficacy of the 7-valent vaccine against invasive disease has been shown to be very high (>95%) and importantly, strain replacement with non-vaccine serotypes did not occur in invasive disease. Furthermore, in Finland, the 7-valent vaccine showed 34% efficacy against all otitis media and 57% protection against otitis media caused by strains included in the vaccine. Finally, the 9-valent vaccine candidate has shown good protective efficacy against invasive disease in HIV-positive (65%) and HIV-negative (83%) infants in South Africa.

In conclusion, studies with pneumococcal conjugate vaccines have shown an impressive reduction in invasive pneumococcal disease with no evidence of an increase in invasive disease with non-vaccine serotypes. There has been a reduction of carriage of vaccine serotypes and of antibiotic resistant strains, although there has been a trend towards strain replacement with non-vaccine serotypes. In addition, a moderate reduction in acute otitis media caused by the vaccine strains has been observed with some evidence of strain replacement.

2.6 Pneumococcal Accelerated Development and Introduction Plan *(Orin Levine)*

The GAVI Pneumococcus Accelerated Development and Introduction Plan (Pneumo-ADIP) was recently established and based at the Johns Hopkins Bloomberg School of Public Health in Baltimore under the direction of Dr Orin Levine. The mission of the Pneumo-ADIP is to accelerate the evaluation of and access to new life-saving pneumococcal vaccines for children in the world's poorest countries. The Pneumo-ADIP is structured around three major objectives:

- to establish the value;
- to communicate the value; and
- to deliver the value of the pneumococcal vaccines, with a team member responsible for each element.

Similar to the Rotavirus ADIP, the Pneumo-ADIP will address issues of vaccine supply and demand.

The role of the Pneumo-ADIP is to generate evidence-based decision-making on pneumococcal vaccine introduction both globally (investment case for the GAVI Board) and locally to support partner efforts at the country level. A second role is to facilitate ongoing efforts by creating a communication strategy to enhance policy decision from the research evidence and to link unconnected activities in countries and regions. Finally, the Pneumo-ADIP can play a role in strategy development to link demand targets and supply or financing resources.

The Pneumo-ADIP is different from other initiatives because it is target driven, and milestone-based in collaboration with manufacturers, with a focused operational team to ensure implementation.

2.7 Agenda for GAVI technology R&D *(Aldo Tagliabue)*

The GAVI R&D New Technologies Working Group established in 2000, was given the task of examining recently developed technologies with the objective of improving routine immunization programmes. Three technologies have been selected for further research and support and are discussed below.

Sugar glassification

The sugar-glass preservation of specific vaccines, such as currently liquid bacterial vaccines, would render them thermostable, which could help to diminish dependence on the costly and difficult to maintain cold chain. This in turn may reduce the wastage due to temperature damage of these vaccines. An added benefit of this would be the lower costs of shipping and storage of the vaccine.

The strategy developed for this new technology includes R&D on vaccine stability, facilitating public/private partnerships for the development and production, and ensuring access to intellectual property rights.

Oral fluid antibody assays

New methods are required, besides the data quality audit, to monitor immunization coverage. A rapid, inexpensive assay to detect tetanus antitoxin antibodies in oral fluids at levels that are considered protective might be of great value. These non-invasive methods will utilize oral fluid (which is a mixture of IgG-rich crevicular fluid [derived by transudation from serum] and IgA-rich saliva) to measure levels of tetanus antitoxin in specimens from older infants and toddlers in surveys. In this way the performance of immunization services in different regions of a country can be objectively assessed.

An extensive validation process will be required in which levels of IgG tetanus antitoxin are compared in serum and oral fluids collected from the same children. In addition, different saliva collection devices will require evaluation for optimal specimen collection.

Needle de-fanging devices

Immunization accounts for 10% of all injections globally and thus presents a major problem with needle-stick injuries and re-use of needles. It was proposed to evaluate the introduction of simple devices to "de-fang" needles after use. Nevertheless, at present the advantage of de-fangers remains theoretical. Well-designed controlled studies are required in developing countries to evaluate the feasibility of the introduction of such devices and their effectiveness. The costs are estimated to fall between US$ 50 and US$ 300 per unit and an estimated 125 million such devices may be required. The lifetime of a unit is currently estimated to be approximately 25 000 de-fanging operations before it would need to be replaced.

2.8 The Measles Aerosol Project *(Ana Maria Henao-Restrepo)*

In the 40+ years since measles vaccine was licensed, it has had an excellent safety record with proven effectiveness in preventing measles morbidity and mortality. However, there are an estimated 500 000 measles deaths per year among children <5 years. The vaccine is heat stable before reconstitution and has a low cost. The Measles Aerosol Project (MAP) has been initiated to consider alternative, easier-to-administer delivery systems for measles vaccine, which should also address issues related to the safety of delivery and the reduction of the safety burden of disposal of needles. Therefore, the objective of the MAP is to develop and license at least one measles vaccine delivery device for the respiratory delivery of the vaccine. Indeed, measles aerosol immunization has shown good safety, is immunogenic and induces an immune response in >80% of infants aged ≥9 months and >10% of preschool and school children. One study in Mexico showed a lower attack rate in those children immunized by aerosol, than by the subcutaneous route.

The major elements of the project include:

- a product file that takes into account current and future directions of the measles programme;
- a targeted workplan with defined milestones and a fast-track regulatory pathway,
- a budget that covers the key activities for licensure, and
- established management and expert advice arrangements to drive the implementation plan.

Current options being considered include nasal spray systems, ultrasonic nebulizers and jet nebulizers. Current studies involve defining the optimal particle size, output flow and consistency of the administration route, measurement of the size and distribution of live viral particles through the devices, and characterization of the classical Mexican aerosol device. Animal studies in cynomologous macaques have shown good safety and efficacy of the aerosol administration. Further studies are planned to examine toxicology. Phase I trials are planned in India, where the initial focus will be on jet nebulizers.

Safety evaluation has received high priority in the MAP. A number of potential safety concerns have been identified (including sensitization of the respiratory tract, safety in HIV-infected individuals, spread of measles virus to the central nervous system, environmental risk, and contamination and cross infection). Ad hoc expert groups have been formed to review the evidence related to each of the safety concerns and to develop optimal methods for their assessment during the animal studies and clinical trials.

Finally, the regulatory pathways have been defined and key activities required for licensure are ongoing. MAP is on track for product delivery by 2007, notwithstanding the technical challenges that remain.

3. Keynote address: strategy of the Bill and Melinda Gates Foundation towards the prevention of infectious diseases

(Regina Rabinovich)

The Bill and Melinda Gates Foundation was founded in January 2000. It has assets of US$ 24 billion, has awarded US$ 5.95 billion in grants and has four major programmes: Global Health, Education, Pacific Northwest and Libraries.

The Global Health Program of the Foundation recognizes the disparity between the enormous burden of disease in developing countries and the limited resources available to fight against it. The situation wherein only 10% of the research budget is spent on diseases that cause 90% of global illness and death results in a global health problem that undermines economic development, as well as social and political stability.

The Foundation's approach is to try to reduce this health gap between the rich and poor countries. However, this requires financial commitment to match the scale of the crisis, targeted resources and proof of the scalability of the chosen interventions.

The fundamental concepts underlying the Foundation's strategy are as follows:

1) to bring innovation into context for people in developing countries;
2) to provide evidence that what is proposed can be accomplished;
3) to focus on results, which should be evaluated and accounted for;
4) to avoid replacement;
5) to promote new partnerships; and
6) to build long-term human and institutional capacity.

The burden from infectious diseases is an enormous problem. The lack of access to relatively simple interventions that could prevent death, the disparity between the problems and the amount spent on research (only 20 out of 1500 drugs approved in the last 25 years address problems in the poorest countries), the multiple barriers to development of needed drugs and vaccines, the unclear future funding for product development partnerships, the "brain drain" of health care professionals from endemic countries and the tension between sector-wide approaches and disease-specific programmes contribute to the problem. To tackle this problem, essential new drugs, vaccines and diagnostics must be made available where they are needed the most.

Human and financial resources need to be mobilized and long-term human capacity built up and innovative financing mechanisms developed to ensure continued access to the health interventions.

The Foundation's strategy for tackling this problem is built around its three basic elements. The **"build it"** strategy has worked and justified investment in the development of essential drugs through the Global Alliance for TB Drug Development, Medicines for Malaria Venture and the Novel Drug for Trypanosomiasis projects and in the development of new vaccines through the Malaria Vaccine Initiative, the International AIDS Vaccine Initiative and the Vaccine for Leishmaniasis project. To **"prove it"**, the foundation has worked in partnership with a number of alliances and initiatives to evaluate the impact of interventions. The Vaccine Fund, GAVI, the Polio Eradication Project and the Global Fund to Fight AIDS, TB and Malaria are examples of the Foundation's programmes to **"sustain it"**.

The malaria programme of the Foundation is an example of how the three basic elements are being undertaken in parallel. New tools for the control of malaria are being developed through the Medicines for Malaria Venture, the Malaria Vaccines Initiative, the Seattle Biomed Research Institute and the Vector Control Concept. New innovative approaches are being tested in the field through the Intermittent Presumptive Therapy in Infants project and the Gates Malaria Programme. Scaling of sustainable interventions is being carried out through the Global Fund for AIDS, TB and Malaria.

Procedures and mechanisms

The Bill and Melinda Gates Foundation receives close to 25 000 grant submissions per year. The procedure to apply for a grant is either a direct response to a formal call for proposals or a letter of inquiry (LOI) for a proposal on a subject that aligns with one of the Foundation's grant-making priorities. If the LOI is accepted, programme staff will solicit a grant proposal for further review. The programme officer assigned will provide proposal guidelines as well as a budget spreadsheet to assist in developing the proposal. The Foundation will support innovative solutions that accelerate development and application and improve sustainability of health interventions that address the diseases and health conditions within their scope. Funding is focused on projects that will have a potential long-term impact on public health in developing countries and that align with strategic approaches of the Foundation: build, prove, and sustain. All submissions are subjected to external review.

4. Regulatory and ethical issues in the development and introduction of new vaccines

4.1 The ethics of vaccine clinical trials in paediatric populations of developing countries *(Claudio Lanata)*

A meeting was convened by WHO in November 2002 in Accra, Ghana, to analyse the specific ethical aspects of vaccine clinical trials in paediatric populations of developing countries. Indeed, these children carry a disproportionately high burden of disease and vaccines are urgently needed to protect the children, but trials to evaluate these vaccines are complicated by the existing poverty and social issues in these countries, as well as by the lack of regulatory mechanisms and ethics committee capacity to ensure high ethical standards in the conduct of these much-needed trials. While guidelines on biomedical ethics are available, they are sometimes inadequate in meeting the particular needs of vaccine trials in children in developing countries.

The meeting was convened to identify ethical issues, explore solutions and provide guidance to local ethics committees and sponsoring bodies. A number of issues were identified during the meeting. These included:

1) The moral imperative to conduct necessary vaccine trials in children in developing countries that carry the highest burden of vaccine-preventable diseases, and the necessity to balance the urgent need to conduct trials with the need to ensure high scientific and ethical standards.
2) The particular vulnerability of children in developing countries who are socioeconomically and medically disadvantaged, are unable to provide informed consent and may be subject to harmful cultural and gender norms, and thus to exploitation.
3) The need to maximize benefits and minimize risks to the child participants and to obtain community approval for the trials.
4) Issues related to the requirement for clinical equipoise at the individual level, and to the choice of the control/comparator.
5) The recognition that improved survival may be the most powerful outcome to trigger public health action, yet one that raises specific ethical issues related to the standard of care provided to trial participants, which is often not optimal in many developing country settings.
6) The timing for moving trials in industrialized countries to developing countries, the de-escalation strategy from trials in adults to children in the target age group, and the complex ethical issues related to the participation of adolescents in trials, especially those where maintaining confidentiality is important, e.g. trials of HIV vaccine.

7) The difficulties in ensuring that consent is truly "informed"; the balance between providing improved medical care while not allowing this to be an inducement for participation; the tension between keeping the language and contents of the consent form understandable and the need to meet legal and regulatory requirements. It was noted that cultural differences may result in conflict between ethics committees of the sponsoring agency and local ethics committees.

8) Issues related to trial oversight, the required regulatory framework, compensation and insurance and access to the product undergoing trial if it is shown to be beneficial.

Each of these is a complex issue, often with no clear-cut answers. The objective of the meeting was to produce a report that provides an open discussion of the issues, provides possible solutions and illustrates the issues with examples from specific trials where these issues were encountered and dealt with. This document was published in December 2003 on the web site of the WHO Initiative for Vaccine Research.

4.2 Prequalification of new vaccines for global use *(Nora Dellepiane)*

The goal of WHO is to ensure that 100% of vaccines used in immunization programmes are of assured quality. Vaccines of assured quality are defined as those produced in a country with a national regulatory authority (NRA) that is both functional and independent of the manufacturers and where the importing country has the capacity to provide the required regulatory oversight. This requires that all countries have an NRA that is able to perform the required critical regulatory functions.

WHO prescribes six critical regulatory functions, of which the NRA must perform two or more depending on whether the country produces vaccine indigenously or procures it by itself or through UN agencies. These are:

1) a published set of requirements for licensing;

2) surveillance for vaccine field performance;

3) a system of lot release;

4) use of the control laboratory, as required;

5) regular inspections for GMP;

6) evaluation of clinical performance for clinical efficacy and safety.

Of these, the first two are required in countries where vaccines are procured through UN agencies, the first four for those who procure vaccines directly and all six for those countries that produce vaccines indigenously. Currently, of the 192 Member States of the UN, 83 procure vaccines through UN agencies, 61 directly from manufacturers and 48 produce vaccine indigenously. The purpose of the prequalification process is to provide UN agencies with an independent opinion on the quality, safety and efficacy of the vaccines they purchase, to ensure that the candidate vaccines are suitable for the needs of the programmes in targeted countries and to guarantee continuing compliance with established standards of quality. This process affects both the vaccine-producing countries as well as those procuring vaccines through UN agencies.

The prequalification is achieved through the following steps:

1) assessment of the NRA using the established indicators;
2) review of the product summary file;
3) consistency testing of the final product samples; and
4) a site visit to the manufacturing facility jointly with the NRA.

If all the steps in the process are satisfactorily fulfilled, the vaccine is accepted for UN purchase and posted on the web-based list of WHO prequalified vaccines. The approval is for a period of two years, at which time a reassessment is carried out. Though the pre-qualification status of the vaccine is reviewed every two years, NRA assessment may take place more frequently, as required.

In recent years, there has been a gradual evolution in the list of prequalified vaccines, with an increasing amount of the traditional Expanded Programme on Immunization (EPI) vaccines being produced by manufacturers in developing countries or countries in transition (DC/TC), and the new or underutilized vaccines (e.g. Hib and hepatitis B) and combination vaccines being produced by industrialized country manufacturers. With the increasing demand for newer and underutilized vaccines and combinations from DC/TC, there will be a need for these demands to be met by developing country manufacturers. Such vaccines may be fully produced from seed in DC/TC, produced in partnership with an industrialized country manufacturer or through purchase of prequalified bulk with finishing and filling done in DC/TC. This move will require the development of new regulatory pathways and training to strengthen and maintain the capacity of NRAs in DC/TC. Several regulatory mechanisms are being considered to meet this need and a programme of NRA assessment, training and ongoing monitoring and evaluation has been developed and implemented through a Global Training Network.

4.3 The EMEA perspective *(Roland Dobbelaer)*

Certain vaccines are needed only in certain countries because of epidemiological, socioeconomic and logistic conditions and are often produced and exported by manufacturers in the EU. Many such importing countries may depend solely on the NRA in the country of manufacture even though the country itself is not using it, e.g. DTP vaccine containing wholecell pertussis (DTwP), oral polio vaccine (OPV) and multidose thiomersal-containing formulations. Currently, the EU has three licensing procedures: (1) licensure in one EU country, which will no longer be the case for newer vaccines; (2) mutual recognition or a decentralized procedure within the EU; and (3) a centralized procedure, which will apply to all new vaccines and recombinant vaccines.

In order to improve transparency and surveillance of the market, the EU proposes a change in practice. In the revised legislation, authorizations will cease to exist if the product is not put on the market in the EU within two or three years. This means that licensure of products that are not marketed locally may not be possible. A possible solution would be an amendment to the legislation allowing the European Medicines Evaluation Agency (EMEA) to give a scientific opinion in cooperation with WHO for the assessment of certain medicinal products for human use intended solely for markets outside the European Community. These would be subject to the principle

that the same standards would be applied as are applied in the EU, that application would be accepted only with the agreement of WHO and that vaccines would be assessed with WHO participation in the process. Under this process, the EMEA would review the dossier, deliver its opinion, and carry out the normal batch release. WHO would be represented in the Committee for Proprietary Medicinal Products (CPMP) to describe and help analyse specific conditions (e.g. risk/benefit related to the conditions in the country of destination). Pharmacovigilance and follow-up would be carried out by the NRA of the country of destination.

This legislation is still being debated and a decision is expected in 2004. This process would also have to be agreed upon by WHO, EU and non-EU countries of destination. In addition, the procedure for identifying the products that would be processed under this provision also needs to be defined.

4.4 The Food and Drug Administration (FDA) perspective
(Michael Brennan)

Vaccine development is a global challenge. The US FDA acknowledges that infectious diseases do not recognize geographical borders and that although the mandate of NRAs is the safety of the people in their countries, the FDA also needs to be involved at a global level.

At the FDA, the Center for Biologics Evaluation and Research (CBER) is involved in a number of international activities. These include serving on WHO/PAHO programmes, preparing reference reagents, and participating in WHO training and inspection programmes as well as in the International Conference on Harmonisation.

The variety of vaccine types, e.g. DNA, recombinant, peptide, live attenuated, new adjuvants, new delivery systems and combination vaccines poses new challenges for regulatory agencies. In the area of TB alone, all the above types of vaccine are being evaluated. Thus, the staff of the FDA have to be familiar with the state of the art technologies.

A number of common questions arise in vaccine development. There are no clear answers to many of them and each may require a case-by-case answer. In order to address the international regulatory challenges a number of factors are required. They include:

- more flexible regulatory guidance;
- improved interaction between developers and regulators in early phases of development, and more GMP-quality facilities to produce and characterize vaccines even in preclinical phases of evaluation;
- standardization of regulatory practices, e.g. for DNA vaccines;
- mechanisms for assessing ri/bebenefit in different epidemiological settings; and
- continued evaluation of import/export polices.

The US FDA aims to assist WHO and other international initiatives in regulatory strategies that help accelerate the uptake of vaccines in the developing world without compromising vaccine safety and effectiveness assessment.

4.5 Perspective of the Korean NRA *(Yeowon Sohn)*

The origins of the Korean FDA (KFDA) can be traced back to the establishment of the National Chemistry Laboratory in 1945. In 1998 the KFDA was established under the Ministry of Health and Welfare, and in 1998 it was reorganized and elevated to the status of an independent agency and included the National Institute of Toxicological Research (NITR). It has six regional offices, employing a total of 329 staff, including 58 researchers and 31 technical staff.

The mission of the KFDA is "to protect and enhance the public health through the regulation of foods, food additives, human drugs, biological products, medical devices and cosmetics". The Biologics Department in the Office of Safety Evaluation is responsible for vaccines. It comprises four divisions – bacterial products, viral products, biotechnology and blood products.

The Biologics Department, together with the NITR, is responsible for licensing, lot release, laboratory access, GMP inspection and clinical evaluation of vaccines. Together with the Korean National Institute of Health it conducts AEFI surveillance.

The future vision of the KFDA is to establish a Centre for Korean Standards of Biologicals, to play a contributory role as a Centre for Regional Biological Standards and be recognized by WHO as such, including as a WHO International Training Centre. To achieve this vision, KFDA is constructing a new laboratory facility, establishing national standards for biologics, and establishing a Global Training Network centre. In order to strengthen the functioning of the National Control Laboratory, KFDA has developed a Laboratory Information Management System (LIMS), a Laboratory Automation System (LAS) and a Data Information Management System (DIMS).

In conclusion, KFDA's objectives are to implement science-based regulations, compatible with international standards, and to facilitate domestic and global vaccine development.

5. Cancer vaccines

5.1 Epidemiology of *Helicobacter pylori* and gastric cancer

(Giuseppe del Giudice on behalf of David Forman)

Despite a general and sharp decline, stomach cancer remains the second cause of cancer-related death worldwide, with 647 000 deaths per year representing 10% of the global cancer mortality. It is associated with high morbidity and poor survival, with the majority of cases and deaths reported in developing countries (543 000 cases and 416 000 deaths, as compared to 333 000 cases and nearly 230 000 deaths in industrialized countries each year). The highest incidence rates are reported in South America, South-East Asia and Eastern Europe. China, Japan and Korea report the highest incidence rates in males with 100, 60 and 40 cases per 100 000 and cumulative risk to 75 years of 19.6%, 11.1% and 4.9% respectively, as compared to 1.5% reported for England *(9)*.

The histopathological sequence of events in the gastric epithelium (inducing a superficial gastritis or atrophic gastritis) has been described since 1975 by Correa and collaborators, and can be initiated by high salt diets and irritants, while concomitantly low vitamin C and carotenoids as well as presence of nitroso compounds can lead to epithelial metaplasias, dysplasia and cancer. In 1983 Marshall found that the curved bacillus in human gastric epithelia was associated with peptic ulcer and gastric cancer. *Helicobacter pylori* are gram negative bacilli, isolated almost exclusively from human gastric epithelium, which evades host immune responses, giving rise to chronic inflammatory reactions. In 1994, the International Agency for Research on Cancer categorized *Helicobacter pylori* as a group 1 carcinogenic agent. It is the most common bacterial infection worldwide, ubiquitous in most developing countries, primarily acquired in childhood, and it is rarely self-limiting (except in children). Infection can be treated effectively by antibiotics, and eradication regimes are complex but relatively successful.

Meta-analysis of results from 12 prospective studies has provided evidence for the association between *H. pylori* infection and gastric cancer *(10)* with an attributable fraction of 65–80%, equivalent to more than 400 000 annual cases worldwide. The question arises as to why 2% of *H. pylori*-infected subjects develop gastric cancer. Different bacterial strains showing increasing risk for cancer induction, different host responses to infection, and different exposure to other environmental factors are among some of the reasons *(11, 12, 13).* Can prevention of *H. pylori* infection decrease gastric cancer? To address this public health concern 11 randomized, long-term, intervention studies have started, most designed to analyse pre-cancerous end-points. Three studies

– two Chinese *(14, 15)* and one Japanese *(16)* – reported that treatment of *H. pylori* infections slowed down the progression of gastric atrophy. In conclusion, *H. pylori* is an important etiological agent for gastric cancer with a substantial attributable risk, and therefore population-based eradication of *H. pylori* may offer cost-effective means of preventing a cancer with considerable morbidity and mortality.

5.2 *Helicobacter pylori* vaccines against gastric cancer *(Giuseppe del Giudice)*

H. pylori infections can be treated by proton pump inhibitors or antibiotics for two to three weeks with over 90% efficacy in controlled trials. However, efficacy at the level of general practitioners is likely to be lower due to possible reinfections, poor compliance to the therapeutic schema, and increasing antibiotics resistance. An effective vaccine against *H. pylori* could overcome these drawbacks in preventing infection and reinfections and potentially eradicate this pathogen. Possible cost-effectiveness of vaccination has been favourably established in both developed and developing countries *(17).* Hence, three vaccine candidates have been tested in humans so far: recombinant urease as antigen combined with wild type LT, administered orally *(18, 19),* as well as urease expressed in *Salmonella* and administered orally *(20, 21),* both showing poor immunogenicity. Inactivated whole-cell extracts combined to LTR192G mutant, despite high immunogenicity, show no therapeutic efficacy *(22).*

A multi-component, pathogenesis-based approach to vaccine development has recently been undertaken, based on the combination of three antigenic components, namely the cytotoxin-associated gene A (CagA), cell vacuolation antigen (VacA) and neutrophil-activating protein (NAP). Prophylactic vaccination of mice and dogs (beagles) using each of these components, with and without adjuvants, showed that it is possible to elicit immune responses and 80% protection. Therefore, recombinant purified CagA/VacA/Nap vaccine candidate in alum was given intramuscularly to *H. pylori*-negative healthy adult volunteers in a randomized, controlled, single-blind, dose ranging study, conducted to establish its safety and immunogenicity profile. Results show significantly high antibody levels following immunization with either a low (10 mg) or a high (25 mg) dose at 0, 1, 4 months, as measured at month 5, with over 80% seroconversion rates. Proliferative responses and IFN-g production were present after immunization, particularly towards CagA. Adverse experiences such as erythema, induration and fever were low.

In conclusion, the multicomponent injectable *H. pylori* vaccine candidate formulated with alum adjuvant is safe and immunogenic. It will be crucial to establish its prophylactic efficacy in areas of high rates of *H. pylori* infection.

5.3 Overview of prevalence of human papillomavirus (HPV) infection – globally and in Thailand *(Saibua Chichareon)*

The incidence of cervical cancer worldwide is highest in some countries of Latin America, Africa and Asia, as compared to North America, Australia, Middle East, and some European countries. HPV was studied as the sexually transmitted etiological agent in cervical neoplasia in 1977, and in 1999 was established as the necessary cause of cervical cancer *(23).* The International Agency for Research on Cancer has started worldwide multicentre studies, including prevalence surveys and case-control studies, establishing the HPV type prevalence in the general population and in cancer cases respectively. In a series of publications, scientists have established that 57.6% of cervical cancers are attributable to HPV-16 infections, 14.1% to HPV-18, and 5.4% to HPV-45.

In the studied populations, the prevalence of HPV infection varies from 26.2% in Nigeria to 1.6% in Hanoi. The prevalence of HPV DNA by age follows different patterns, with some populations showing highest levels under 25 years, decreasing with age, such as in Argentina, Korea and Thailand, while others show increased prevalence in older ages, such as in Columbia and Mexico. Interestingly, in Thailand and Viet Nam there is a south-north difference in HPV prevalence, the city of Hanoi in North Viet Nam reporting low HPV prevalence (in all age groups studied: 1–3%), and the city of Ho Chi Minh in the south reporting high prevalence, particularly in young women under 25 years (22%), but declining with age. Similarly, the province of Lampang, in the north of Thailand reports high prevalence (15%), decreasing steadily with age, and the province of Songkla in the south reports moderate prevalence rates (7%) in both young and old, but lower in middle-aged women. In Thailand the overall HPV prevalence is 6.3% among women studied, and the most common types found are HPV types 16, 52 and 72. Despite geographical variations in HPV type distribution and prevalence, a good correlation between cervical cancer incidence and HPV prevalence among women aged 35–64 years has been established.

5.4 Clinical trials of HPV and cervical cancer vaccines *(John Boslego)*

Knowing that HPV infection is a necessary cause of cervical and anal cancers, and to respond to the global burden of disease, a vaccine that prevents infection with common pathogenic HPV types will be a major advance in anogenital cancer control. Although systematic Papanicolau testing of cervical smears has reduced the cervical cancer rates by about 75% in some countries, it has significant drawbacks as it has limited sensitivity and specificity, it requires repeated testing, which entails extensive resources and high cost, and it has not proven successful in developing countries.

Candidate vaccines based on recombinant L1 major capsid protein, which self-assembles into virus-like particles (VLPs), have been tested in animal models of species-specific papillomavirus infection/disease. Merck's VLPs are manufactured in *Saccharomyces cerevisiae* using a technology similar to that used for hepatitis B vaccine (Recombivax HB). In preclinical studies, vaccination resulted in protection from infection and disease, and passive transfer of antibodies also conferred protection – an indication that efficacy may be associated with development of neutralizing

antibodies. Considering the natural history of HPV disease, the possible end-points for evaluation of prophylactic vaccine efficacy in humans may be HPV infections or cervical intraepithelial neoplasia (CIN) development: CIN1 (low grade) and CIN2/3 (moderate and high grade).

Merck has developed a quadrivalent HPV-L1-VLP vaccine candidate, including HPV types 6, 11, 16 and 18, which will target 70% of all CIN2/3 cervical and anal cancers, 50% of all CIN1, and 90% of all genital warts. To date over 13 000 subjects have received the VLP vaccine in alum, which proved to be safe and well tolerated. Vaccination induced high-titre anti-HPV antibodies, up to 145 times higher than titres observed following natural infection. In a phase II/III efficacy study, a monovalent HPV 16 vaccine showed 100% efficacy against HPV 16 persistent infections and CIN. A similar study by GSK, using a bivalent HPV 16+18 L1 VLP vaccine candidate formulated in alum and 3-0-decacylated-monophosphoryl lipid A, has reported comparable results with 100% efficacy against HPV 16+18 persistent infections. A phase III clinical programme is under way at Merck to define the tolerability, immunogenicity and efficacy against HPV-6/11-related genital warts, HPV-6/11/16/18-related CIN-1, and HPV-16/18-related CIN2/3 or worse, in women at high risk in both industrialized and developing countries. Academic, industry and public health collaboration are needed to accelerate the demonstration of HPV vaccine effectiveness in developing countries and to facilitate vaccine introduction into these populations in the near future.

5.5 Epidemiology of HCV and hepatocarcinoma

(Michael Houghton on behalf of Chris Loffredo)

The hepatitis C virus (HCV) is the sole representative of the hepacivirus genus, and a member of the *Flaviviridae* family of viruses, which includes flaviviruses (yellow fever, dengue viruses) and pestiviruses. C virus strains exhibit up to 30% diversity in their amino acid sequences. HCV prevalence is high in South America, in central and North Africa, and in South-East Asia *(24).* HCV can be transmitted by blood transfusion, use of injectable drugs, hemodialysis, organ transplant, use of contaminated needles or surgery material, tattooing, sexual contact, perinatal mother-to-child contacts, and others. Injectable drug use remains the main route of transmission in the USA, accounting for nearly 90% of new HCV infections. Acute HCV infection manifests as jaundice in 25% of cases, and in about 50% of subjects the virus persists over years, leading potentially to chronic persistent hepatitis, chronic active hepatitis (CAH), and liver cirrhosis/fibrosis in about 20% of CAH. Eventually, 20% and 7% of cases of cirrhosis/fibrosis progress to liver failure and hepatocellular carcinoma (HCC), respectively. Spontaneous clearance of infection occurs in 15–50% of cases, and convalescent subjects are 12 times less likely to develop chronicity following reinfection. Cirrhosis and HCC take 20–25 years to develop. Other extrahepatic HCV-associated diseases may occur, such as mixed cryoglomebulinemia, glomerulonephritis, porphyria cutanea, B-cell lymphoma, and others. In the USA, incidence of hospitalization due to HCV diseases showed a significant increase between 1993 and 1998. Incidence rates of HCC among patients with HCV-related cirrhosis is highest in Japan *(25).*

Some HCV vaccine candidates have been designed to prevent the onset of chronic infection and associated diseases. Native heterodimer complex comprising both envelope glycoproteins gpE1 and gpE2 have been produced in Chinese Hamster Ovary (CHO) or HeLa cells and, upon intramuscular administration, can elicit the secretion of neutralizing antibodies and CD4+ T-cell responses. When tested in the chimpanzee challenge model, high titres of neutralizing antibodies seem to confer protection. Phase I clinical trials with HCV-E1 or E2 vaccine candidates are in progress. Phase II trials of vaccination of chronic HCV infected patients will follow. A vaccine candidate based on recombinant E1 in alum, developed by Innogenetics, has been suggested to have therapeutic value in HCV carriers either alone or in combination with standard care treatments such as interferon á. This vaccine candidate has reached phase II trials in non-responders to interferon treatment. Results show that it is well tolerated and able to raise anti-E1 antibody titres and to arrest or slow down the progression of liver fibrosis. However, no changes in plasma HCV RNA levels were detected, despite decreased antigen levels in the liver.

Recovery from acute hepatitis is associated with broad and early major histocompatibility complex (MCH) class II-CD4+ responses and MHC class I-CD8+ responses to HCV, in the absence of antibodies. Based on this paradigm, an immunostimulatory complex formulation (ISCOM) of HCV polypeptides, which may be able to prime CD8+ and CD4+ cells to associated antigens, has been studied by CSL Ltd. in phase I trials. Overall, this vaccine candidate seems to be safe and well tolerated, with no dose-related increase in frequency of adverse events, and may have both prophylactic and therapeutic value.

6. Regional diseases

6.1 Live-attenuated dengue vaccine development at Mahidol University *(Sutee Yoksan)*

Dengue viruses are the most widespread arthropod-borne viruses. It is estimated that there are 100 million cases of dengue fever, 500 000 cases of dengue haemorrhagic fever and 25 000 deaths attributable to dengue annually.

In 1980, Mahidol University committed itself to developing a live attenuated tetravalent dengue (DEN) vaccine. The DEN-1, and DEN-2 obtained from dengue haemorrhagic fever patients and DEN-4 obtained from a dengue fever patient were serially passaged in primary dog kidney (PDK) cells certified to be free from human and canine infectious agents. The DEN-3 strain obtained from a dengue haemorrhagic fever patient was passaged in primary green monkey kidney cells and finally in certified fetal Rhesus lung (FRhL) cells. The targeted degree of attenuation was empirically based on the profile of certain biological marker parameters. All tests were performed in GLP-compliant laboratories.

Bulk seeds were prepared in the pilot production facilities at the Center for Vaccine Development at Salaya Campus of Mahidol University. They were subjected to general safety and monkey neurovirulence tests in accordance with the US FDA requirements for live viral vaccines. The candidate dengue vaccines were further recommended for clinical evaluation by a WHO appointed Scientific Peer Review Committee and by the Thai Ethical Review Committee of the Ministry of Public Health.

The monovalent live-attenuated strains corresponding to all four serotypes were evaluated first in flavivirus non-immune adult subjects, followed by testing of bivalent, trivalent and tetravalent vaccine formulations. Twelve different dengue vaccine formulations were then evaluated for confirmation of safety and immunogenicity profiles in phase I trials in children. The formulations were assessed as safe, and some of them elicited satisfactory immune responses.

At the next step of clinical development, researchers evaluated seroneutralizing response elicited by two selected tetravalent formulations of dengue vaccine given as two doses three to five months apart to healthy, flavivirus-seronegative Thai children aged 5–12 years. The formulation 1 (F_1) contained 3, 2, 1 and 2 $\log_{10}$ $CCID_{50}$ of the serotypes 1, 2, 3 and 4 vaccine strains per dose, respectively; formulation 2 (F2) contained 3, 3, 1 and 3 $\log_{10}$ $CCID_{50}$ of the same vaccine strains. The results show that vaccination with two doses of both formulations of dengue vaccine were safe and elicited an immune response in children.

The master seeds corresponding to the four live attenuated virus strains were provided to Aventis Pasteur (France) for production on industrial scale following good manufacturing practice guidelines. At present, the tetravalent dengue vaccine candidate produced by this manufacturer is undergoing further clinical trial assessment in dengue-endemic countries.

6.2 The Paediatric Dengue Vaccine Initiative *(Scott Halstead)*

During the last few decades, dengue (DEN) has progressively spread throughout the tropical countries, achieving pandemic status and annually causing tens of millions of cases of dengue fever (DF); since 1960 more than 5 million hospitalizations of children with 70 000 deaths have been reported due to dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Dengue shock and fatal cases occur in older children, peaking at age 8–9 years. Dengue epidemics exact a high economic and social toll in over 100 tropical countries. In the Asian and American regions studies have found the global economic burden of DHF and DF to be 1289 DALYs per million. While supportive intensive care can be life saving, specific treatments are not available. The single preventive measure of comprehensive mosquito control has conspicuously failed. Vaccines offer a realistic and near-term solution to control the 20th and 21st century dengue pandemic that rages as a result of contemporary demographic and life-style trends: population explosion, urbanization and rapid transportation of large numbers of people.

Different technologies have been used for the development of dengue vaccines including live-attenuated strains, genetically altered and chimeric viruses, DNA, killed and subunit vaccines. Some robust live attenuated dengue vaccine candidates have been submitted for testing in phase I or II clinical trials. One or more of these candidates may be eligible for phase III trials in the near future. Importantly, dengue vaccines must be able to protect against all four dengue viruses and offer a lifetime of protective immunity.

To accelerate the introduction of safe and effective dengue vaccines a new alliance, the Paediatric Dengue Vaccine Initiative (PDVI), has been established with the following objectives:

- to measure the burden of dengue illness in affected countries;
- to establish two dengue field sites in preparation for phase III clinical trials;
- to carry out targeted research to evaluate the potential safe and effective long-term vaccine-induced protection against severe dengue disease; and
- to negotiate and form vaccine development partnerships to promote products designed for dengue-endemic countries.

The PDVI is not an incorporated entity but a consortium of stakeholders, a virtual body involving public and private sectors, universities, research institutes, international organizations and endemic countries. The PDVI will partner with its host institution, the International Vaccine Institute, Seoul, Republic of Korea. Governance is provided by the PDVI board of councillors and the IVI board of trustees. Programme management is the responsibility of the director, who will be counselled by programme-specific scientific advisory committees and supported by a secretariat at IVI headquarters.

6.3 Research and development of vaccines against typhoid fever *(Mike Levine)*

Typhoid fever is a major health problem in many countries. In the absence of effective antibiotics, typhoid fever is associated with a case fatality rate of 10–20%. Complications of typhoid fever include intestinal perforation and haemorrhage, typhoid hepatitis, myocarditis and acute psychosis. Severe forms of typhoid fever were seen in Java in the 1970s and 1980s with a 50% case-fatality rate, and reasons underlying these exceptional clinical manifestations are still unclear. In addition, since circa 1990, *Salmonella enterica* serovar typhi strains from many countries in Asia are carrying an R factor plasmid encoding multiple antibiotic resistances; this reinforces the need for effective vaccines.

A heat-inactivated, phenol-preserved, parenteral typhoid vaccine was evaluated in WHO-sponsored trials in the 1960s. It provided 51–68% protection. However, it was highly reactogenic as adverse reactions were reported in 7–29% of vaccinated subjects. In the 1980s and early 1990s, a purified Vi polysaccharide parenteral vaccine and a Ty21a live oral vaccine were licensed.

The oral Ty21a attenuated vaccine has been shown to be safe, well tolerated and effective at providing long-term protection. This oral vaccine is highly suitable for school-based immunization, although it is also immunogenic in preschool children. Vaccination induces mucosal and serum O and H antibodies and cell-mediated immunity with participation of cytokine-producing proliferative and cytotoxic lymphocytes. Immunological correlates of protection have been identified through the evaluation of this vaccine in the field.

Parenteral immunization with purified Vi antigen was shown to be well tolerated and to mediate protection by stimulating the production of serum Vi-specific antibodies. A single dose of vaccine elicited moderate protection. As Vi capsular polysaccharide is a "T independent" antigen, the immunity induced by Vi cannot be boosted and protection appears to wane over three years. In addition, this polysaccharide vaccine is poorly immunogenic in infants. Regrettably, in the 1980/90s no field trials were carried out to assess the absolute efficacy of vaccination with both Vi and Ty21a. Lessons learned with Ty21a and Vi vaccines have guided further research in the development of a new generation of typhoid vaccines. Main characteristics of typhoid vaccines that would extend access to immunization in developing countries include: needle-free administration, high level of protection after one or two doses, long-term protection, safety in immunocompromised individuals, compatibility with other vaccines, and resistance to excessive heat and cold. The questions raised in relation to the development of new vaccines are the following. Can better parenteral Vi-based and live oral vaccines be designed? Can a live oral vaccine elicit Vi antibody in addition to other immune responses?

A new parenteral Vi vaccine was developed by conjugation with recombinant *Pseudomonas aeruginosa* exotoxin A. Vaccination was well tolerated in adults and children, elicited higher titres of anti-Vi antibody than unconjugated Vi and induced immunological memory. High efficacy of this vaccine was shown in two- to five-year old Vietnamese children.

Several strains of *S. typhi* have been developed as potential candidates for future live oral vaccines. Preliminary data on their reactogenicity and immunogenicity were obtained in laboratory tests and animal models. Some of these strains have undergone phases I–II clinical trials with highly encouraging results.

6.4 Research and development of vaccines against Japanese encephalitis *(Ichiro Kurane)*

Japanese encephalitis (JE) is a viral infection, transmitted by mosquitos in mostly rural areas inhabited by Asia's poorest populations. Approximately 50 000 cases are reported to WHO annually. Of clinical cases of acute JE, 40% are fatal, with severe neurological impairment occurring in 10–30% of survivors. Paralysis and neuro-psychiatric disabilities make the incidence of JE infection a significant public health burden with high social and economic costs.

Human vaccination is the only effective long-term control measure against JE, and all at-risk residents should receive a safe and effective vaccine as part of the national immunization programmes. At present, only mouse-brain-derived inactivated JE vaccine is internationally accepted for practical use. It is produced by several manufacturers in Japan, the Republic of Korea, Thailand and Viet Nam. However, there is a shortfall between global request and production facilities of this biological. While the vaccine has dramatically reduced Japanese encephalitis incidence in some counties, these results are marred by short-term protection, and reports of neurological reactions (all in industrialized country settings) after vaccination.

Live attenuated JE vaccine (SA-14-14-2) was developed in China. It was prepared in primary hamster kidney cells, not a widely accepted substrate for production and licensure of vaccines in some countries. The vaccine appears to be safe and effective in annual immunization programmes involving millions of children and successfully controlled the disease in the area of its use. However, it has not been prequalified by WHO for global use. To help manufacturers to produce this vaccine in accordance with international norms and regulations, WHO has developed guidelines for production and quality control of live attenuated JE vaccine. More information on efficacy and adverse reactions in other countries has been requested. In addition, PHK cell-derived inactivated JE vaccine is produced in China, but the production level has declined in the last few years.

Several manufacturers in China, Japan and the USA are dealing with the development of Vero cell-derived inactivated vaccine. In phase I clinical trials these vaccines were well tolerated and induced 100% seroconversion in adult vaccinees. Phase III clinical trials are being conducted in paediatric child populations in Japan. There is good reason to suggest that at least one Vero cell-derived inactivated vaccine will be licensed in the next two to three years.

A promising approach is based on chimeric viruses in which viral envelope genes of JE replace corresponding genes of the existing licensed YF17D vaccine against yellow fever (YF). This vaccine was well tolerated in clinical trials in adult volunteers. It was immunogenic in JE immunologically naive subjects and volunteers with pre-existing antibodies against yellow fever virus and induced immunological memory. A phase II trial is now in progress in WHO's Western Pacific Region.

Introduction of second generation vaccines to practical use will probably meet the global need for this biological. It is anticipated that mouse-brain-derived inactivated vaccine will still be needed in the short and medium term. However, it will eventually be replaced by Vero cell-derived inactivated vaccine, live attenuated SA14-14-2 vaccine or YF-JE chimeric vaccine. Development of criteria for evaluating vaccine efficacy continues to be an area of high research priority.

6.5 The importance of translational research in accelerating JE vaccine introduction *(Zhi Yi Xu)*

The objective of translational research is to provide practical information needed by policy makers and donors to support introduction of vaccines into developing countries. They include characterization of disease burden, cost effectiveness of immunization, policy research to evaluate potential determinants for vaccine introduction, and immunization demonstration projects. The International Vaccine Institute (IVI) in the Republic of Korea is conducting a research project to accelerate introduction of JE vaccines into Asian countries. The main reasons why JE disease burden continues to be underestimated in many countries include the lack of population-based surveillance and infrequent use of appropriate laboratory tests for confirmation of disease.

A study in Bali, Indonesia, has shown that JE is hyperendemic on this island; this contradicts the common opinion that JE is more rare nearer the equator. Age distribution of JE cases shows "shift to the left" with an unusually high percentage in children <5 years. JE is transmitted year round, with a peak in the rainy season, when there is an abundance of mosquitos. The distribution of cases was geographically dispersed throughout the island, suggesting that focused immunization will not be effective. Pigs appear to be amplifying hosts for JE in Bali.

A retrospective, controlled cohort study on long-term post-JE disability has been carried out in China. Results of the study confirm that JE is associated with a high rate of long-term neurological sequelae that persist for years after the acute disease. Moreover, post-JE patients exhibit a high rate of mental retardation and deficits in the ability to carry out basic daily activities. Incidence rates of JE as identified in the study do not adequately capture the disease burden and policy decisions about introducing JE vaccines must also account for the disability that occurs in JE survivors. A cost-effectiveness model of vaccination against JE, using actual incidence and cost data from Shanghai, has demonstrated that vaccination has a marked impact on the incidence of JE and that vaccination with inactivated and live vaccines is cost effective for the health system.

Policy analysis of JE immunization is now in progress in several Asian countries. Policy problems raised in Viet Nam include limited scope of JE vaccination through the national immunization programme, limited funding sources for EPI vaccines, limited age groups covered by JE vaccination, and disparity of locally produced vaccine to GMP requirements. Proposed solutions should include an increased rate of JE vaccination coverage in the country, a broader target age group for JE immunization through EPI, increased funding for JE immunization and reduced user fees for the poor. There is also a need for more data on the feasibility, acceptability and affordability of wide-scale JE vaccination from demonstration projects as well as more data on the economic impact of vaccination from cost-effectiveness studies.

Policy analyses completed in China show that JE vaccine is not an EPI vaccine in most provinces and no national JE policy on vaccination indications and schedules exists. Only local vaccines are used in the country and their production does not adhere to GMP. Children are over-vaccinated in some provinces, causing higher than usual rates of side-effects among persons given the inactivated mouse-brain-derived vaccine. Proposed solutions include rationalizing vaccine dosing by specifying a clear national policy for immunization, producing the vaccines at GMP standard, increasing budgets for JE immunization and integrating JE vaccine into national immunization programmes.

7. Discussion and summary of the 2003 Global Vaccine Research Forum

(Meeting co-chairs and secretariat)

The 2003 Global Vaccine Research Forum (GVRF) was special in at least three ways:

1) The Forum was convened in Seoul, Republic of Korea, representing the first time that the meeting was held outside of Switzerland. This increased the opportunity for regional scientists and health authorities to participate. This was met with many favourable comments and enthusiasm to hold future meetings, on occasion, in other regions of the world on a rotating basis.

2) The meeting was planned to juxtapose with the inauguration of the International Vaccine Institute's impressive new building in Seoul.

3) For the first time, a session was held that addressed problems of a specific region of the world (Asia). This recognizes that the developing world is heterogeneous with respect to the relative importance of certain public health problems. For example, some infections such as Japanese encephalitis virus infections, dengue haemorrhagic fever and multiple antibiotic-resistant typhoid fever have exceptional importance in much of Asia.

As has become traditional at the GVRF, overview updates were provided on the status of development of vaccines to prevent "the big three", HIV/AIDS, malaria and TB. Notably, because of the site of this year's meeting, in each of these presentations the situation in Asia was emphasized. One special highlight was a detailed summary of the results of the phase III field trial evaluating a gp120 candidate HIV vaccine in Thailand.

Participants also learned of progress in the evolution of the European and Developing Countries Clinical Trials Partnership (EDCTP). This new initiative that is coming on line will focus on Africa. It will bring new resources for testing HIV, malaria and TB vaccine candidates, will build clinical trials infrastructure and will train African clinical trialists.

As always at the GVRF, a session was held to provide updates on the specific research activities of special interest and sponsorship of GAVI. Thus the status of the recently commissioned accelerated development and introduction plans (ADIPs) for rotavirus and pneumococcal vaccines were provided. The ADIPs are aiming to establish the value of rotavirus and pneumococcal vaccines through relevant evidence-based surveys and clinical trials, to communicate that value to decision-makers in developing countries, to help quantify the demand for these vaccines and to assure adequate supplies to meet demand. An update was also given on the Meningitis Vaccine Project to develop a meningococcal A conjugate vaccine.

An update was also provided on three "vaccine technologies" that aim to make vaccination simpler, safer and more efficient. These specific technologies include: (a) sugar glassification to make some vaccines resistant to extreme temperatures, thereby diminishing dependence on the over-burdened cold chain; (b) a simple kit to measure tetanus antitoxin in oral fluid (which contains a transudate of serum IgG), as an objective tool to assess vaccine coverage and the efficiency of immunization services; (c) "de-fangers", simple robust devices that remove potentially infectious needles from syringes, thereby improving the handling of infectious wastes generated by immunization services. In addition, in the GAVI session an update was provided on WHO's initiative to license at least one device to administer a currently licensed measles vaccine by aerosol route. The safety and efficacy (seroconversion) of aerosolized measles vaccine has been established in several settings, including Mexico and South Africa. However, the devices to deliver the vaccine have not been standardized. Much progress has been made in this project.

The keynote lecture shared information on the activities of the Bill and Melinda Gates Foundation, an entity that has revolutionized research on vaccines to prevent infections of particular importance in populations in developing countries and, through its contributions to the Vaccine Fund, has had a profound impact on the introduction of new vaccines and strengthening immunization services. The fundamental concepts underlying the Foundation's strategy are:

1) to bring innovation into context for people in developing countries;
2) to provide evidence that what is proposed can be accomplished;
3) to focus on results which should be evaluated and accounted for;
4) to avoid replacement;
5) to promote new partnerships; and
6) to build long-term human and institutional capacity.

In broad terms, the Foundation has been supporting vaccine research activities that involve "building it" (i.e., making new vaccine candidates), "proving it" (supporting studies to demonstrate that the vaccines accomplish what they are supposed to do) and "sustaining it" (exploring ways to make the interventions sustainable for developing countries).

A session was held on aspects of clinical trials and regulatory issues of vaccines. A summary was presented of the WHO/IVR meeting in Ghana that addressed ethical issues of performing clinical trials in paediatric subjects in developing countries. New information was provided about the UN agencies prequalification process for new vaccines. This is an important subject as fundamental changes are taking place in the global supply of vaccines for populations in developing countries and the regulatory aspects must keep pace in order to assure that adequate supplies of vaccine are available. An update was provided on the status of licensing procedures for vaccines produced in European Union countries. It was explained that consideration is being given to pass an amendment to existing legislation that would allow the EMEA to give a scientific opinion, in the context of cooperation with WHO, for the assessment of certain biological products for human use that are intended solely for distribution outside the European Community. EMEA would review the product dossier and deliver its technical opinion and would carry out the normal batch release. WHO

would help analyse specific-use conditions (e.g. the risk–benefit in the country of destination). Pharmacovigilance and follow-up would be carried out by the NRA of the country of destination. A decision on this legislation is expected in 2004. In another presentation in this session, the FDA's regulatory perspective was provided. Examples were given of the ways in which the FDA actively participates in the international arena. To accelerate introduction and uptake of new vaccines in developing countries, the FDA recognizes several areas that need strengthening by regulatory authorities on the global level. These include:

1) a need for more flexible regulatory guidance;
2) improved interaction between developers and regulators in early phases of development, and more GMP-quality facilities to produce and characterize vaccines;
3) standardization of regulatory practices, e.g. for DNA vaccines;
4) mechanisms for assessing risk/benefit in different epidemiological settings; and
5) continued evaluation of import/export policies. Another presentation in this session provided a description of the Korean FDA, which was established in 1998 as an independent agency.

In the 2003 Forum's session on cancer vaccines, it was emphasized that several vaccine-preventable cancers caused by viruses or bacteria are disproportionately significant public health burdens in developing countries. These include gastric carcinoma (associated with chronic *Helicobacter pylori* infection), cervical carcinoma (associated with human papillomavirus infection) and hepatocellular carcinoma (a proportion of which are associated with chronic hepatitis C infection). The status of vaccines to prevent *H. pylori*, papillomavirus and hepatitis C infections and thereby to prevent associated cancers was reviewed. Remarkable progress has been made.

Because this GVRF was convened in Asia, another session focused on vaccine-preventable diseases of interest to countries in Asia and the Western Pacific. Among the regional diseases of special importance in the WHO Western Pacific and South-East Asia Regions are dengue fever (particularly dengue haemorrhagic fever), typhoid fever and Japanese encephalitis virus disease. Updates were given on the epidemiological burden of these diseases in Asia and the Western Pacific and the development or introduction of vaccines to prevent these infections.

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