

# Proceedings of the Sixth Global Vaccine Research Forum and Parallel Satellite Symposia

12–15 June 2005  
Salvador da Bahia, Brazil

**Immunization, Vaccines and Biologicals**

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World Health  
Organization

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# Abbreviations and acronyms

AAVP	WHO African AIDS Vaccine Programme
ACHR	WHO Advisory Committee on Health Research
ADIP	Accelerated Development and Introduction Plan
AFRO	WHO Regional Office for Africa
ALM	autoclaved <i>Leishmania major</i>
AIDS	acquired immuno deficiency syndrome
AMRO	WHO Regional Office for the Americas
APC	antigen presenting cell
ARI	acute respiratory infection
ART	anti-retroviral therapy
BCG	<i>Bacillus Calmette-Guérin</i> (vaccine)
cDNA	complimentary deoxyribonucleic acid
CIOMS	Council For International Organizations of Medical Sciences
CL	cutaneous leishmaniasis
CF	colonizing factor
CFU	colony forming unit
CPB	cysteine proteinase b
CSP	circumsporozoite protein
CTB	cholera toxin B subunit
CVD	Centre for Vaccine Development, University of Maryland, USA
CYBER	Centre for Biologics Evaluation and Research, USA
DCGI	Drug and Controller General India (Indian national regulatory authority)
DCVM	Developing Country Vaccine Manufacturers
DCPP	Disease Control Priority Projects
DOMI	Diseases of the Most Impoverished (International Vaccine Institute, Republic of Korea)
DTP	diphtheria–tetanus–pertussis (vaccine)
ELISA	enzyme-linked immunosorbent assay
ELISPOT	technique to evaluate cellular immune responses
EMA	European Agency for the Evaluation of Medicinal Products
EPI	Expanded Programme on Immunization
ETEC	enterotoxigenic <i>Escherichia coli</i>

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FDA	Food and Drug Administration, USA
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GIVS	Global Immunization Vision and Strategy
GNI	gross national income
GSK	GlaxoSmithKline Biologicals
GVRF	Global Vaccine Research Forum
HepB	hepatitis B (vaccine)
Hib	<i>Haemophilus influenzae</i> type b (vaccine)
HibRAT	Hib Rapid Assessment Tool
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HPV	human papillomavirus
HVI	WHO HIV Vaccine Initiative
IDRI	Infectious Disease Research Institute, USA
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
ICH	International Conference on Harmonization
IFFIm	International Finance Facility for Immunization
IgG	immunoglobulin G
ISCOM	immunostimulating complexes
LPS	lipopolysaccharide
LST	Leishmanin skin test
LT	labile toxin
MDG	Millennium Development Goal
MDSC	Multi-Disease Surveillance Center
MPL	monophosphorylipid A
MRC	Medical Research Council
MVA	modified vaccine Ankara (non-replicative vaccinia virus strain)
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NID	national immunization day
NIH	National Institutes of Health (USA)
NPV	net present value
NRA	national regulatory authority
OPA	opsonophagocytic activity
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health (USA)
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PEPFAR	American President's Emergency Plan for AIDS Relief
PPD	purified protein derivative (skin test for tuberculosis)

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PPP	public–private partnership
PSF	product summary file
PRR	pattern recognition receptors
R&D	research and development
RSV	respiratory syncytial virus
RTS,S	malaria vaccine candidate based on a fusion of CSP with hepatitis B surface antigen
RVP	Rotavirus Vaccine Program
SEARO	WHO Regional Office for South-East Asia
SIIL	Serum Institute of India Limited
ST	stable toxin
TB	tuberculosis
TLR	toll-like receptor
TRM	Technology Road-Mapping process
UN	United Nations
UNAIDS	United Nations Programme on AIDS
UNICEF	United Nations Children’s Fund
VL	visceral leishmaniasis
WG	working group
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific
WRAIR	Walter Reed Army Institute of Research, USA

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and

## World Health Organization (WHO)

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# Introduction

Co-chairs Drs Helena Makelä and Ciro de Quadros warmly welcomed the participants and thanked them for attending this gathering of specialists in vaccine research and development. The Sixth Global Vaccine Research Forum (GVRF) is the tenth meeting in a series previously referred to as the Montreux meetings, and it is the sixth joint WHO/GAVI meeting on global vaccine research.

The broad objectives of the Global Vaccine Research Forum are to:

- provide an opportunity for GAVI partners to participate in shaping a global research and development agenda;
- analyse the current status of vaccine research and development against AIDS, malaria and tuberculosis;
- identify opportunities for vaccine research and development within WHO;
- review new vaccine technologies; and
- review opportunities and bottlenecks in vaccine research, development and introduction as perceived by the vaccine industry.

The global vaccine market is worth US\$ 6 billion dollars, and although 85% of its consumers live in developing countries, 82% of its profits come from sales in industrialized countries. It is no surprise, then, that 90% of the industry's vaccine research and development (R&D) efforts are focused on vaccines for industrialized countries, while 10% of R&D efforts are focused on vaccines needed in developing countries. Indeed, while developing countries have far and away the most to gain from vaccines that address health problems in developing countries, pharmaceutical companies have the most to gain from producing vaccines that address health problems in industrialized countries. In this context, the Global Vaccine Research Forum aims to stimulate R&D efforts on new vaccines, especially those needed to fight infectious diseases in developing countries.

Dr Marie-Paule Kieny, Director of WHO's Initiative for Vaccine Research (IVR), opened the meeting with a WHO perspective on vaccine research and development.



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# 1. Highlights of recent WHO activities on the research and development of new vaccines

Over the period June 2004–June 2005, a number of important new developments have occurred in the field of vaccines and immunization.

The first event of global significance is the formulation by WHO and UNICEF of a Global Immunization Vision and Strategy (GIVS) for the period 2006–2015. This strategy, which was approved by the World Health Assembly in May 2005, provides a unifying vision of the main thrusts of immunization. Four strategic areas have been identified to realize the vision:

- protecting more people in a changing world;
- introducing new vaccines and technologies;
- integrating immunization, other linked interventions and surveillance in the health systems context; and
- immunizing in a context of global interdependence.

Vaccine R&D is of particular relevance for the second area, “Introducing New Vaccines and Technologies”, which aims at improving country decision-making, making new vaccines available through sustained supply and financing, scaling up R&D for new vaccines and ensuring equitable access to these vaccines.

How will GIVS take immunization to new levels of performance? The following avenues have been identified:

- unprecedented attention to reaching the hard-to-reach;
- anticipating the introduction and widespread use of new vaccines and technologies;
- encouraging a package of interventions to reduce child morbidity and mortality;
- taking immunization beyond infants into other age groups; and
- further emphasizing data-driven problem-solving to improve programme effectiveness.

Another important event for global immunization is the upcoming transition from GAVI Phase 1 to GAVI Phase 2. This follows an analysis of the achievements of GAVI during its phase 1, consultation with the global immunization community and definition of the main objectives for Phase 2, in line with GIVS. In support of Phase 2, new pledges were recently received by GAVI from donors, and prospects are very optimistic for the future availability of US\$ 4 billion from the International Finance Facility for Immunization (IFFIm) (see section 3.6).

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During the past 12 months many new vaccines were licensed or have progressed to an advanced clinical testing phase. Further, vaccines already licensed showed excellent results in developing country populations. Among those, the most notable are the following:

- Rotavirus
  - Rotarix® (GlaxoSmithKline/GSK) was licensed in Mexico and the Dominican Republic.
  - RotaTeq® (Merck) is expected to be licensed by the United States Food and Drug Administration (FDA) in 2006.
- Meningococcal meningitis
  - A tetravalent conjugate vaccine (Sanofi Pasteur) was licensed in the USA.
  - A heptavalent vaccine (GSK) combining diphtheria–tetanus–pertussis (DTP), hepatitis B (HepB), *Haemophilus influenzae* type b (Hib) and meningitis AC (MenAC) is planned to be licensed in 2007.
- Pneumococcus
  - An experimental 9-valent conjugate vaccine (Wyeth) provided 16% protection against overall child mortality in the Gambia.
- Human papillomavirus (HPV) and cervical cancer
  - A bivalent human papillomavirus 16/18 (HPV16/18) vaccine (GSK) and a tetravalent HPV6/11/16/18 (Merck) vaccine progressed to phase III evaluation.
- Malaria
  - The RTS,S vaccine candidate (GSK) showed 58% protection against severe disease in a phase II trial among children in Mozambique.
- Cholera
  - A killed oral vaccine (SBL) showed close to 80% protective efficacy in a highly endemic urban area of Beira, Mozambique.
- Japanese encephalitis
  - The Chinese live vaccine SA14-14-2 (Chendzu) will be submitted shortly for prequalification to WHO.

Lastly, vaccine R&D in IVR has also made substantial progress. Examples of these include:

- The Meningitis Vaccine Project (MVP)

Clinical lots of a meningitis A (MenA) conjugate candidate vaccine were produced by Serum Institute of India (SIIL), using a conjugation technology transferred from FDA/Center for Biologics Evaluation and Research (CBER), USA. The final approval to start phase I was given by the Indian national regulatory authority (Drug and Controller General India, DCGI) on 20 May 2005, and the phase I study (PsA-TT-001) will be initiated imminently in three sites in India.

- 
- The Measles Aerosol Project

Three devices have been selected and preparations are under way for a phase I clinical trial in India (healthy adults) and a phase II clinical trial in Mexico (children 12 months of age).
  - Malaria vaccine R&D

IVR is engaged with the Malaria Vaccine Initiative (MVI), the Bill and Melinda Gates Foundation and the Wellcome Trust in the Malaria Vaccine Technology Road-Mapping (TRM) process. This intends to develop a common research and development (R&D) framework targeting malaria vaccine challenges, as well as pathways and activities to meet the challenges.
  - Facilitation of tuberculosis (TB) vaccine development

A generic protocol was developed for testing TB vaccine candidates in a non-human primate challenge model, and consensus was achieved on standardized immunological assays for phase II (and possibly phase III) clinical trials of TB vaccines.
  - Pneumococcal conjugate vaccine immunogenicity studies

A study of immune responses to pneumococcal conjugate vaccines in HIV-infected children was completed in South Africa, enrolment for the first phase of a study evaluating safety and immunogenicity of a neonatal dose of conjugate vaccine was completed in Kilifi, Kenya, and agreements are in place for two studies evaluating alternative schedules of pneumococcal conjugate vaccine.
  - HIV vaccines: guidance and coordination

IVR conducted two international consultations to address key policy issues: Gender, Age, Ethnicity in HIV vaccine-research and clinical trials (Lausanne, August 2004) and Regional Strategic Planning for HIV vaccine R&D (Lausanne, September 2004). An important meeting was also held in Malawi (March 2005) to examine issues of ethics and access to care and treatment in vaccine clinical trial volunteers.
  - HPV and cervical cancer

IVR is the recipient of a five-year research grant on HPV vaccine R&D funded by the Bill and Melinda Gates Foundation. The main three objectives of this project are to:

    - harmonize and standardize laboratory procedures and create a global HPV laboratory network to facilitate vaccine licensure and monitoring in developing countries;
    - create an international multi-disciplinary policy platform, and set a global agenda for future HPV vaccine introduction;
    - facilitate global, regional and country-specific decisions on current and novel options for cervical cancer prevention, through a WHO information centre on HPV and cervical cancer.

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## 2. Development of new vaccines in the Americas: PAHO perspective

In the context of reducing inequities in health, rapidly reducing morbidity and mortality of vaccine preventable diseases, and strengthening public health infrastructure, the Pan American Health Organization (PAHO) considers the introduction of underutilized and new vaccines a top priority.

When introducing underutilized and new vaccines, renewed emphasis on reducing inequities is critical in order that these technologies reach the people who need them most. This is certainly the case with rubella vaccine, which is now appropriately linked with efforts to sustain measles elimination in the Americas.

Whether for underutilized or new vaccines, countries must make evidence-based policy decisions with the best and most comprehensive data available. To that end, PAHO assists countries with the critical factors of defining: disease burden, perception of risk, political commitment, vaccine characteristics, logistics, capacity to accurately forecast vaccine supply, post-marketing surveillance and partnerships required to support country decisions. Using these factors, the vaccines most likely to be considered for introduction in countries of the Americas include vaccines against: rotavirus, influenza, pneumococcus and HPV infections.

Technical justification using excellent science, supported with the essential political commitment, will be paramount for introducing underutilized and new vaccines that address priority public health problems and reduce inequities in health in the Americas.

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## 3. The GAVI vaccine R&D projects

### 3.1 Accelerating life-saving rotavirus and pneumococcal vaccines: updates on GAVI's Accelerated Development and Introduction Plans (ADIPs) (*Orin Levine*)

The GAVI pneumococcus and rotavirus Accelerated Development and Introduction Plans – pneumo ADIP and Rotavirus Vaccine Program (RVP) – were established in 2003 and are based at the Johns Hopkins Bloomberg School of Public Health in Baltimore under the direction of Dr Orin Levine (pneumo ADIP) and the Program for Appropriate Technology in Health (PATH) in Seattle under the direction of John Wecker (RVP). The mission of both ADIPs is to accelerate the evaluation of and access to new life-saving pneumococcal and rotavirus vaccines for children in the world's poorest countries. They are structured around three major objectives: to establish, communicate and deliver the value of these vaccines, and also to address issues of vaccine supply and demand.

Pneumococcus and rotavirus vaccines were chosen as targets for the ADIPs for the following reasons.

- *S. pneumoniae* and rotavirus are major causes of death worldwide.
- Effective vaccines exist or are about to be licensed.
- Countries and donors should have a solid investment case on which to decide whether to support accelerated vaccine introduction.
- History shows that without a dedicated effort 15–20 years will pass before these vaccines save lives in the poorest countries.

The pneumo ADIP has two strategic goals: (1) to provide information that will enable national decision-makers, the GAVI Board and the GAVI partners to make an evidence-based decision regarding the use of vaccine; and (2) to accelerate the availability of affordable, new vaccines appropriate for use in developing countries. It aims to create a “virtuous” circle, in which predictable demand would lead to increased production capacity and lower prices. In order to build the investment case, this ADIP intends to:

- **“establish the value”** of pneumo vaccines by: (a) providing support to selected vaccine trials; (b) heavily investing in surveillance studies, networks and methods for disease burden estimation (with WHO as a major collaborator in both areas); and (c) addressing cost-effectiveness (global and regional, top-down models and methods/models for local calculations).

- 
- **“deliver the value”** of pneumo vaccines by assessing the demand, supply and finance/delivery options.

It is argued that in the current situation, the efforts of three forces: industry/supply, donors/financing, countries/introduction and delivery do not overlap. The pneumo ADIP works towards finding “solution space” where all three converge. The pneumo ADIP has developed an innovative tool to calculate strategic demand forecasts and net present value (NPV) for suppliers, where:

- demand is tied to willingness to pay (which results in sustainable pricing); and
- supply depends on a neutral to positive NPV.

This allows donors, countries, and suppliers to find possible solution space.

Similar strategies, but specific to rotavirus vaccines, are being followed for RVP. In 2006 the ADIPs should present the GAVI Board with investment cases for continued support for accelerating the pneumococcal and rotavirus vaccines development and introduction process. In the meantime, they will continue: (a) to invest in research and surveillance through GAVI partners such as WHO in order to strengthen the evidence-base; and (b) to work with suppliers, donors and countries to find the solution space that allows for a sustainable, affordable vaccine supply and deployment.

### *Discussion*

The following points were raised during the discussion.

The question of pneumococcus serotype replacement is seen as a major concern. However, compared to the effect of herd immunity achieved with the vaccine, the effect of replacement is much less important. Concerns were also expressed about whether this applies to both invasive and non-invasive pneumonia.

Another question was whether the 7-valent vaccine should be used while waiting for a vaccine better adapted to the epidemiological conditions prevailing in developing countries. Indeed, the use of such a vaccine in Africa would only induce partial protection. There was a consensus that it should be used but only in places where surveillance is good.

On the subject of sustainability: the example of the recently completed Gambian trial was raised to illustrate the present concerns that countries with the greatest needs may not have access to the vaccine due to availability and price. Emphasis should be placed on the real value of vaccines; countries should be asked to be responsible in this regard and to explore real options, placing immunization within a larger envelope for health.

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### 3.2 Meningitis Vaccine Project update and first clinical trial (Kader Konde)

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 for vaccination.

MVP was created in June 2001 with support from the Bill and Melinda Gates Foundation as a 10-year partnership between WHO and PATH. The goal is to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of *conjugate* meningococcal vaccines.

Prior discussions with African public health officials had highlighted that the most important factor in introduction of the vaccine was cost. Meningitis belt countries are among the poorest in the world, and the vaccine price should therefore not exceed US\$ 0.50 per dose. The overwhelming proportion of meningococcal epidemics cases are due to group A in this area of the world, and no manufacturer was producing a monovalent conjugate meningitis A vaccine. Taking all these points into consideration, MVP concentrated on serogroup A only for the development of a new product, with the added advantages of simplicity, lower risk, and solid public health impact together. However, because of a recent outbreak of *N. meningitidis* serogroup W135 in Burkina Faso, MVP has a secure back-up strategy, with improved surveillance being one of the most important elements of the programme.

The intention is to use the serogroup A vaccine as a single dose in mass vaccination campaigns throughout the meningitis belt for individuals between 1 and 29 years of age (target population: approximately 250 million people in 18–21 countries; modelled after the meningitis C programme in the United Kingdom). In addition, it might be used in the Expanded Programme on Immunization (EPI) in children under one year of age (two doses; at 14 weeks with DTP3 and at nine months with measles). Therefore, the most appropriate strategy for meningitis A vaccine introduction is to start with mass campaign vaccination with one dose of vaccine, followed by routine EPI immunization with two doses of conjugate A vaccine.

The MVP development model combines raw materials from one group (SynCo Bio Partners, the Netherlands), a conjugation method from FDA/CBER and production through tech-transfer to a third partner (SIIL), with a projected price of US\$ 0.40 per dose. MVP is a complex endeavour with pharmaceutical, clinical and introduction plans. The clinical plan encompasses a series of studies in India and Africa. The phase I trial protocol has been approved by the DCGI and is ready to start. Registration of the vaccine in India is anticipated by 2009.

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In addition, MVP is investing in important related issues:

- 1) surveillance of the meningitis epidemiology in the meningitis belt with the WHO Multi-Disease Surveillance Center (MDSC);
- 2) strengthening of national regulatory authorities (NRAs), with emphasis on the ethical aspects;
- 3) communication and advocacy; and
- 4) stimulation of new markets (South/South).

In conclusion, MVP is a true private–public partnership, with a very focused goal, which entails:

- a strict vaccine development plan;
- the supply of vaccine at an affordable price of US\$ 0.40 per dose;
- a future product with a high social value, and for which a commitment is expected at the highest national level in countries.

### *Discussion*

Interest was expressed in the strategy of campaigns followed by routine immunization, but some concerns were expressed in terms of availability of the vaccine and financing of the campaigns if there are simultaneous requests by several countries.

GSK indicated that the company was currently developing a meningitis A conjugate-containing heptavalent vaccine (DTP/HepB/Hib/Men AC). This product should be available in 2007, and GSK is currently addressing the issue of its affordability for countries of the African meningitis belt.

### **3.3 Pneumococcus: update on clinical trials –The Gambia** *(Thomas Cherian on behalf of Felicity Cutts, who was unable to attend)*

Pneumonia is one of the leading causes of mortality worldwide, with rates of pneumonia and deaths substantially higher in developing countries. Dr Cherian presented the recently published results of the Gambian trial (Cutts et al.),<sup>1</sup> on behalf of Dr Felicity Cutts. Earlier studies had already established the high efficacy of the conjugate vaccine against vaccine-type invasive disease in the USA and South Africa. Therefore this study was planned in the Gambia with the following design.

- Children were enrolled at approximately 110 governmental vaccination clinics.
- Either a pneumococcus vaccine (9-valent, representing the most relevant serotypes) or placebo mixed with DTP–Hib (Tetramune®) was given according to the EPI schedule.
- Home visits were made every three months until age 30 months or until 30 April 2004 for mortality surveillance.

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<sup>1</sup> Cutts et al. *Lancet*, 2005, 365:1139–1146.

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- Surveillance for pneumonia and invasive pneumococcal disease was carried out at Basse Health Centre (Upper River Division, The Gambia) and Bansang Hospital (Central River Division, The Gambia), with referrals of children from peripheral health centres to hospitals.
  - 16 344 children entered per-protocol analysis, with a median age at dose one of 11 weeks and a median age at dose three of 24 weeks.
  - Study end-points were as follows: (a) primary: radiologically confirmed pneumonia; (b) secondary: clinical and severe clinical pneumonia, invasive pneumococcal disease, all-cause hospital admissions, safety; (c) other a-priori analyses: all-cause mortality, admissions with clinical syndromes related to potential invasive pneumococcal disease (IPD).

With a 37% efficacy against radiologically confirmed pneumonia and 16% against all-cause mortality, the major conclusions of this study were that: (a) pneumococcal disease represents a significant burden in terms of childhood morbidity in the Gambia; and (b) anti-pneumococcal vaccination can prevent a large proportion of these illnesses, significantly reducing mortality among children in a typical rural African setting, especially in hard-to-reach populations.

### *Discussion*

The importance of improving surveillance and health care management following the introduction of Hib vaccination was stressed.

It is important to take into account the effect of herd immunity, which in turn influences cost-effectiveness calculations. This has been done in the United Kingdom, and provided additional support for the introduction of the vaccine.

### **3.4 Pneumococcus: update on clinical trials –The Philippines** *(Marilla Lucero)*

In the Philippines, pneumonia is the third highest cause of mortality in children of all ages and the first in infants under one year of age. Following successful phase II immunogenicity studies with the 11-valent pneumococcal conjugate vaccine (PCV) in Luzon and Bohol, a randomized placebo-controlled double-blind phase III clinical trial to assess the efficacy of an 11-valent pneumococcal conjugate vaccine is taking place, sponsored by the ARIVAC consortium<sup>2</sup> and involving several hospitals in the country.

The trial design is as follows.

- The primary objectives are to determine the efficacy of 11-PCV compared to saline placebo, against first episodes of radiologically confirmed pneumonia among Filipino infants.

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<sup>2</sup> The ARIVAC Consortium concerns itself with vaccines against acute respiratory infections (ARI). It is composed of the Research Institute for Tropical Medicine (The Philippines), the National Public Health Institute (Finland), the University of Queensland (Australia) and Sanofi Pasteur (France).

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- The secondary objectives are:
    - vaccine efficacy against clinical pneumonia (WHO definition) and invasive pneumococcal disease;
    - safety evaluation; and
    - immunogenicity and opsonophagocytic activity (OPA) in 11-PCV and saline placebo recipients in a nested study.
  - The tertiary objectives are:
    - correlates of protection (in nested study);
    - surveillance of respiratory syncytial virus (RSV) and other viral pneumonia;
    - protection against mixed viral–bacterial pneumonia;
    - efficacy in preventing pneumonia of differing degrees of severity; and
    - prevention of nasopharyngeal colonization with pneumococci.
    - A number of satellite studies include evaluation of herd immunity, calculation of cost–effectiveness and testing of the prevention of acute otitis media.

Milestones so far are: (a) enrollment period: 5 July 2000 to 18 December 2003; (b) follow-up period: until 31 December 2004; (c) total of 12 194 children enrolled, individually randomized to receive 11-PCV or saline placebo as a control in a double-blind controlled way; (c) analysis by the ARIVAC consortium and the breaking of the code in the second half of 2005.

### 3.5 Update from the Enteric Vaccines Satellite Symposium (Jan Holmgren)

The focus of the symposium was typhoid, cholera (for which licensed vaccines have been available for a number of years), and rotavirus. ETEC and *Shigella* vaccines were discussed during the main GVRF meeting. The presentations addressed the question whether introduction plans for rotavirus, typhoid and cholera vaccines are credible investment cases for developing countries.

The main conclusions of this satellite symposium were as follows.

- There is a global need for enteric vaccines, and rotavirus, typhoid and cholera are all **credible investment cases** for developing countries; these investments should be based on disease burden, cost–effectiveness estimates, demonstration projects and vaccine availability and financing.
- As is the case for rotavirus vaccines, for which an ADIP already exists, **a focused investment** could be considered for **typhoid vaccines**.
- Good progress has been achieved with the rotavirus ADIP but it is very important to generate good **rotavirus efficacy data for Africa and Asia** in addition to the existing data in Latin America, in order to properly assess the global performance of the new vaccines.

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- Cholera vaccines need a double approach for high endemic settings and epidemic control. There is an urgent need for recommendations on **how to use the vaccine** and on the establishment of a **stockpile**.

For enteric vaccines in general, a few hurdles should be overcome before wider use:

- more effective communication of the importance of enteric infections and the potential of vaccines to save lives in a cost-effective manner;
- communication of the obvious – that vaccines are complements, and not replacements or threats, to other useful control methods;
- advocacy that the search for the “ideal” should not be the enemy of the “good” – that existing products should be used while promoting improvements in existing vaccine formulations and R&D into new vaccines; and
- definition of the complexities and provision of solutions to “challenges”, which are not “insurmountable problems”.

More specifically, for **typhoid fever vaccines** the following applies.

- Since antibiotic resistance is rising and water and sanitation improvement is a long-term goal, vaccines are the only viable intervention to control typhoid in the short term and medium term.
- Typhoid fever causes significant mortality/morbidity and major direct and indirect economic losses; large-scale introduction of a typhoid vaccine is an opportunity to make a significant contribution to the Millennium Development Goals (MDGs) and GAVI objectives.
- There are safe and effective, available, licensed vaccines; vaccination is feasible, acceptable and affordable.
- There is a cost-competitive supply of vaccine and there are ways to rationally vaccinate populations at highest risk in a financially sustainable way.
- There is a perceived value and interest on the part of country-level decision-makers.

More specifically, for **rotavirus vaccines**:

- There is a need for safe, efficacious and affordable vaccines. Rotavirus vaccines for the industrialized world will be available soon, but will a live, oral rotavirus vaccine work in infants in developing countries where it is needed most? This remains a key question.
- In addition to the two most advanced candidates, there are multiple additional vaccine candidates and producers interested in manufacturing rotavirus vaccines in developing countries.
- In view of the above, it is important that NRAs in developing countries continue to be strengthened by WHO, and that work continues on standardization of quality control and safety (production process, facility, candidate strain...).

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More specifically for **cholera vaccines**:

- When should cholera vaccines be used? Should it be: (a) in high-endemic settings, and/or (b) as adjuncts for epidemic control? Guidance on this point is expected from WHO.
- A recently published study in Mozambique showed that vaccine was highly effective against clinically significant cholera in an urban African population with a high prevalence of HIV infection.
- The establishment of a cholera vaccine stockpile has recently been discussed. However, there are still many challenges for the use of vaccines in disaster and outbreak situations.
- There is a need for WHO recommendations on how to use cholera vaccines.

### **3.6 GAVI and the International Finance Facility for Immunization** *(Patrick Lydon on behalf of Julian Lob-Levyt, who was unable to attend)*

The IFFIm is a proposed novel financing mechanism, particularly applied to immunization. The following points were addressed during the presentation.

- Why an International Finance Facility (IFF)?
- How does it work?
- Why an IFF for immunization?
- Is it ready for launch?

The world – especially sub-Saharan Africa – is not on track to meet the MDGs. It is postulated that with adequate resources the MDGs could be achieved on – or close to – schedule. Although rich countries have pledged to increase overseas development assistance to 0.7%, this will not happen quickly enough, and other resources are needed to bridge the gap and catalyse real change. Gradual increases will not meet the financial requirements, estimated at an additional US\$ 50 billion per year, to meet the goals.

Under a proposed new mechanism called the IFF, the urgent financing required would be raised by selling bonds in the international capital markets, based on legally binding long-term donor commitments. The result: frontloaded financing, with a substantial increase in development funds available immediately – in predictable and stable aid flows – for the poorest countries. This mechanism, while generating the flexibility of large up-front financing, incurs some borrowing and transaction costs, making it more expensive than traditional aid, necessitating that it be used for activities that can accomplish benefits rapidly.

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The IFF for immunization, the IFFIm, has been proposed as a pilot for the “larger” IFF. Immunization is ideal for IFF funds as it:

- is an essential and highly cost-effective intervention that helps strengthen health systems;
- can be scaled up quickly, even in resource-poor settings;
- can have an immediate impact on child mortality;
- has significant internal rates of return that far outweigh any costs of the IFF mechanism; and
- can use front-loaded funds to accelerate vaccine market forces.

GAVI is the vehicle for IFFIm, focusing during its phase II on 72 of the poorest countries (less than US\$ 1000 GNI per capita), where disease burden is greatest, and with two windows of support: (a) providing new and underused vaccines (support for combination vaccines, DTP+HepB, DTP+HepB+Hib; accelerating the introduction of new vaccines, e.g. rotavirus and pneumococcus); and (b) strengthening country health systems. Importantly, funds provided through the IFFIm will not be a substitute, but will add to those already available to GAVI through more classical donor pledges.

IFFIm will help create sustainable prices for new and underused vaccines, help create a polio vaccine stockpile, strengthen immunization systems and support measles and tetanus vaccination campaigns.

The key founding principles for governance and allocation policies for the GAVI IFFIm are:

- country-driven strategies based on multi-year plans for immunization;
- processes compatible with national planning cycles and budgeting for the health sector;
- allocations that strengthen the ability of countries to finance immunization on a sustainable basis;
- prioritization of funding to areas which are appropriately prone to “frontloading”; and
- light and coordinated reporting requirements for monitoring and evaluation.

To date, the governments of France, Sweden and the United Kingdom have announced their participation in the IFFIm and negotiations are ongoing with other potential donors. Whether or not the IFFIm will exist depends on the European Statistical Agency (Eurostat) ruling on how the pledges to the IFFIm are treated in national accounts. Eurostat is expected to issue its decision in the coming months and IFFIm funds may be available for disbursement before the end of 2005. The GAVI Board will review during its July 2005 meeting a number of investment cases for possible first utilization of IFFIm funds.

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### *Discussion*

Concerns were expressed with the statement that IFFIm could bring down the price of vaccines. So far it has not happened, but this may be due, at least in part, to the fact that there are no long-term strategies to date for purchase of vaccines.

For an oral polio vaccine (OPV) stockpile, where payment needs to be upfront, the IFFIm can prove to be a very good mechanism.

The question was raised whether non-GAVI eligible countries, for instance middle-income countries, could be considered for financing through the IFFIm. There are/ will be country consultations with GAVI, and a plea for revision and criteria for consideration of eligible countries will be discussed. This dialogue has actually already started.

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# 4. *Haemophilus influenzae* type b (Hib) introduction and challenges: lessons learned

## 4.1 Current status of Hib vaccine introduction (*Samba Sow*)

Lack of local data on disease burden has been an obstacle for the introduction of Hib vaccine in many developing countries. Data from a carefully conducted surveillance study at l'Hôpital Gabriel Touré, Mali, was instrumental in paving the way for Hib vaccine introduction in that country. While this hospital has high rates of admission of children with fever, with high case fatality rates (24%), the cause of illness remained undetermined in the absence of a bacteriology laboratory to establish the etiology of disease. With the help of the University of Maryland (USA), a clinical bacteriology laboratory, a data management unit and a facility to conduct clinical trials, meeting International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) requirements with 24-hour laboratory services, were established. Following this, systematic investigation of children 0 to 15 years with possible invasive bacterial disease was initiated.

From June 2002 to May 2004, 207 children with invasive Hib disease were identified, including 81 from blood alone, giving an estimated incidence of 158 in 100 000 in children under one year and 45 in 100 000 in children under five years. This was considered to be an underestimation since: surveillance was only carried out in one large hospital; there were high rates of antibiotics use in the community; and there were technical difficulties in the laboratory.

Data were presented to the President and also to the Minister and Deputy Minister of Health in Mali. This resulted in a presidential instruction to initiate plans for Hib vaccine introduction in the national immunization programme. Following a successful application to GAVI, a three-step introduction plan has been proposed, starting with the Bamako district in 2005–2006; followed by regional capitals in 2006–2007 and the rest of the country in 2007–2012. Impact assessment is planned through periodic serosurveys and surveillance for Hib disease at Hôpital Gabriel Touré. Financial sustainability plans for the post-GAVI-support phase are in place.

## 4.2 Panel discussion on Hib

### 4.2.1 *Assessment of disease burden, different methods available, pros and cons of each technique* (Anne Schuchat)

There may be several reasons to measure the burden of disease. The method chosen will depend on what the information is used for. There are a variety of methods for measuring Hib disease burden. These include measurement of laboratory-confirmed disease, surveillance of clinical syndromes caused by Hib with determination of the

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Hib vaccine-preventable fraction based on clinical trial data, or estimation of burden of disease using surrogate markers such as nasopharyngeal colonization. There is a range of methods for measuring these outcomes, which vary in complexity, cost and the time taken to generate data. The choice of method would depend on the balance of sensitivity and specificity required, the available resources and time.

The introduction of Hib vaccine resulted in a dramatic decline in disease in the USA. Even when vaccine was given at 18 months, rates of disease dropped in younger infants, showing the significant herd effect of the vaccine. Surveillance was possible because of the existing health care system along with a national surveillance system in place to monitor trends and break down the data by age, even though it was based on passive surveillance. Similar systems in other countries, including Brazil, were able to demonstrate similar trends.

Sometimes a combination of methods provides a better assessment of the actual impact of vaccination. For example, surveillance in a single hospital in the Dominican Republic to document the impact of Hib vaccination confirmed the importance of Hib disease, as immunization resulted in a drastic decrease of laboratory-confirmed cases. An even greater impact was seen on the number of meningitis cases with no laboratory confirmation of etiology. However, when other pathogens (e.g. meningococcus) play a substantial role in meningitis burden (e.g. in the Niger) the impact of Hib vaccine may be masked if only syndromic surveillance is being carried out.

The time when the impact of vaccination may become evident would depend on whether a catch-up campaign was used or not. Catch-up campaigns result in very quick decline of disease rates and should be considered when quick results are needed for maintaining governmental support. When such campaigns are not implemented, disease reduction may not be evident during the initial two years after introduction of the vaccine and longer surveillance should be maintained before decisions are made about sustaining the programme.

The Hib Rapid Assessment Tool (HibRAT) has been very successfully used in several African countries where the estimated incidence was close to that seen in prospective studies. However, rates in Asia and Eastern Europe using this approach were quite low.

In some regions where the burden remains uncertain, the vaccine probe approach, albeit very complex and expensive, may be the most appropriate approach. The value of this approach was demonstrated in the Lombok study<sup>3</sup> where the rates of preventable meningitis were several fold higher than the laboratory-confirmed burden. However, a similar preventable burden of pneumonia could not be documented.

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<sup>3</sup> Incidence and clinical features of hospitalization because of respiratory syncytial virus lower respiratory illness among children less than two years of age in a rural Asian setting. *Pediatric Infectious Disease Journal*, February 2003, 22(2):150–156.

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#### 4.2.2 *Cost–effectiveness studies* (Damian Walker)

There are relatively few data to demonstrate the cost–effectiveness of Hib vaccine in low and middle-income countries. Furthermore, the studies have each used different methods and outcome measures, which makes direct comparison of results difficult. Differences in the assumptions and methods used may explain the different conclusions from several of these studies.

The use of benchmarks established by the WHO Advisory Committee on Health Research (ACHR) is a useful way to assess the value of vaccines and assist in decision-making. The report *Disease Control Priority Projects* (DCPP)<sup>4</sup> 2005 is due to be published and will allow comparison of Hib vaccination with other public health interventions.

However, the above assumes that decision-making is always evidence-based. Experience shows that a number of other factors, including the personal experience of politicians and other high-level officials may play an important role. Therefore, efforts need to be made to ensure that cost–effectiveness data help policy-makers to make informed decisions on vaccine policy in countries. To achieve this, data need to be presented to them in a more understandable way. The Hib Initiative aims to generate more extensive cost–effectiveness data to facilitate rational decision-making, both by synthesizing already existing data and by performing additional studies.

#### 4.2.3 *Financial sustainability* (Patrick Lydon)

The GAVI model of financial sustainability was based on several assumptions. These included reduction in vaccine prices over time, increased resources from governments and partners to sustain vaccine use, and sufficient time (two to three years) to plan the transition from GAVI funding for Hib vaccine to funding from national and partner resources. However, prices of Hib vaccine have not actually gone down as expected, especially when combo vaccines are considered. Future financing is still very vulnerable, and government plans for sustaining vaccination are often not mature.

Based on the lessons learnt from the first phase, GAVI intends to correct this by: (a) supporting better evidence-based decision-making; (b) initiating measures to stimulate downward pressure on prices by developing and implementing a long-term vaccine procurement strategy; and (c) supporting countries on a trajectory towards financial sustainability, e.g. during the “bridge period” until the vaccine prices reach a mature value, more affordable to countries and their partners.

A study by GAVI and the World Bank indicates that there are many new products in the vaccine pipeline and that this could be used to influence prices and promote financial sustainability.

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<sup>4</sup> The DCPP is a joint project of the International Fogarty Center of the National Institutes of Health (USA), WHO and the World Bank, financed through a grant of US\$ 3.5 million from the Bill and Melinda Gates Foundation and foreseen to end in 2005.

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#### **4.2.4 *Lessons learnt of sustainable introduction in the Americas*** **(Jon Andrus)**

The institution of the PAHO Revolving Fund helped bring down and sustain low prices of vaccines in the region of the Americas. Experience showed that the accuracy of the demand forecasts had a strong influence on the pricing obtained.

While the revolving fund is a powerful tool, its success was dependent on certain rules that were formulated at its inception. These included:

- strict enforcement of the 60-day rule during which time countries were expected to make payment for vaccine received;
- requirement of a national EPI manager; and
- inclusion of a budget line for immunization in the national health budget.

Another significant factor that contributed to the sustainability of vaccination was the strong commitment that countries made through the enactment of vaccine laws that acknowledged access to vaccines as a right. However, an analysis of the success or downfall of these laws needs to be made and understood in order to use them successfully in other regions.

#### **4.2.5 *The Gambian experience with Hib vaccination*** (Richard Adegbola)

The Gambia has one of the most successful EPI programmes in Africa and a history of taking the lead in new vaccine introduction. The country also has high rates of acute respiratory infections (ARI) and meningitis. Hib and *S. pneumoniae* are the common pathogens responsible for these syndromes.

The burden of Hib disease was established through several studies conducted during 1987–1993. This was followed by a number of vaccine trials, including a large efficacy trial during 1990–1995 that demonstrated the value of the vaccine.

The vaccine was introduced following a donation from the manufacturer and an effectiveness study was conducted during 1997–2002, with support from WHO, to document the impact of vaccination. Prior to vaccine introduction, the rate of invasive Hib disease was 200 in 100 000 children under five years of age. Following vaccination, even though vaccine supply was erratic and consequently vaccine coverage in young infants was suboptimal, Hib disease rapidly decreased and since 2002 there have been no reported cases of Hib meningitis in the surveillance area.

In the Gambia, Hib vaccine was shown to be safe, very effective and capable of contributing substantially to achieving the MDGs.

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#### ***4.2.6 Production of Hib monovalent and combination vaccines by the Developing Country Vaccine Manufacturers Network (DCVMN) (Suresh Jadhav)***

Several Hib vaccine formulations are available, either singly or in combination with other antigens, but currently the supply will not meet requirements should the vaccine be included in the routine immunization programmes of all countries.

Most of the disease burden appears to be in developing countries, but in many countries the burden is currently unclear. Should all the countries decide to introduce the vaccine, 280–300 million doses will be required annually. Such a large-scale production of the vaccine could lead to reduction in price, which is currently a major impediment to vaccine uptake in developing countries.

There are several emerging manufacturers with an interest in producing Hib-containing vaccines. Several companies are doing vaccine development in partnership with large multinational manufacturers. Many have monovalent and combination vaccines containing Hib in clinical trials, and it is expected that numerous products will be registered in the country of manufacture by 2006–2007 and available for WHO prequalification shortly thereafter.

#### ***4.2.7 General discussion***

What has been learnt about duration of protection and the optimal schedules (including requirement for booster doses) in the Gambia?

- Two doses are as effective as three. Current surveillance has not revealed the emergence of cases in older age groups but further surveillance will be required to document this point.
- Peru used the strategy of offering vaccine to the most disadvantaged first and then expanded its programme to include other communities. This may be considered by other countries facing financing problems.
- The revolving fund could not be implemented in other regions since its success is dependent on countries being accountable and strictly following the 60-day rule for payment. This is difficult to implement in all regions.
- Dose-ranging studies are in the product development plan of the SIIL Hib containing vaccines, given the results of studies in developing countries showing the immunogenicity of fractional doses.

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# 5. The case for orphan vaccines: the example of leishmaniasis

Human infections with *Leishmania* species induce diseases ranging from self-healing cutaneous to mucosal and disseminated lesions and visceral leishmaniasis. Clinical outcomes depend largely on the specific immune responses to *Leishmania* antigens. In addition, intrinsic parasite virulence factors could contribute to the clinical polymorphism of *Leishmania* infection.

## 5.1 Epidemiology of leishmaniasis (*Aldina Barral*)

Leishmaniasis is a parasitic tropical disease transmitted by the bite of a sandfly. Rodents and dogs serve as a zoonotic reservoir for some strains of the parasite, humans being infected secondarily. In addition, anthroponotic transmission involves humans as a reservoir. It is found in some 80 different countries including India, Iran, Mexico, Sudan and several others. There are about 20 different species of *Leishmania*, which can cause the disease, with varying degrees of severity. The parasite invades the host macrophages, eliciting an intense immune response. In general, leishmaniasis as a disease is divided into two categories.

- Cutaneous leishmaniasis (CL) results in skin lesion(s) that last several months (sometimes years) and are often self-healing. (CL is sometimes further divided into the more severe categories of mucocutaneous and diffuse cutaneous leishmaniases.) Recovery from CL results in immunity to reinfection by *Leishmania*.
- Visceral leishmaniasis (VL, sometimes referred to as kala-azar and principally caused by *L. infantum*, *L. donovani* and *L. chagasi*) is the most serious form of the disease, with parasites in the macrophages of the spleen, liver, lymph nodes and skin and is fatal if left untreated.

Drug treatment typically consists of pentavalent antimonials given systemically for VL or injected at the periphery of the lesions for CL. Because of the diversity of the epidemiology of the different forms of the disease, control is very difficult in endemic areas. Increasing risk factors making leishmaniasis a renewed public concern include population migration, urbanization with inadequate housing, lack of sanitation and deforestation.

Based on years of studies on mice, it is generally accepted that a protective response to *Leishmania* infection must be a Th1-type response – involving cell-mediated immunity, gamma-interferon (INF-g) production, and little or no interleukin-4 (IL-4). Antibodies may also play a role but largely in the context of the Th1 response. However, the actual mechanism of protection in humans is not fully understood, making it difficult to readily evaluate vaccine candidates.

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Sandflies (*Lutzomyia longipalpis*) inject saliva into the mammalian host when probing for a blood meal. Understanding the initial vertebrate reactions against sandfly saliva is important for possible interventions because these insects transmit diseases to humans and other animals. Little is known of these reactions to New World sandflies, but immune responses against saliva components can be demonstrated in individuals from an endemic area for VL. Immunoglobulin-G (IgG) from these individuals reacts predominantly with four major protein bands (35, 43, 44 and 45 kD) of the insect saliva by Western blot. In addition, repeated exposure of BALB/c<sup>5</sup> mice to *L. longipalpis* bites leads to local inflammatory cell infiltration comprised of neutrophils, macrophages and eosinophils. Hamsters immunized with plasmid cDNA encoding salivary gland proteins of *L. longipalpis* were partially protected against *Leishmania chagasi* challenge. Therefore, there is a possibility to use components of the sandfly saliva as part of vaccines against infection by *Leishmania*.

## 5.2 First-generation vaccines: successes and failures (*Ivan Dario Velez*)

Unlike some parasites, *Leishmania* can be easily grown in cell-free media, making whole parasite vaccine preparations possible. First-generation *Leishmania* vaccines consist of whole, killed *Leishmania* parasites with or without BCG or Alum as an adjuvant. Early studies in Brazil (Mayrink, Antunes *et al.*), in Venezuela (Convit *et al.*), and Ecuador (Armijos *et al.*) have indicated that these vaccines were immunogenic and could have a synergistic effect with drugs in the treatment of leishmaniasis. Prophylactic utilization showed little success.

Phase III efficacy trials of first-generation leishmania vaccines were further conducted in both Sudan (VL and CL) and the Islamic Republic of Iran (CL) with ALM (autoclaved *L. major*) – with or without BCG as an adjuvant. They were also conducted in Colombia (CL) with MLA (merthiolate-treated *L. amazonensis*). In addition, two phase II immunogenicity studies were more recently conducted in Sudan and the Islamic Republic of Iran with ALM adjuvanted with alum and BCG. In the latter trial, volunteers were challenged with wild-type *L. major* to assess the protection induced by the vaccine. These randomized, double-blind trials showed that the vaccine induced significant leishmanin skin test (LST) conversion (an indicator of exposure and of cellular immune response to *Leishmania*) but no significant overall protection as compared to controls. In certain studies, there did seem to be some correlation between LST conversion and protection from leishmaniasis. Thus, although there was a positive immune response to the first-generation vaccines, it was not potent enough to induce a high level of protection.

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<sup>5</sup> Sub-strain name.

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### 5.3 Second-generation vaccine trials in South America (*Alexandro Llanos Cuentas*)

The Leish-111f second-generation vaccine – Infectious Disease Research Institute (IDRI), USA – consists of a recombinant three-antigen (TSA, LmSTI1 and LeIF) Leishmania fusion protein Leish-111f, and the adjuvant MPL-SE.

The TSA antigen elicits *in vitro* proliferative responses from peripheral blood mononuclear cells of human leishmaniasis patients. The LmSTI1 antigen induces strong T-cell responses with a Th1 bias. The LeIF antigen, an *L. major* protein, was identified as an immunodominant antigen that stimulates PBMCs from *Leishmania*-infected patients to proliferate, produce a Th1-type cytokine profile, and down-regulate expression of IL-10. Monophosphorylipid A (MPL) is a promising Th1 stimulatory adjuvant, which derives from the lipopolysaccharide (LPS) of *Salmonella minnesota*. MPL is formulated as a stable emulsion for injection called MPL-SE, capable of inducing a Th1 immune response.

The immunogenicity and efficacy of the Leish-111f + MPL-SE vaccine formulation were shown in BALB/c mice, and a phase I trial conducted in the USA demonstrated the safety, tolerability and immunogenicity of this candidate vaccine.

Two phase I clinical trials were further approved in Brazil and Peru to evaluate the therapeutic activity of the Leish-111f vaccine combined with sodium stiboglucomate in cutaneous and mucosal leishmania patients, respectively. In Peru, four cohorts of 12 patients were randomized to receive (at day 0, 28 and 56) 5, 10 or 20 mg of Leish-111f/25 mg MPL-SE or placebo. All patients received conventional drug treatment. Preliminary results of the trial indicate that the vaccine is safe in adult patients and may accelerate cure when given in addition to standard chemotherapy. Further trials are planned to assess the therapeutic (Brazil, India, Peru, and Venezuela) and prophylactic (Colombia and India) value of this second-generation vaccine.

### 5.4 Live attenuated *Leishmania* as vaccine candidate (*Noushin Davoudi*)

Vaccination in humans with live *Leishmania major* (“Leishmanization”) has been shown to often yield life-long protective immunity against reinfection with the same parasite. Although the procedure was found to be generally safe, leishmanization has been discontinued because of problems associated with virulence of wild-type parasite strains. To circumvent this, various approaches using the most recent technologies are being developed to generate attenuated parasite strains.

The use of live attenuated parasites has proven to be particularly successful against murine leishmaniasis. One type of attenuated strain consists of genetically engineered parasites with “suicidal cassettes” for self-destruction. Auxotrophic mutants like cysteine proteinase b-deficient, *dhfr-ts*<sup>-/-</sup> and phosphoglycan-deficient *L. mexicana* and *L. major* mutants, have been demonstrated to protect highly susceptible mouse strains against challenge with wild-type virulent *Leishmania*. Moreover, as recovery from *L. major* also protects against *L. mexicana* and possibly *L. donovani* infections, protection provided by a live *L. major* vaccine is expected to be broad.

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## *Discussion*

Leishmaniasis is among the most serious infectious diseases in developing countries. In spite of control measures through case finding, treatment and vector/reservoir control, the rate of infection with *Leishmania* remains high. That the majority of individuals who have previously developed active leishmaniasis or asymptomatic infection are resistant to a subsequent clinical infection provides a rationale for vaccine development. However, the mechanisms responsible for the effective protective immune response are not fully understood, and their definition is crucial for vaccine design and evaluation.

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# 6. Panel discussion on new regulatory approaches to vaccine licensing in developing countries

## 6.1 Introduction (*Julie Milstien*)

The first presentation on “Regulatory Pathways for Developing Market Vaccines” to the Global Vaccine Research Forum occurred in 2002. Since that time, the following progress has been made.

- The European Agency for the Evaluation of Medicinal Products (EMA) procedure for Scientific Opinion on behalf of WHO has been finalized.
- There is an increase in manufacturing of new products in developing countries (for example, the meningococcal A conjugate at the SIIIL).
- Some industrialized country manufacturers are registering vaccines first in developing countries (for example the GSK rotavirus vaccine made in Belgium, finished and registered in Mexico).
- The Developing Countries’ Vaccine Regulators (DCVR) Network has been launched.
- Regional approaches to strengthen regulatory processes are under development.

## 6.2 The Developing Countries’ Vaccine Regulators Network (*Sergio Nishioka*)

The regulatory responsibility for follow-up of clinical development and for the licensing of new vaccines is falling more and more on the NRAs of developing countries. WHO promotes the strengthening of procedures for evaluation of clinical trial proposals and clinical data, through the establishment of a network of developing country regulators.

The following eligibility criteria are used to select member developing countries participating in this network:

- countries which produce at least one WHO prequalified vaccine, i.e. WHO has given positive advice to UN agencies on the acceptability, in principle, of the quality of one particular vaccine manufactured in this country;
- countries with:
  - a functional NRA that meets the six critical regulatory functions as defined by WHO (these relate to: licensing of vaccines; post-marketing surveillance; lot release procedures; access to control laboratory when needed; performance of regulatory inspections; and authorization and supervision of clinical trials); *or*
  - a government-endorsed workplan with timelines to achieve this;

- 
- countries with domestic expertise in research on new and combination vaccines, and with recognized medical institutions for clinical research targeted on the control of infectious diseases; and
  - countries which are likely to be the first to perform trials or license new vaccines.

Nine countries from five regions were selected as founding members: Brazil, China, Cuba, India, Indonesia, the Republic of Korea, Russia, South Africa and Thailand.

An initial meeting took place in Geneva in November 2002. During this meeting participants gained a better understanding of the regulatory processes for licensure/registration of new vaccines by each NRA, made an inventory of the current situation of the clinical evaluation function, and set up a plan of action for establishing the network. It was decided that each country would have two representatives officially nominated by their Ministry of Health.

After a long and formal process, the network was officially established in Bangkok, Thailand, on 17 September 2004. The name chosen was DCVR Network and representatives from the nine countries signed the Terms of Reference. The mission of the Network, as approved by the founding members, is:

“to promote and support the strengthening of the regulatory capacity of NRAs of participating and other developing countries for evaluation of clinical trial proposals (including pre-clinical data and product development processes) and clinical trial data through expertise and exchange of relevant information”.

The network is mainly a forum for consultation among NRA members on regulatory challenges relevant to new vaccines; the members may also develop guidelines where necessary and assist other non-member NRAs.

The DCVR Network met a second time in May 2005 in Geneva. Members: reviewed the activities performed since establishment; assessed strengths and limitations; developed a methodology of work for joint reviews of clinical trial applications based on a case study; assessed the need for external expertise and prepared a plan to build a database of experts from member countries; developed a plan for fund-raising; established three committees (Scientific Events, Advocacy and Fund-raising, Network Meetings); and agreed on a plan of work for the second half of 2005.

Achievements to date include:

- realization of potential benefits to be gained from collaborating in the assessment of novel/new vaccine dossiers: the capacity-building activity in Bangkok (evaluation of clinical data from two novel vaccines) has had an impact on regulatory decisions;
- sharing/exchange of information:
  - NRA members have shared procedures for assessment of clinical trial applications and monitoring of clinical trials with less developed NRAs.
  - Reports from participation in scientific meetings have been shared within the Network.

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Future expectations include:

- reaching consensus on the methodology of evaluation of clinical trial applications and vaccine dossiers, with a developing country perspective;
- strengthening the capability of individual NRAs for such evaluations;
- ensuring compliance of developing country manufacturers to internationally accepted requirements;
- initiating a dialogue with multinational manufacturers in order to plan for the development of novel vaccines, taking into account developing countries' perspectives; and
- providing guidance to less developed NRAs / supporting regional initiatives.

The DCVR Network has the potential to make a great impact in improving regulation of vaccines worldwide. In order to achieve this, strong commitment and political will of member countries is required.

### **6.3 WHO's initiatives for strengthening regulatory pathways for new vaccines (*Liliana Chocarro*)**

In the past few years, many changes have taken place in the development and regulatory framework of vaccines. Some vaccines that are still used in developing countries are no longer employed in the industrialized countries that manufacture them (DTP with whole-cell pertussis component, or OPV, for example), and some vaccines are developed exclusively for diseases that are endemic in developing countries (malaria, dengue and some new combinations). Emerging manufacturers from developing countries are major suppliers of priority vaccines. These manufacturers and their regulatory authorities have therefore to demonstrate to countries purchasing their vaccines that they operate at the same level of quality as corresponding producers and institutions in industrialized countries. In addition, new technologies used to manufacture vaccines pose new challenges to the regulators, starting during clinical development but impacting also on registration and post-approval changes.

EMA will not license new vaccines for exclusive use outside of the European Community, nor will it renew existing licenses if the product is not in the Community's market for three consecutive years. In collaboration with WHO, EMA has developed a regulatory procedure by which EMA will evaluate vaccines upon WHO's request, and provide a Scientific Opinion for those vaccines manufactured in Europe (or by any manufacturer with representation in Europe) that are for exclusive use outside of the Community. The evaluation procedure will be equivalent to that performed for licensing through the centralized procedure and includes a mechanism to ensure ongoing regulatory oversight. EMA will issue the Scientific Opinion on condition that the manufacturer provides a commitment that it will implement a programme for post-marketing surveillance.

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Although the Scientific Opinion procedure will address the new problem arising from the impossibility of obtaining a licence from EMEA for products not intended for the European Union market, the authorization of clinical trials for products developed in Europe or in the USA and intended only for export is not addressed by the regulatory agencies of the manufacturing countries. Therefore, if EMEA and the FDA do not authorize the clinical trials and the NRAs of the target countries do not have the capacity or are not informed about them, these clinical trials could be performed without regulatory oversight. To avoid such a situation, the NRAs of countries that have clinical trial sites need expert support to assess clinical trial applications and monitor clinical trials in their countries.

The DCVR Network is addressing this issue in participating countries. For other countries, there are additional WHO initiatives to support the establishment of regional regulatory networks and to facilitate/coordinate joint activities. A regional approach has been chosen because of the following.

- There is a need to address the issue now, prior to the completion of activities planned for strengthening of individual NRAs.
- Coordination of joint activities for common regulatory issues is needed: WHO will help those countries with the same challenge to combine efforts and access whatever expertise is required to carry out a proper assessment of clinical trial applications.
- Optimization of resources is required (local expertise and a pool of experts for different vaccines).

The potential areas of collaboration of regional regulatory networks are:

- development of harmonized procedures for evaluation of clinical trial applications and monitoring of clinical trials;
- joint review of clinical trial proposals; and
- attendance at meetings relevant to clinical trials of vaccines in the region (and sharing the knowledge with other NRAs).

Several regional initiatives are already in progress. In the WHO Africa Region, countries that are targeted for clinical trials of a meningococcal A conjugate vaccine and of HIV vaccines have participated in NRA planning workshops, have attended training in clinical evaluation and will participate in a workshop for evaluation of their legal framework and development of procedures for authorization and monitoring of clinical trials. This sequence of activities prepares the NRAs for joint evaluation of clinical trial applications or evaluation of clinical data in registration dossiers. The aim is to expand this African network into a Regional Regulatory Network in the near future.

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In the South-East Asia Region and the Western Pacific Region, the Association of Southeast Asian Nations (ASEAN)<sup>6</sup> has approved a WHO proposal to expand their pharmaceutical working group to biologicals. A proposal for an agreement between ASEAN and WHO for a bi-regional network for clinical evaluation of vaccines has been discussed during the annual ASEAN meeting in August 2005 in Singapore.

#### **6.4 From NRA assessment to prequalification to procurement by UNICEF and the PAHO revolving fund (*Liliana Chocarro on behalf of Nora Dellepiane, who was unable to attend*)**

WHO advises UNICEF and other UN procuring agencies on the acceptability, in principle, of vaccines from different sources. The objectives of this process, called prequalification, are to provide UN purchasing agencies with an independent opinion on the quality, safety and efficacy of vaccines available for purchase, to ensure that candidate vaccines are suitable for the target population, meet the needs of the immunization programmes and comply with specifications and established standards of quality.

The prerequisite for WHO to consider a product from any given manufacturer for prequalification is the functionality of the NRA. Therefore, the NRA is assessed for performance against a set of established indicators for the six critical functions mentioned above (see 6.2). The NRA indicators were revised in June 2004. Some indicators were defined as critical for adequate performance of the regulatory function. Therefore, if the authority fails even one critical indicator the function is deemed not to be exercised to a level which complies with the requirements for prequalification. For those NRAs that had been assessed using pre-June 2004 indicators, a grace period of 18 months was granted for full implementation of the new criteria.

The prequalification process consists of a review of the product summary file (PSF), a testing of consistency lots, a consultation with the NRA and a site visit to manufacturing facilities. The procedure has been recently updated to increase involvement of the NRAs, to adapt the process to new challenges, including clinical evaluation of novel vaccines, to make the process more flexible where possible and faster (target: one year between submission of the prequalification dossier by the manufacturer and decision) and to address increasing workload. There is now a defined schedule for submission of PSFs, more flexibility in the testing and reassessment procedures and more guidance on the information required for clinical trials. In addition, conditions have been laid down for an evaluation in parallel with the review undertaken by an NRA for the first licensing of a new product.

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<sup>6</sup> ASEAN has the following Member Countries: Brunei Darussalam, Cambodia, Indonesia, the Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Viet Nam.

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## *Discussion*

The EMEA Scientific Opinion process elicited a number of questions. Some of the meeting participants suggested that care must be taken to ensure that the Scientific Opinion reflects the perspective of the countries that will use the product. In addition, it is very important to ensure that the process is viewed as rigorous and does not reflect regulatory shortcuts.

An additional area for discussion involved the strengthening of developing countries' capacity and infrastructure for clinical trial review and regulatory oversight. It was noted that while ethics committees are becoming stronger in many countries where clinical trials for new vaccines are being conducted, regulatory oversight is often overlooked. Participants felt that it is a sponsor's responsibility to ensure that this capacity and infrastructure is developed in countries where it undertakes clinical trials.

Finally, the issue of developing capacity for evaluating risks/benefits in the regulatory approval process was discussed. It was noted by several participants that such an issue was of paramount importance, and that WHO could play a lead role in drawing attention to the need for and solutions to developing such capacity.

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# 7. Prospects for new vaccines against influenza

## 7.1 Review of the epidemiological situation with avian flu (*Albert Osterhaus*)

Influenza pandemics in the 20<sup>th</sup> century killed approximately 50 million people; and pandemic influenza is currently considered as one of the most important global public health threats. Avian influenza is caused by type A viruses. Although 15 subtypes of influenza A virus are known, to date all outbreaks of highly pathogenic forms of avian influenza have been caused by subtypes H5N1, H7N7 and H9N2. An outbreak of H7N7 virus in the Netherlands in 2003 caused 89 cases of infection in humans (one patient died and the rest experienced common flu symptoms). H9N2 influenza virus has been among the most prevalent subtypes of avian flu circulating among birds in China, including the Special Administrative Region (SAR) of Hong Kong, infecting at least eight individuals in the region. An outbreak of H5N1 was reported in Hong Kong and southern China in 1997, killing six people. Since late 2003, H5N1 viruses have led to 100 cases of human disease causing 54 deaths in Cambodia, Thailand and Viet Nam. The most vulnerable human populations are farmers and their families. Since 1997, the original H5N1 viruses have evolved, resulting in changes in their antigenic structure, internal gene constellation, host range, virulence and intra-species transmission.

Migratory waterfowl – most notably wild ducks – are the natural reservoir of all influenza A viruses and have historically carried low-pathogenic viruses, without symptoms of disease. However, recent findings suggest that the role of migratory waterfowl in the evolution and maintenance of highly pathogenic H5N1 may be changing. Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza. Viruses can survive for a long period in the environment and are readily transmitted from farm to farm by mechanical means: contaminated equipment, vehicles, food, cages and clothing. Viruses can moreover spread from county to country through international trade of live poultry and via migratory birds.

The current H5N1 virus is fatal for tigers and leopards. In experimentally infected domestic cats, H5N1 virus was identified histologically in different organs and tissues. The high pathogenicity of the H5N1 virus in mammals is possibly related to extra-respiratory viral replication and to the severity of associated lesions.

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Changes in the ecology and behaviour of the virus have created multiple opportunities for a pandemic H5N1 virus to emerge. With the virus now endemic, this probability has increased. H5N1 viruses have not yet gained the ability to transmit readily from person to person but, if they do, the virus could spread across the world within months, and the consequences for global public health are difficult to predict.

There is an urgent need to improve the molecular diagnostic capability in Asia, and to increase the collection rate of serological and autopsy data from affected areas. WHO recently issued a revised global influenza preparedness plan that provides recommendations for national measures before and during pandemics.

## **7.2 The Hong Kong SAR surveillance system for avian influenza: results (*Shuk Kwan Chuang*)**

A number of human outbreaks of influenza A viruses has occurred in recent years in Hong Kong SAR:

- 1997 (H5N1: 18 confirmed cases and 6 deaths)
- 1999 (H9N2: 2 confirmed cases)
- 2003 (H5N1: 2 confirmed cases and 1 death)

Control strategies to prevent dissemination of these viruses in humans include surveillance of avian influenza virus infection, immunization against influenza of workers involved in bird culling, use of antivirals in high-risk groups, strengthening of laboratory support, sustained public education and communication, development and use of pandemic influenza response plans. Control strategies in poultry focus on vaccination, regulation of local farms, tightened biosecurity measures, import control, market rest days when all markets are simultaneously emptied and cleaned, hygiene requirements on wholesale markets and retail outlets, animal surveillance and rapid responses to outbreaks. In order to avert a pandemic in 1997, Hong Kong reacted by destroying its entire poultry population of 1.5 million birds. The main goals of control strategy have been achieved by model interagency cooperation between the Hong Kong departments of health, agriculture, and food and safety and with Hong Kong University.

Compulsory notification of influenza H5, H9 and H7 was introduced in Hong Kong in 2004 and reporting criteria were developed. Since January 2004, 18 suspected cases have been investigated and no avian influenza infection has been confirmed. The number of outpatient clinics involved in human surveillance was increased from 29 in 1998 to 44 in 2004. Both public and private sectors are providing confirmatory testing for influenza. In 2004, more than 53 000 specimens from poultry and birds were tested in laboratories. Typing and subtyping of all influenza isolates are performed at the Public Health Laboratory Services Branch and antigenically atypical isolates are forwarded to WHO Collaborating Centres for further analysis. A procedure for exchange of data with neighbouring towns (Guangdong and Makao) and countries was established with the objective of providing outbreak monitoring of avian influenza in the region. Dissemination of information include web-based weekly updates and periodical publications.

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### 7.3 Development of broad spectrum influenza vaccines and update on clinical trials with H5N1 vaccines (*John Wood*)

#### *Development, production and evaluation of pandemic vaccines*

Vaccination is the most effective weapon to combat pandemics. However, in the past, influenza vaccines have never been available early enough and in sufficient quantity to have a considerable impact on morbidity and mortality during a pandemic. For instance, only 20 million doses of vaccine were available in 1968 in the USA five months after the emergence of the pandemic H3N2 strain and two months after the beginning of vaccine production.

It is estimated that billions of people might benefit from influenza vaccination in case of a global pandemic. However, at this time, the world's total vaccine production capacity is limited to about 900 million doses of monovalent vaccine, which is realistically insufficient to meet global demand, taking into account that two doses may be needed to elicit satisfactory immune responses in immunologically naive populations. As a new vaccine for seasonal influenza is produced each year, requirements for production and licensing are similar. In contrast to this, manufacturing of a vaccine against pandemic virus faces significant challenges, as all steps are, of course, carried out under emergency conditions.

One way to potentially increase vaccine supply would be to lower the quantity of antigen per dose and to use an adjuvant. Another solution would be to improve current vaccine production technologies based on propagation of vaccine virus in fertilized chicken eggs. Several pharmaceutical companies are considering projects to develop cell-derived vaccines, as this could help overcome current vaccine production bottlenecks, limited availability of pathogen-free egg supply and time constraints. Intradermal application of vaccine might also stretch vaccine supplies. In addition, it has become possible to save time by using a reverse genetic technique for the development of prototype vaccine strains.

In November 2004, WHO convened a meeting to explore ways to expedite the development of vaccines against H5N1 pandemic virus. WHO influenza reference laboratories developed H5N1 prototype virus seed stocks to be used for vaccine production, and made these available to manufacturers in April 2004. Prototype viruses were developed using traditional reassortment and reverse genetic techniques. Manufacturers involved in the development of pilot H5N1 pandemic vaccine are located in Australia, Canada, China, Japan, France and the USA. Inactivated vaccines with or without adjuvant and live attenuated vaccine are currently in development. At least three vaccines have already entered clinical trials. Others are at the level of industrial development, production and evaluation in animals. Some manufacturers are dealing with production and evaluation of H9N2 pandemic vaccine in clinical trials. In November 2005, WHO will hold a meeting on influenza pandemic vaccines to review the development of prototype vaccine strains, review recent data on the evaluation of pandemic vaccines in animals and clinical trials and recommend research/activities to accelerate availability of effective vaccine.

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### *Development of broad spectrum influenza vaccines*

Control of influenza virus through vaccination is limited by relatively short-term past vaccination immunity and by continual antigenic variation of the major viral surface glycoproteins, in particular haemagglutinin (HA), against which neutralizing antibodies are directed. When inactivated vaccine contains antigens that are well matched with those presented by the circulating strains, they are effective in preventing influenza in the majority of the population. However, when those antigens are not well matched, protection post-vaccination is reduced.

In 2003, WHO established a research project to promote the development of novel influenza vaccines that induce broad spectrum and long-lasting immune responses, and provide protection against divergent influenza viruses. Such vaccines could help to overcome the problem of the current vaccination strategy based on annual intervention and contribute to the control of epidemics and potential pandemics.

This project builds on previous research which has accumulated the following results:

- Through the use of animal models, it has been shown that mucosal delivery of inactivated vaccine is superior to parenteral vaccination for induction of cross-protection against multiple influenza viruses, including those with pandemic potential.
- In order to overcome some limitations of inactivated vaccines, studies were performed to evaluate the capacity of various adjuvants to stimulate immune responses. It was demonstrated that influenza immunostimulating complexes (ISCOMs) induced cross-protection in vaccinated laboratory animals.
- Experimental vaccines containing M2 protein and/or nucleoprotein are effective in protecting animals against challenge with heterologous viruses.

However, these studies are fragmented and WHO experts identified the following lines for future research: (a) mucosal application of inactivated and live vaccines; (b) use of adjuvants to improve immunogenicity of vaccines; and (c) generation of vaccines that target conserved viral proteins (M2, nucleoprotein).

The role of WHO is to provide a forum for coordination of international efforts in the development of new vaccines, to review and update biological standards, to facilitate the harmonization of regulatory requirements for vaccine development, and to coordinate research to accelerate the availability of vaccines for pandemic influenza. In January 2005, experts attending a WHO consultation identified specific activities to be carried out in the area of immunological assays for evaluating the immunogenicity and efficacy of new influenza vaccines. An international collaborative study is now underway to standardize neutralization tests for influenza viruses. The project includes the development of a standardized protocol and the establishment of a reference reagent bank.

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## *Discussion*

During the discussion, several observations were made.

- As with human influenza viruses, prolonged circulation of an avian H5N1 virus in nature results in a change of its antigenic and genetic characteristics. Establishment of a repository of H5N1 strains isolated at different times and in different countries could contribute to future research programmes and to the development of effective vaccines and sensitive diagnostic assays.
- Monitoring of virological, serological and clinical parameters of H5N1 infection in humans, poultry, wild birds and animals is needed. There is also a need to characterize pathology in detailed autopsies and to establish appropriate animal models to evaluate available intervention strategies.
- The actions of the Hong Kong Public Health and Veterinary Services illustrate how control of avian influenza can be obtained. However, certain components of the Hong Kong model might be too costly for introduction into some larger countries.
- Vaccination of poultry is an important strategic element in gaining global control of the circulation of pandemic virus. However, agricultural vaccines are of variable quality and the establishment of a single international standard for vaccines is recommended.
- At present, the main manufacturers of influenza vaccine are located in Europe and North America. Some developing countries expressed their interest in establishing facilities for vaccine production and this initiative should be encouraged.
- There are ongoing pilot projects to develop, produce and evaluate H5N1 and H9N2 influenza vaccines.
- Those pandemic vaccines currently in clinical trials will provide important information on vaccine safety and immunogenicity and should prove useful in establishing technology to produce large quantities of vaccine in a short time.
- Local immunity is important for protection for vaccines delivered via the respiratory tract, and improved methods are needed to evaluate this immunity.
- In many animal studies, the status of T-cell immune response correlates with protection caused by infection or vaccination. However, there is limited information to link T-cell assay results with protection in humans. Further studies should determine the role of T cells in controlling infection in humans and improved methods should be developed in order to reach this goal.

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## 8. Keynote address: polio eradication (*Déó Nshimiramana*)

Polio eradication is in its final phase. During the last few years significant progress has been made in most remaining polio-endemic areas and it has been confirmed that global eradication of poliomyelitis is technically feasible. Global routine vaccination coverage among infants with three doses of OPV was estimated at 78% in 2003. Reported coverage varied among WHO regions from 91% in Europe to 61% in the African Region, with wide-ranging country-level estimates. To raise population immunity, supplementary immunization activities (SIAs) to vaccinate children were conducted in 2004 in 44 countries. Progress has been made in terms of reducing transmission in many endemic countries in Asia, such as Afghanistan, India and Pakistan. There is a decrease in the number of polio cases reported from Asian countries, from 336 in 2003 to 193 in 2004, and in 2004 India reported the lowest number of cases ever.

However, global progress was threatened by a resurgence of polio in Africa in 2003–2005, which spread from Nigeria into 14 previously polio-free countries. Local transmission was re-established in six African countries. In 2004, Nigeria reported the highest number of new cases (792) in the world. The Sudan outbreak subsequently led to virus importation into Ethiopia, Indonesia and Saudi Arabia. This situation is explained by a decrease in number, extent and quality of SIAs in several African countries.

In response to the resurgence of polio in Africa, national immunization days (NIDs) in 23 western and central African countries and Sudan were synchronized in 2004, reaching more than 80 million children. In 2005 the synchronization of NIDs between 21 countries continued.

The *Ad Hoc* Advisory Committee for Global Polio Eradication met in September 2005 to review epidemiological data and determine actions which should be taken to reduce this risk.

### *Discussion*

During the discussion, several observations were made.

- Tremendous progress was made by the Polio Eradication Initiative from 1988 to 2003. However, the current funding gap may jeopardize the ultimate goal of interruption of polio transmission by 2005.
- New vaccines are an important tool in reaching the objectives of the Polio Eradication Initiative. Monovalent OPV type 1 has recently been licensed and is being used in the final stage of eradication. Monovalent types 2 and 3 will also need to be licensed in order to establish stockpiles of OPV for the post-eradication era.

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# 9. Adjuvants and immodulators

## 9.1 Overview and mechanisms (*Derrick O'Hagan*)

Adjuvants have historically played a critical role in the development of successful vaccines: in the simplest form they have permitted the induction of protective levels of antibodies by non-live vaccines, but at a finer level they have increased functional (e.g. neutralizing) antibody titres, permitted the use of smaller doses of antigen, decreased the number of doses required, enhanced immunity in specific populations such as geriatrics, permitted the induction of cell-mediated immunity, and have promoted the induction of local immunity to mucosally administered antigen. It is likely that existing and novel adjuvants will be required for new vaccines against diseases for which we do not yet have vaccines (notably against HIV, malaria and tuberculosis).

It is useful to classify adjuvants into two basic groups.

- 1) Antigen delivery systems, which physically carry or present antigen to the immune system. Examples of antigen delivery systems include aluminium salts, emulsions, virosomes and microparticles.
- 2) Immunopotentiators, which stimulate the innate immune response by activating innate immune cells and/or modify intracellular processing of the antigen. Examples of immunopotentiators used in vaccines include the following:
  - Monophosphorylipid A (MPL, manufactured by the Corixa Corporation, USA, now GSK) derived from the lipopolysaccharide of *S. Minnesota*. This molecule interacts with TLR-4. GSK uses it formulated with alum (referred to as AS04) and with oil-in-water emulsion (referred to as AS02). Over 27 000 humans have been immunized with antigens formulated with MPL so far. It is used in the already licensed Fendrix™ (HepB vaccine) and soon-to-be-licensed Cervarix™ (HPV vaccine).
  - QS21 (manufactured by Antigenics, USA). This is a highly purified fraction of Quil-A saponin extract from the bark of the *Quilalaria saponaria* tree, currently in clinical trials combined with oil-in-water emulsions (GSK's AS02). Less pure fractions are used in the formulation of ISCOMS. The mode of action is not fully understood but may involve modified intracellular processing.
  - Oligonucleotide-based adjuvants. Several competing approaches including CpG, ISS and IMO are available. These optimized non-methylated DNA sequences are recognized primarily by TLR-9, although there is significant complexity since TLR-9 is different in different species. Concerns have been raised about the potential of these molecules to trigger autoimmunity.

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Key signals for successful immune induction can be viewed as comprising:

- signal 1: the antigen, whose effect can be prolonged or enhanced by delivery systems through depot effects and promotion of antigen presenting cell (APC) uptake;
- signal 2: co-stimulatory (non-self) molecules; and
- signal 0: pattern recognition receptors (PRRs), whose activation can stimulate innate immune responses. This generates a qualitative difference in the immune response (Th1 vs Th2) and can enhance signal 2 (through cytokine production etc.).

There is therefore a potential synergy between delivery systems and immunopotentiators. Particular examples provided from Chiron's research programme showed synergy between antigen delivery systems using microparticles and immunopotentiators.

- Microparticles may have several potential advantages including their ability to deliver antigens directly to the APCs, to present multimeric copies of antigen on the surface for optimal B-cell interaction, and to permit the co-delivery of immune potentiator and antigen. Being made of a biodegradable polymer, microparticles leave no residue in the body. The Chiron approach is to bind the antigen to the surface of the particle through ionic interaction, rather than to entrap the antigen.
- The antigen MB1 on microparticles to which CpG has been added is far more immunogenic than on microparticles without CpG, which is itself more immunogenic than MB1 adsorbed on alum or free MB1 admixed with CpG. This demonstrates a synergy between the microparticles and the CpG immunopotentiator.
- A similar synergy was seen for the gp120 HIV antigen added to microparticles containing the low-molecular weight immunopotentiator Resiquimod. It is of note that for Resiquimod it is essential that the immunopotentiator is entrapped within the microparticles.

MF59, an oil-in-water emulsion, was given as an example of another antigen delivery system. This adjuvant is already in licensed products (flu vaccine) and has been shown to significantly enhance immunogenicity of the vaccine. In non-human primate studies with Hib and meningitis-C conjugate vaccines, MF59 was also a significantly better enhancer of the immune response than alum.

The adjuvant effect of MF59 can be further enhanced by the addition of immunopotentiators such as CpG. This was shown in mice using the hepatitis C virus E1E2 antigen: addition of CpG enhanced the total IgG by 60% compared to antigen in MF59 alone. More importantly, the MF59-CpG combination redirected the immune response from a Th2 response to a Th1 response with IFN-g secreting cells and a high IgG2a:IgG1 ratio.

In conclusion, we are only beginning to understand how to select immunopotentiators and how to formulate antigens and immunopotentiators in a rational manner. This seems to be best achieved by associating the antigen with an antigen delivery system, and combining this with a stimulator of the innate immune response.

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Our understanding of the innate immune response now opens up the possibility of performing high-throughput screening for adjuvants, and combining this with high-throughput antigen screening to streamline the vaccine discovery process.

## **9.2 Review of the risks of non-specific immune stimulation by adjuvants** *(Heather Davis)*

Immunostimulatory oligonucleotides such as oligonucleotides containing non-methylated CpG sequences are recognized by the intracellular toll-like receptor 9 (TLR-9). This receptor evolved to recognize bacterial and viral DNA and to respond with rapid induction of the innate immune response. As outlined above, induction of the innate immune response in the presence of foreign antigen results in an enhanced induction of the adaptive immune response.

CpG-containing oligonucleotides (referred to as CpG) have been widely demonstrated as effective adjuvants in animal models for all types of antigens (for polysaccharide antigens the CpG must be conjugated to the sugar). They have been shown to allow 10 to 1000-fold dose sparing of antigen, to be effective in immunodeficient animals (e.g. in orangutans hyporesponsive to hepatitis B vaccines) and also to be effective with vaccines administered via the mucosal route.

Many clinical evaluations have been performed using a CpG-containing oligonucleotide sequence referred to as CpG 7909 – selected for its potent in vitro activity on human primary blood mononuclear cells (PBMCs). Examples include the following.

- **Phase Ia studies in healthy volunteers of CpG with Engerix B** (hepatitis B vaccine from GSK). Here the addition of CpG to the commercial vaccine resulted in earlier antibody responses and seroconversion, higher antibody levels over all time periods, and greater avidity of the antibodies for the antigen. Local and systemic reactions to the vaccine were not significantly different compared to Engerix B alone.
- **Phase Ib studies of CpG with Engerix B in HIV-infected subjects** (including subjects in whom previous administration of Engerix B had failed to induce an immune response). 100% of subjects receiving the CpG-adjuvanted vaccine seroconverted, and after three years the percentage of volunteers who still had titres of >10mIU/ml was 90%, compared with 20% for the vaccine without CpG. The CpG-containing vaccine also induced HBsAg specific lymphoproliferative response in HIV+ subjects.

## **9.3 The challenges to developing adjuvant systems: examples of AS04 and AS02** *(Nathalie Garçon)*

Developing adjuvant systems that can be reliably used in commercial vaccines is complex. The particular examples of AS04 and AS02, both among GSK's lead adjuvant systems, were described.

AS04 is a combination of alum with MPL. MPL presents numerous formulation challenges in that it is a heterogenous complex mixture of molecules, is hydrophobic and insoluble, and tends to aggregate and clump. These factors affect the biological activity and also the ease of processing (for example sterilization presents a challenge).

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MPL was identified as a useful adjuvant in 1985 and was licensed to GSK for its vaccine programme in the late 1980s. The technical challenges to its use, however, resulted in a very long delay (to 2003) before its first registration in a product (Fendrix; HepB vaccine). It is a component of GSK's Cervarix (HPV vaccine) soon to be licensed. In Cervarix, the addition of MPL was shown to enhance the antibody titres significantly.

AS02 is a combination of an oil-in-water emulsion, with MPL and QS21. QS21 presents several formulation challenges, including the fact that it is chemically unstable (it hydrolyses at pH above 6 resulting in a product which has no adjuvant activity), and is reactogenic upon injection.

The utility of QS21 as an adjuvant in vaccines was identified in the mid-1980s, and it was licensed to GSK in the early 1990s. Overcoming formulation challenges, and recognizing that QS21 was best used in combination with another immunopotentiator (MPL) and an antigen delivery system (oil-in-water emulsion) took several years (until the mid-1990s), and proof of concept in human trials has only just been achieved using the malaria vaccine RTS,S.

The advantage of AS02 (oil-in-water emulsion + QS21 + MPL over AS04 (alum + MPL) or AS03 (oil-in-water emulsion alone) was demonstrated in malaria challenge models where AS02-adjuvanted vaccine protected six out of seven volunteers, while AS03 protected only two out of seven, and AS04 only one out of eight.

In conclusion, the development of adjuvant systems is a lengthy and complex process, and having access to the immunostimulant or antigen delivery system is only the start. Numerous other factors need to be taken into consideration, including securing raw material, ensuring adequate read-outs and their validation, and developing a commercially viable process etc. This activity can more readily be justified when there is a pipeline of vaccines, which would benefit from the development, rather than doing all the development for a single vaccine candidate.

#### **9.4 Mucosal adjuvants and the challenge of mucosal immunization with recombinant antigens (*David Lewis*)**

Mucosal adjuvants, as has been described for parenteral adjuvants, can be classified into antigen delivery systems and immunomodulators.

- The delivery systems protect the mucosally delivered antigen against expulsion (ciliary action, peristalsis) and enzymatic degradation, and promote transport across the epithelia. Examples include: cationic polysaccharides such as chitin, which act as mucosal adhesives; microparticles based on polylactide-glycolide and ISCOMS, which target M cells and the associated lymphoid tissue; stabilization systems such as enteric coats which protect against gastric acidity in order to deliver antigens to the ileum; and cell-surface binding molecules such as fimbriae, lectins etc., which attach the antigen to epithelia.

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An example of the adjuvant activity of a chitosan was provided: dry meningitis-C conjugate vaccine was mixed with dry chitosan, and the powder delivered nasally to human volunteers using a pipette. Immune responses in naive individuals following two nasal administrations of the powder were comparable to that achieved after intramuscular injection of the vaccine. In individuals who had received previous intramuscular priming, a single nasal administration boosted the antibody response significantly.

- Mucosal immune modulators include cytokines, toll-like receptor agonists such as CpG, poly (I:C), imiquimod etc., and also bacterial toxins including cholera toxin (CT), *E. coli* heat labile toxin (LT), cytotoxic necrotizing factor1, *Pasteurella multocida* toxin, and various mutated forms of these.

The mechanism of action of the bacterial toxins is not precisely known, but may include enhanced expression of costimulatory molecules, cytokine expression, increased membrane permeability etc.

The most widely investigated of these is LT and mutated forms of LT where genetic mutations have been introduced to diminish toxicity while maintaining adjuvanticity. Of these, LTK63 appears the most promising, having no detectable toxicity while maintaining significant adjuvant activity. Another lead candidate is CTA1-DD which comprises the cholera-toxin A component (enzymatic activity) linked to *Staphylococcus aureus* cell-binding protein. This appears to have greater adjuvant activity than LTK63.

The risk of using bacterial toxins for nasal vaccines has been illustrated by the occurrence of an adverse event (Bell Palsy) following use of LT in an intranasal flu vaccine (Berna Biotech, Switzerland). This risk was not detected in preclinical toxicity studies, nor in clinical trials, and was only seen through post-market surveillance. A mechanism for this phenomenon was later proposed whereby LT binds ganglioside M1 on the facial nerve and causes inflammation.

In conclusion, mucosal vaccines can induce effective immunity in humans. For non-live vaccines an antigen delivery system or immunostimulator or both will be required – numerous possibilities exist which are currently entering phase I trials.

## 9.5 General discussion: access for public sector development (*moderated by Martin Friede*)

Vaccine formulation is frequently the weakest link in public sector and biotech vaccine development. While significant experience and resources are available to identify antigens, express and purify them, and later to evaluate preclinical and clinical immunogenicity, the process of formulation is esoteric and often receives little attention. It is a topic not taught in university courses, and the few people with a broad experience in this area are generally in industry. Yet inappropriate formulation can result in a potentially useful vaccine failing, or being too complex to develop commercially.

Many parameters need to be taken into account when considering how to formulate vaccines, including the nature of the antigen, the type of immune response desired, the route of administration, target population etc., and access to the adjuvant is only one of these.

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Access of public-sector vaccine development groups to effective adjuvants is seen as a limiting factor in the development of novel vaccines against diseases such as tuberculosis, HIV and malaria. Several proposals to address this bottleneck were presented.

- The public sector could purchase licences for the use of particular adjuvants in these vaccines, and allow public sector developers to use them. One of the caveats of this approach is that without extensive know-how on how to use the adjuvants, simple access is insufficient. Going from having access to having a product is a lengthy and costly process.
- The public sector could develop novel adjuvants by, for example, promoting research screening for TLR agonists and paying for their development. This too is a lengthy and costly process.
- More useful may be the concept of a public-sector formulation centre, facilitating access to proprietary adjuvants, providing a source of experience and know-how to developer groups on how to formulate their vaccine, and potentially providing a formulation service.

During discussions, there was general agreement that such a centre would be an asset for public sector developers. However, it was clear that the question of how to provide such a service and how to address intellectual property rights issues requires a lot of further thinking and discussion.

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# 10. New vaccines against *Shigella* and ETEC

## 10.1 Panel discussion on ETEC diarrhoea disease burden study results

### 10.1.1 Overview of global ETEC disease burden (Firdausi Qadri)

Enterotoxigenic *E. coli* (ETEC) is a common cause of watery diarrhoea in all ages, in particular in children one to four years of age. It is estimated to cause some 280 million episodes of disease and some 400 000 deaths annually. Moreover, it is believed to account for some 20–25% of all cases of diarrhoea in children, and up to 40% of cases of traveller diarrhoea. Repeated episodes of disease in children are associated with long-term morbidity, manifested by malnutrition and growth faltering.

Global prevalence of ETEC in diarrhoeal patients has been demonstrated in case-control studies. However, ETEC isolated from patients in various geographic areas differ by toxin profile. Isolates produce either heat labile toxin or heat stable toxin (ST) or both (LT/ST); in addition more than 25 colonizing factors (CF) have been identified. More than 100 different ETEC O-antigen serogroups can be differentiated, out of which some seven to eight are common, and this diversity has hampered inclusion of O antigens in the vaccine development pipeline.

In Bangladesh, ETEC disease burden studies have been conducted in conjunction with studies on *V. cholerae*. Birth cohort studies of natural ETEC infection at Mirpur field site revealed some 6.6 diarrhoea-days per child and per year, and a prevalence of ETEC diarrhoea of 19%, higher than for any other enteric pathogen isolated from diarrhoeal stools. Stratification by hospital and community setting, however, shows the highest prevalence of rotavirus in hospitalized cases, whereas ETEC remains highest in community cases, pointing towards greater severity of rotavirus disease. Prospective data has revealed that, at least for some CFs, protection is conferred against symptomatic reinfection with ETEC expressing the homologous CF.

ETEC can be a major cause of watery diarrhoea in disease epidemics associated with flooding, and the environment has been established as a critical source for perpetuation of ETEC infections. Increased antimicrobial resistance has been observed in ETEC isolates with some 50% of isolates being resistant to ampicillin and 16% to ciprofloxacin. Other control measures, in particular improved sanitation and vaccines, are thus urgently needed.

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### 10.1.2 *Disease burden in the Americas (Olga Torres)*

Multiple studies have been conducted in the Americas to determine disease burden due to ETEC, and studies have shown very variable results, with prevalence ranging from 75% (Mexico) to 3.8% (Brazil). A detailed disease burden study was conducted in Guatemalan children (2001–2003) and visitors (1999–2003) to determine the relative importance of ETEC as a cause of diarrhoea in hospital and community settings. In children 6–36 months of age, some 14% of mild–moderate cases of diarrhoea were due to ETEC infection, and the prevalence was up to 26.5% for the severe, hospitalized cases. A strong seasonality, with a peak during the rainy season, could be observed. Up to 30% of Guatemalan visitors coming down with diarrhoea were diagnosed with ETEC infection. Striking differences were seen in CF profiles of strains collected from children and visitors.

The study suggests that ETEC may be underreported in many countries, likely due to the lack of commercially available rapid and simple diagnostic tools. No ELISA tests are yet available and molecular methods remain largely within research settings.

## 10.2 Panel discussion on *Shigella* diarrhoea disease burden study results

### 10.2.1 *Global burden of disease due to Shigella infections (Karen Kotloff)*

The estimation of the burden of disease due to *Shigella* infection is important information for prioritization of interventions, for the design of appropriate case management strategies, and finally to guide efforts to develop vaccines. Here, a meta-analysis was presented to estimate the global burden of disease and the relative contribution to diarrhoeal disease mortality, which accounts for 15% of total mortality in children below the age of five years.

The meta-analysis was based on a literature review covering multilingual publications between 1966 and 1997. Some 305 eligible publications were used to gain information on 10 population strata, covering different age groups as well as industrialized and developing countries. In developing countries, the highest average annual incidence of bacillary dysentery is in children 0–11 months with 3.9 episodes per child and year.

To classify diarrhoea by disease severity, clinical setting was used as a proxy. In children below age five, 88–92% of cases were mild (domiciliary setting), 8–10% were moderate (outpatient) and 0.2–1.5% were classified as severe (hospitalized).

With the proportion of diarrhoeal episodes estimated to be attributed to *Shigella* in different age strata, the annual total shigellosis episodes in children 0–4 years of age in developing countries was estimated at 113 million. Mortality rates for hospitalized cases were derived from studies conducted at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) in the late 1980s and adjusted for out-of-hospital mortality, leading to some estimated 462 000 deaths in the 0–11 months age group and 205 000 in children 1–4 years. Hence, annual mortality in children under five years of age from shigellosis in developing countries was projected to be 667 000 deaths.

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Further analysis on serogroup distribution by region showed considerable geographical variation. *S. flexneri* shows highest prevalence in developing countries, whereas *S. sonnei* dominates in industrialized country isolates. Less prevalent are *S. dysenteriae* and *S. boydii*.

### **10.2.2 Global burden of *Shigella* – a different view (Claudio Lanata)**

A different meta-analysis was presented to assess the global impact of disease due to *Shigella* infection in children over five years of age. Eligible studies were conducted between 1990 and 2002, outbreak investigations being excluded from the literature survey. In total, some 239 articles covering 266 studies looking at all etiologies of diarrhoea were included in the meta-analysis. Selected studies were classified into community-based and health-facility-based studies, including inpatient and outpatient settings.

Estimation of the proportion of diarrhoeal diseases in community studies by etiology suggest only some 4.6% to be due to *Shigella*, whereas ETEC represent some 14% of cases and a quarter of all cases have unknown etiology. In outpatient and inpatient settings, the proportion of cases attributed to *Shigella* was 5.8% and 5.6%, respectively. A significant increase in proportion was observed for rotavirus disease in inpatient settings. Inpatient etiologic proportions were then used as proxy for diarrhoea mortality proportion using the WHO global mortality estimation of 1.8 million in 2000 in the over five age group,<sup>7</sup> leading to an estimated 108 000 deaths due to *Shigella* infection. In contrast, rotavirus was found to account for 500 000 deaths and ETEC for 170 000 deaths, according to this calculation.

This figure contrasts dramatically with the estimate derived from Dr Kotloff's meta-analysis (above) and calls for explanations. A comparison of methodological differences reveals that Dr Kotloff based her assessment on publications that appeared between 1966 and 1997, whereas Dr Lanata's study used more recent publications (1990–2000). Moreover, in contrast to Dr Kotloff's study, Dr Lanata's analysis applied specific exclusion criteria as well as a recent official mortality envelope. Most importantly, however, appears the application of a case-fatality rate to Dr Kotloff's study that has been derived from a study conducted in Bangladesh during the 1980s. More recent estimates of case fatality rates suggest that the figure has decreased substantially during the last two decades.

Both studies suggest that there is a need for standardization of methods, verification of mortality assumptions and for additional studies on the etiology of diarrhoeal diseases.

### **10.2.3 Global burden of *Shigella* – the Asian perspective (Lorenz von Seidlein)**

This study was conducted in the context of the Diseases Of the Most Impoverished (DOMI) project, benefiting from a grant from the Bill and Melinda Gates Foundation. The study objectives were to provide support to the rational development of *Shigella* vaccines by measuring shigellosis disease burden in target countries and by typing *Shigella* species and serotypes. Three rural and three urban study sites from six different countries (Bangladesh, China, Indonesia, Pakistan, Thailand and Viet Nam) were enrolled in the study. Defined catchment areas covered some 600 000 subjects.

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High culture-confirmed shigellosis rates were observed, with the highest being observed in Bangladesh (urban site) with some 57 shigellosis episodes per 1000 per year. Culture-confirmed shigellosis incidence was highest in children of age 0–4 years, decreased towards adulthood, and increased again in the elderly.

To detect sequelae and mortality following shigellosis episodes, follow-up visits and case report forms were completed at several time points up to 90 days after disease. Cases were paired by matched controls. Most importantly, no mortality was observed following shigellosis, and the most frequent sequelae appeared to be pneumonia (6.3% versus 2.5% in the control group). Considerable antibiotic resistance was measured in *S. flexneri* isolates from all sites, but figures were most alarming from the Chinese study site.

Better understanding of the prevalence of different *Shigella* species and serotypes is critical for vaccine development, as type-specific immunity has been demonstrated unequivocally. As expected, the most dominant *Shigella* species is *S. flexneri*, with the exception of Thailand, where *S. sonnei* is most prevalent, hence resembling the pattern observed in industrialized countries. Analysis of *S. flexneri* serotypes revealed complex country-specific patterns, with an overall dominance of serotype 2a. The nine most dominant serotypes cover some 90% of *S. flexneri* isolates.

While the study revealed very high shigellosis rates in target countries, they are likely to be underestimated for a number of methodological reasons. Among those are non-reporting of patients to health care and failures in microbiological detection. Modern approaches such as real time polymerase chain reaction (PCR) can reveal *Shigella* in culture-negative samples and allow quantitative assessment of bacterial load.

### *Discussion*

Discussions addressed the striking differences in mortality observed in the studies presented. Conflicting numbers were considered to be largely due to different assumptions with respect to case fatality rates, rather than to the different methods employed. In fact, both meta-analyses were considered to be very transparent as all assumptions were clearly spelled out. Participants expressed caution about basing assumptions on historical data. The reason for the mortality drop remains unclear, but key contributors could be measles vaccination and vitamin A supplementation.

### **10.3 Current status of *Shigella* vaccine development** (*Mike Levine*)

A critical question for any vaccine is the definition of the target population and public health use. *S. dysenteriae*, while not a common cause of endemic shigellosis, is a causative agent of many epidemics in confined populations, and vaccine would need to be suitable for a reactive public health response. For other *Shigella* species, in particular *S. flexneri*, population-based immunization through EPI would appear more appropriate. Given the species and serotype distribution, a *Shigella* vaccine needs to be multivalent to warrant a sizeable public health impact.

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Several lines of evidence suggest that immunity to *Shigella* can be achieved following infection (this was demonstrated in cohort field studies and challenge studies in volunteers). However, this infection-induced immunity – which can reach levels of up to 80% – only functions against homologous challenge. Multiple candidate vaccines have been developed for both oral and parenteral application. Live attenuated strains for oral vaccination and conjugate vaccine for parenteral administration were discussed in more detail.

Live, rationally attenuated vaccines have been developed at Institut Pasteur (IP, France), the Walter Reed Army Institute of Research (WRAIR, USA) and the Centre for Vaccine Development of the University of Maryland (CVD, USA). Initial studies with a streptomycin-dependent *Shigella* vaccine were conducted in the former Yugoslavia showing efficacy in field trials of up to 93% against *S. flexneri* 1 & 2a. Dosage has been very critical in these vaccines to balance reactogenicity and immunogenicity. CVD supported clinical trials with SC602, an *S. flexneri* 2a mutant, and IP trials with SC599, a *S. dysenteriae* 1 mutant. At a given dose of 10<sup>6</sup> CFU, the candidate was fairly reactogenic in American adults, but very well tolerated in Bangladeshi toddlers. Additional studies corroborate the view that vaccine strains were overattenuated for the target populations, suggesting that the non-immune adult in industrialized countries is not a suitable model to develop vaccines for use in children in developing countries.

O-specific polysaccharide conjugate vaccines have been developed for *S. sonnei* and *S. flexneri* 2a. An efficacy trial is ongoing in preschool children in Israel (*S. sonnei*), and a phase II study with *S. flexneri* conjugate is scheduled for Angola.

Key obstacles for *Shigella* vaccine development remain the multiple target strains, which will require multivalent vaccines or common protein-based approaches. Other barriers include the diminished immunogenicity of oral vaccines in infants and children living under poor conditions in developing countries, letting many vaccine strains appear over-attenuated. The phenomenon of environmental enteropathy needs further investigation and strategies to elicit protective immunity under that condition are yet to be refined. Given these observations, the importance of evaluation of candidate vaccines in target populations is becoming increasingly apparent.

#### **10.4 Current status of ETEC vaccine development** (*Ann-Mari Svennerholm*)

There is good evidence to suggest that a vaccine against ETEC is feasible, based on observations of naturally occurring infections, as well as of challenge studies and protection against LT+ ETEC by oral cholera toxin B subunit (CTB) in field trials. Protective efficacy of oral CTB-WC cholera vaccine against LT+ ETEC diarrhoea has been up to 67% in a field study in Bangladesh. Protective immune mechanisms include antibodies against CFs and LT. Antibodies against homologous O-antigen can also protect. ST has not yet been shown to be protective due to its poor immunogenicity. However, the production and testing of conjugates is envisaged.

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Several vaccine strategies have been developed based on ETEC toxoids. SBL Vaccine is currently evaluating a recombinant CTB toxoid as an oral vaccine. Its safety has been demonstrated and short-term efficacy against LT and LT/ST ETEC is 50–70%. The IOMAI Corporation (USA) is developing an *E. coli* LT for transcutaneous immunization; safety and immunogenicity have been established. Another approach, still at the laboratory stage, is being pursued by expressing LT B subunit in edible crops, such as corn or potatoes.

CF antigens are being tested both as subunit and whole-cell vaccines. While purification of CF has not proven feasible, recombinant antigen has been produced for micro encapsulation and oral delivery, or transcutaneous delivery. Whole-cell inactivated vaccine (four strains of CF-expressing ETEC), combined with recombinant CTB for oral delivery is being developed by SBL Vaccine (rCTB CF-ETEC); clinical trials in travellers suggest good protection against severe diarrhoea but only moderate protection against mild disease. A paediatric phase III efficacy trial of rCTB CF-ETEC was conducted in children of 6–18 months of age in rural Egypt, and preliminary data suggest low protective efficacy in this setting.

The results of this study corroborate other findings to suggest that efficacy of orally delivered vaccine is inferior in children living in low income, high disease burden countries, as compared to volunteers from developed countries. Possible explanations include interference with breast milk antibodies, concomitant infections in the gut by helminths and other enteropathogens, or nutritional deficiencies. Studies are being planned to address the possible impact of some of these factors.

Live ETEC vaccine candidates include attenuated shigellae expressing ETEC antigens (University of Maryland, USA), and toxin-deleted ETEC strains expressing CFs (Cambridge Biostability, UK). The latter have been assessed in phase I studies and have demonstrated a promising safety and immunogenicity profile. It remains to be determined if all relevant ETEC antigens can be expressed in a single strain, or whether cocktails of strains need to be developed.

### ***Discussion***

The difficulty in establishing protective efficacy by orally delivered vaccines in high disease burden settings was the central topic of discussion. It was concluded that, although immunogenicity was lower in these settings as compared to that observed in industrialized countries, the difference is not likely to account for the major difference seen in efficacy. To understand oral vaccine failure, a much better understanding of gut immunology is necessary in children constantly exposed to enteropathogens. Indeed, histological studies suggest major changes in gut tissue and high activity level of the innate immune system. Following on from these observations, there was discussion on dose-ranging typically established in healthy adults, and whether it would be appropriate in developing country settings. On the other hand, an increase of the dose into ranges that elicit strong reactogenicity in healthy adults could hardly be justified for use in paediatric trials.

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# 11. Development of vaccines against HIV, malaria and tuberculosis

## 11.1 Tuberculosis: results of the BCG-MVA85A clinical trial in the Gambia: prospect for further developments in children or adults (Roger Brookes)

Recombinant modified vaccinia virus Ankara expressing antigen 85A (MVA85A) of *Mycobacterium tuberculosis* – a secreted antigen which is highly conserved among all mycobacterial species – is among the most advanced of a group of innovative new TB vaccine candidates. After showing in animal models that (a) this vaccine boosts the AG85A T cell response primed by BCG; and that (b) MVA85A boosting protects better than BCG alone in both mouse and guinea pigs, it has been decided to use this vaccine, together with BCG, in a prime-boost strategy (with BCG as the priming partner). A first phase I clinical trial with the vaccine in a low endemicity country, i.e. the UK, has shown a normal safety profile for a vaccine of this type and substantially better boosting in BCG-vaccinated individuals than in mycobacteria-naive individuals.

Based on these encouraging results, the MVA85A vaccine has now entered the second phase of its clinical evaluation in a highly endemic country (The Gambia). This country was chosen – apart from logistic and infrastructural considerations – mainly because of its low HIV prevalence, one of the lowest in Africa (2–3%). Two broad areas of tuberculosis work were considered at the laboratory of the British Medical Research Council (MRC): (a) description of the natural history of infection using a case-contact study; and (b) new drug/vaccine trials.

The objective of the Gambian trial was to determine safety and immunogenicity of MVA85A in individuals characterized as “mycobacteria-naive”, as can be identified in a country highly endemic for TB, highly prevalent for saprophytic mycobacteria and with high BCG coverage rates. The criteria that was chosen for selection of the mycobacteria-naive individuals were tuberculin skin test negativity as well as low ex-vivo INF-g ELISPOT responses against a range of mycobacterial antigens such as PPD, ESAT-6 and CFP-10. Among the selected individuals, two groups were formed; one comprising BCG skin-scar positive and the other BCG scar-negative individuals.

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BCG scar-negative individuals were immunized twice with  $5 \times 10^7$  pfu of MVA85A at an interval of three weeks. BCG skin-scar positive individuals received only one shot of the vaccine at the same single dose. IFN- $\gamma$  ELISPOT was used to determine immunogenicity end-points with the following antigens: Ag85 protein, Ag85A peptides and pools thereof, PPD-A (*Mycobacterium avium*-derived) and PPD-T (*Mycobacterium tuberculosis*- derived). The results show that the vaccine boosted a fast (day seven), high frequency response to both AG85A protein and peptides in 100% of volunteers, irrespective of their BCG scar status. The observed response was exceptionally high in BCG scar-negative people, higher and broader in fact than in skin scar-positive individuals. The latter finding indicates that there is not much difference in the immune status of scar-negative and scar-positive individuals. This observation also sparks hope that it may be possible to use this vaccine in African high endemicity countries as a stand-alone in non-infant populations, but this needs to be confirmed in larger population samples. However, what the trial has definitely shown is that the MVA85A vaccine is safe and immunogenic in a developing country setting such as that in the Gambia.

## 11.2 Malaria: RTS,S/AS02 results and future developments (Joe Cohen)

The overall objective of GSK's malaria vaccine programme is to develop a vaccine that protects infants/children residing in malaria endemic regions from clinical disease and severe malaria resulting from infection with *Plasmodium (P.) falciparum*. As important logistic criterion, such a vaccine should be deliverable in the context of EPI childhood vaccination and malaria control programmes.

The strategy used includes a pre-erythrocytic approach, targeting both endemic populations and travellers. Furthermore, the vaccine should be non-living and induce both blocking antibodies and T-cell responses. The antigen that meets these requirements is the circumsporozoite (CS) antigen of *P. falciparum*, which was first cloned in 1984 and which has since been developed jointly by WRAIR and GSK. In order to improve antigen presentation, the RTS,S vaccine is produced as a particulate antigen based on the hepatitis B surface antigen.<sup>8</sup> As an adjuvant system fulfilling the criteria of inducing both a strong antibody response and cell-mediated immunity, AS02 was developed.<sup>9</sup>

The safety and efficacy of RTS,S, was first demonstrated in sporozoite challenge studies performed at WRAIR. Results after 1–3 doses of RTS,S, showed complete (sterile) protection in 40–45% of individuals plus a long delay before the appearance of parasitaemia in the majority of non-protected individuals. In a subsequent phase IIb trial in the Gambia in semi-immune adults the efficacy after three doses of vaccine was shown to be a 31% decrease in clinical manifestations, 34% in time to infection. Efficacy was not strain-specific and could be boosted by a fourth shot in the second year. High antibody titres against the CS protein as well as high frequencies of CS-specific T cells were observed in immunized individuals.

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<sup>7</sup> WHO child health epidemiology reference group CHERG.

<sup>8</sup> RTS,S: a self-assembling mixture containing 1 part of a fusion protein composed of (antibody-inducing) CS repeat, CS T-cell epitopes and the hepatitis surface antigen plus 4 parts of hepatitis surface antigen.

<sup>9</sup> AS02: GSK-proprietary oil-in-water emulsion containing QS21, a saponin from bark of *Quillaja saponaria* and monophosphoryl lipid A.

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Based on the rationale that fewer infections could have an important impact on incidence of clinical episodes and severe disease and that a “leaky” vaccine would “buy time” for acquired immunity to develop, GSK and the Malaria Vaccine Initiative (MVI) at PATH established a “public–private partnership” (PPP) to start paediatric development of RTS,S.

Under the PPP agreement, phase I dose-escalation/age de-escalation trials were performed in 5–11 year old children in the Gambia and eventually in 1–4 year olds in a malaria-endemic region of Mozambique. This was followed by a double-blind randomized controlled phase IIb study to evaluate the safety, immunogenicity and efficacy of RTS,S/AS02, administered intramuscularly according to a 0, 1 and 2 month vaccination schedule in over 2000 toddlers and children aged 1–4 years in a malaria-endemic region of Mozambique. The trial was performed in two cohorts at two different sites, one using passive follow-up for the evaluation of clinical efficacy and the other using active follow-up for the determination of efficacy against infection.

The findings of that trial indicated that RTS,S/AS02 was safe and well tolerated. The vaccine induced very high titres of anti-CS antibodies and was not inferior to Engerix-B® in terms of anti-hepatitis B surface antigen responses. Antibody responses declined by approximately 75% over six months but still remained relatively high at the end of follow-up. Children responded better than adults. Efficacy against infection (Cohort 2) was 45% and that against clinical disease was 30% (Cohort 1). The most encouraging finding from that trial was the high efficacy observed against severe malaria (Cohort 1), 58% overall and 77% in children under 24 months.

Between 2005 and 2007, another 6–8 phase I/II trials are planned to optimize schedules and to determine efficacy in yet younger children. Around 2007 a pivotal phase III efficacy trial is intended to start.

Critical next steps to accelerating the availability of the vaccine include:

- agreeing on and implementing clinical development plans;
- developing a commercial-scale manufacturing facility;
- exploring the regulatory landscape, identifying and advocating for the fastest registration path possible;
- building consensus on the value of the vaccine;
- encouraging creative ideas to ensure access to vaccine (advance purchase contracts, tiered pricing, create Malaria Vaccine Fund etc.);
- anticipating and integrating other malaria control measures into a development programme;
- building on success of public–private partnerships; and
- improving the vaccine (improved adjuvant formulation, other antigens, different modes of delivery).

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### 11.3 Malaria Vaccine Technology Roadmapping: outcome and applicability to other vaccine R&D areas (*Melinda Moree*)

Many promising research efforts to develop a malaria vaccine are progressing and yielding impressive advances, yet there remains an urgent need to accelerate the pace of progress in creating, systematically evaluating and optimizing candidate malaria vaccines. A large number of high-level studies are in progress, from diverse disciplines. At a time where the number of potential antigens, adjuvants and platforms is growing, and new tools for understanding the human immune response are emerging, better coordination is needed within the global health community to use all new knowledge, development and resources efficiently to move this scientific effort forward.

One important step that the malaria community is taking to accelerate vaccine development is to create a Malaria Vaccine Technology Roadmap. The Roadmap development process will engage leading scientists, donors, vaccine developers and industry leaders from around the globe to identify the salient scientific problems, the most promising technology pathways, and the most productive collaborations to tackle this complex challenge. A Roadmap Working Group (WG) has been established to assist in the planning process for the Malaria Vaccine Technology Roadmap effort. This WG has defined the scope of the Roadmap, namely the development of a commercially viable vaccine against *P. falciparum*, mainly targeted at children under five years of age in sub-Saharan Africa, with a focus on “pre-competitive” R&D collaboration among research organizations, private companies and governments. Furthermore, the WG has organized two meetings to date, a “vision” meeting and a technology “roadmap” meeting to follow up on the technological challenges arising from the vision meeting.

The first meeting was held in October 2004 in Hinxton, United Kingdom. It was charged with developing a shared vision of success and strategic goals to support the vision as well as the identification of key challenges and questions to be answered in order to address these challenges. The vision, to be achieved through improved global coordination and cooperation, is to have available, by 2015, an effective malaria vaccine to help reduce death and severe illness among young children in sub-Saharan Africa and, by 2025, a vaccine with even greater efficacy. The definitions of desired efficacy were defined as follows: by 2015, license a vaccine that is at least 50% effective against mortality and morbidity for a duration of at least one year and, by 2025, license a vaccine that is at least 80% effective against clinical disease for a duration of at least four years.

In addition to this vision, the meeting identified a number of big questions, which were grouped into eight Roadmap Topic Areas:

- Scientific discovery
- Vaccine design
- Enabling technologies
- Clinical trials
- Policy and commercialization
- Cross-cutting activities
- Process enhancements

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These Roadmap Topic Areas provided the formal structure for a subsequent Technology Roadmap meeting, that was held in March 2005 in St Cyr-sur-Mer, France. Subgroups were formed among the meeting participants and were charged with identifying a set of strategies to tackle the big questions in each respective area. This process led to the definition of a list of 10 potential top priority initiatives in the three following categories.

### **Advancing science**

- 1) **Improved understanding of parasite-host interactions** – to use new technologies in genomics, proteomics and other disciplines to study parasite biology and parasite-host interactions to enhance scientific understanding of the human immune response induced by *P. falciparum*;
- 2) **Correlates of protection** – to identify and validate correlates of protection, which would greatly expedite vaccine design and facilitate prediction of efficacy;
- 3) **Standardized assays and reagents** – to develop standardized “tool kits” of validated assays, reagents and operating procedures to enable comparison of results from models, field trials and other experiments;
- 4) **Process development capabilities** – to improve access to robust process development capabilities for GMP production of vaccine test lots to facilitate the transition of the most promising vaccine candidates from the laboratory to clinical trials;
- 5) **Standardized trial end-points** – to clearly define standard end-points and measurement methodologies for use in clinical trials. Producing comparable field metrics can extend the value of clinical trials beyond the efficacy of a particular vaccine candidate.

### **Improving Processes**

- 6) **Shared go/no-go criteria** – to develop a common set of measurable criteria to guide scientific and investment decisions at various stages along the entire vaccine development process;
- 7) **Increased and sustained clinical trial capacity** – to increase the capacity of endemic regions to provide epidemiologically diverse sites with good clinical practice (GCP) capability to support planned clinical trials;
- 8) **Balanced global portfolio** – to create a structured process to help guide and manage a balanced global portfolio of malaria vaccine R&D and to focus investments on the most critical needs.

### **Shaping policies and commercialization**

- 9) **Novel regulatory strategies** – to develop innovative regulatory strategies to prepare endemic countries and global bodies to evaluate a future malaria vaccine. Early attention to regulatory processes can avoid delays due to the special challenges of deploying a malaria vaccine, such as effective integration with existing intervention strategies;
- 10) **Innovative financing mechanisms** – to pursue innovative financing mechanisms that are supported by country-level decision-making processes to stimulate market pull and ensure a viable market in endemic countries.

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Several of the efforts addressed by the draft roadmap have already been initiated, such as capacity-building efforts for conduction of clinical trials for malaria vaccines and drugs and the establishment by WHO and the US National Institutes of Health (NIH) of a working group on assay standardization. Meetings to discuss structural options for roadmap implementation have been held and management options are currently being explored. Within the roadmap process, the above only constitutes the first phase. As concrete next steps, regional stakeholder meetings have been held in the USA and in South Africa; others will continue to be held. The Malaria Technology Roadmap document is currently circulating in the community for input and feedback. Publication of the document is planned for later in 2005.

#### **11.4 Role of WHO in promoting HIV Vaccine R&D (*Saladin Osmanov*)**

HIV Vaccine R&D in WHO is under the purview of the HIV Vaccine Initiative (HVI), a joint programme of WHO and UNAIDS. The role of HVI is threefold:

- advocacy, guidance and coordination;
- facilitation of HIV vaccine development; and
- cost-effectiveness and delivery studies of HIV vaccines.

Examples of advocacy work are the National AIDS Vaccine Plans/Strategies, the drafting of which is done in a participatory in-country process under facilitation by HVI. These National AIDS Vaccine Plans highlight not only the technical components (virology, clinical trials, etc.) of the plan, but also include sections on the supporting environment (community support, access to care, etc.) and the normative (regulatory, legal, etc.) framework. Guidance documents such as ethical considerations specifically relating to HIV preventive research are another stronghold of HVI's activities.

The African AIDS Vaccine Programme (AAVP) is a network of African scientists and community, working together to promote and facilitate HIV vaccine research and evaluation in Africa, through capacity building and regional and international collaboration ("the voice of Africa"). Activities are being developed and implemented through six thematic working groups: (1) advocacy, information and resource mobilization; (2) biomedical sciences (laboratory and clinical); (3) population studies (epidemiology and socio-behavioural issues); (4) ethics, law and human rights; (5) national strategic planning; and (6) communities.

Many vaccine candidates are currently being developed by academia and the pharmaceutical industry, directed against different sub-types of HIV, using various antigens and a multitude of different delivery systems. Vaccine trials will have to be undertaken, in particular in developing countries. Therefore, there is an urgent need to increase worldwide capacity for HIV vaccine clinical trials. Multiple sites will be required to test different candidate vaccines in populations with different transmission patterns. Comprehensively developed sites could be used for vaccines and other HIV preventive research (including microbicides). Finally, the impact of scaling-up anti-retroviral therapy (ART) in vaccine trials will have to be considered in terms of HIV incidence, level of care, etc. It must be ensured that the "most appropriate" candidate vaccines are tested with the "most appropriate" and highest scientific and ethical standards. This in turn will require a great deal of goodwill from all partners, and intense international collaboration and coordination.

## 11.5 Ethical considerations in trials: summary of the Satellite Symposium (Daniel Tarantola)

While vaccine trials in countries with weak health systems are expanding, ethical principles such as justice, equality, reciprocity and beneficence call for access to care by research participants for conditions targeted by vaccine candidates. However, there are a number of questions which are not or only insufficiently addressed by existing guidelines (Helsinki, Council for International Organizations of Medical Sciences, UNAIDS), e.g. what type, level and duration of care should be given; should non-participants (screened-out, families, etc.) be eligible; which other severe conditions that are not targeted by the vaccine should be considered; who bears responsibility for providing care?

In order to address these issues and to develop a more meaningful guidance related to the provision of care, WHO organized a consultation in March 2005 in Malawi. The outcome of this meeting has been summarized in a matrix approach addressing on one axis, the type of conditions and care, and on the other the levels of responsibility and boundaries of treatment and care provision (see Table 1).

**Table 1: Outcome of meeting on ethical considerations in trials**

Type of care	Level of responsibility and boundaries of care and treatment provisions		
	<i>Obligation (part of the ethics review process)</i>	<i>Agreement on "best practices" through improved "research governance"</i>	<i>Morally praiseworthy</i>
<i>For conditions against which the vaccine is intended (obligations during trial period)</i>	Yes	Determination of boundaries of care and treatment – SOC – for whom, by whom, for how long, costs, feasibility, sustainability, responsibility	Optimize prevention and care standards for the disease. Enhance primary health care systems; health system improvements
<i>For conditions detected as part of vaccine trial design (obligations during trial period)</i>	Yes	All of the above considerations; specific for the conditions	Enhance primary health care systems; health system improvements
<i>For conditions incidentally detected during the trial</i>	Referral within local system treatment within local system	Determination of care and	
<i>Long-term access to care/post-trial access</i>	Referral within local system	Determination of care and treatment within local system	

The objectives of the symposium organized in Salvador were to present the outcome of the Malawi meeting to participants engaged in vaccine R&D, and to obtain their views on issues deserving focused attention and work, and on further steps.

It was made clear that the current efforts to obtain consensus on standards of access to treatment and care in the context of vaccine trials in particular are not an attempt to build bureaucratic hurdles but to create a supportive environment for research. Indeed, the current absence of definitive rules is the biggest obstacle to speedy resolution of conflicts over access to treatment and care. It was obvious that details of the matrix require further elucidation, such as the question “is referral to the local system consistent with obligation to provide treatment”. Each cell of the matrix would benefit from criteria applicable to decision-making.

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The matrix introduces the notion of “best research governance” as a formalized quality control framework for health research and care. This requires further clarification, in particular on which type of decisions “best research governance” includes and at which level it occurs (local or national). Likewise, the role of international or intergovernmental bodies should be explored further. In the course of the discussions, it became clear that while each country must decide on its own mechanism of research governance, companies may be tempted to select countries presenting the most favourable conditions to the detriment of others that apply more stringent rules. In these areas, a clear need was identified for international organizations to develop global framework and tools, and to support local/national decision-making and capacity building.

Discussions on the type of care and treatment focused on sustainability of treatment, and the question “is there an obligation to treat all conditions identified as well as unrelated adverse events?” The influence of new developments such as the WHO “Three by Five” Initiative,<sup>10</sup> the American President’s Emergency Plan For AIDS Relief (PEPFAR) and improved standards of care based on new discoveries and expanding capacity were investigated, as was the possibility of referral to treatment trials. Opinions on two-tiered systems – providing different levels of care and treatment – were polled; these ranged from unacceptable, or problematic but ethically acceptable, to the view that provision of treatment for vaccine trial participants is not “another tier” of an existing system. Furthermore, the complex issues of individual and collective benefits for the participants was considered. This included issues such as payment to volunteers, provision of the vaccine once licensed, providing (other) vaccines to participants in the placebo arm as well as planning for downstream benefits such as attribution of intellectual property rights, non-exclusive licensing and preferential pricing.

Finally, next steps in the consultation process were highlighted. They include a continuation of an iterative discussion process (by disciplines, regions, institutions) of which this meeting is a part, the posting of a working paper on the IVR website, publication of a discussion paper in peer-reviewed journals and production of tools for local/national decision-making.

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<sup>10</sup> One of WHO’s priority programmes, particularly focusing on the target of providing three million people in developing countries with anti-retroviral drugs by the end of 2005.

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# 12. The 2005 GVRF: lessons learnt

(Meeting Co-Chairs and Secretariat)

Infectious diseases are killing close to 15 million people every year.<sup>11</sup> Of those deaths, nearly seven million<sup>12</sup> occur among children under five years of age. There are, however, reasons to be optimistic. Vaccines are effective at combating diseases, as shown by the success of the polio eradication campaign, which has reduced the global incidence of this disease by more than 99%. Mortality due to measles globally has been reduced by close to 30% from 800 000 in 1999, following the implementation of the WHO–UNICEF 2001–2005 measles mortality reduction strategic plan. Effective new vaccines have been introduced in most industrialized countries against infections caused by hepatitis B virus, *H. influenzae* type b and *N. meningitidis*. These products are now progressively being incorporated into the immunization programmes of developing countries, through the financial support of GAVI. Thanks to the strengthening of immunization services, 78% of the world's targeted population is reached with immunization, as measured by three doses of vaccine against diphtheria, tetanus and pertussis, by the end of 2003. In addition, many candidate vaccines against most infectious diseases of public health importance are in various stages of development. The Global Vaccine Research Forum provided an opportunity to review the state of the art of these new developments. The highlights of the conference are summarized below.

## The GAVI R&D projects: summary and conclusions

The **pneumo ADIP** has achieved excellent progress with surveillance and development of an innovative tool to calculate strategic demand forecasts. The project continues to work with suppliers, donors and countries to find the “solution space” that would allow for a sustainable, affordable vaccine supply.

With a 37% efficacy against pneumonia and 16% against all-cause mortality, the Gambia pneumococcal trial (PCV-9) has demonstrated that pneumococcal vaccine can prevent a large proportion of these illnesses and can significantly reduce mortality among children in a typical rural African setting. In addition, results are expected soon of another key pneumococcal trial to determine efficacy of a PCV-11 among Filipino infants.

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<sup>11</sup> *The World Health Report 2004: Changing history*, Annex Table 2. Geneva, World Health Organization, 2004: 120–122.

<sup>12</sup> *The World Health Report 2005: Make every mother and child count*, Annex Table 3 and Table 4. Geneva, World Health Organization, 2005:190.

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The **Meningitis** Vaccine Project, a WHO–PATH partnership, with the Serum Institute of India as the vaccine manufacturer, has reached several milestones, including technology transfer for the production of a MenA conjugate, the imminent initiation of a phase I study in India, the establishment of a clinical development plan, commitment from the African belt countries together with an affordable price of US\$ 0.40 per dose. All point towards a successful public–private partnership.

There has also been good progress with the **rotavirus** ADIP (RVP) but generating good rotavirus efficacy data for Africa and Asia in addition to the existing data in Latin America is of critical importance.

The International Finance Facility (IFF) is a novel mechanism for funding international development. An IFF pilot for immunization, IFFIm has been selected to demonstrate the concept, with a goal of raising US\$ 4 billion over 10 years. IFFIm resources will be channelled through the GAVI mechanisms to support strengthening of immunization services and the introduction of new vaccines.

### ***Haemophilus influenzae* type b introduction and challenges**

Several tools are available to use for measuring Hib disease burden, varying in cost and complexity. Cost-effectiveness studies are important for evidence-based decision-making on Hib vaccines; and use of benchmarks enable assessment of the value of vaccines and place them in the context of other public health interventions.

Hib vaccine was introduced in the Gambia in 1997, resulting in a rapid decrease of Hib meningitis from a high rate of meningitis of 200/100 000 under five to no reported cases since 2002. The Mali experience exemplifies how data from a well-conducted study led to the decision to introduce vaccine.

Several emerging manufacturers have monovalent and combination Hib vaccines in clinical trials and it is expected that several products will be registered in the country of manufacture by 2006–2007 and available for WHO prequalification.

### **Leishmaniasis**

Leishmaniasis is prevalent in all parts of the world, with a total of 88 countries affected. Its overall prevalence is estimated at 12 million with a population at risk of 350 million.

Various types of vaccines against leishmaniasis have been or are being evaluated, including whole parasite killed vaccines. There has been some activity in immunotherapeutic applications but there is no evidence of protection against infection. The first purified recombinant candidate is currently undergoing clinical trials in South America.

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## **Regulatory approaches to vaccine licensing in developing countries**

The newly formed Developing Country Vaccine Regulators Network will be instrumental in guiding regulators on challenges relevant to clinical evaluation and registration of new vaccines. In addition, there is a need to strengthen regulatory mechanisms in countries for the authorization and monitoring of clinical trials.

### **Polio**

There has been tremendous progress in the Polio Eradication Initiative from 1988 to 2003. Nevertheless, scaling down of polio activities in non-endemic countries in Africa due to a funding gap, and suspension of immunization activities in northern Nigeria, resulted in the resurgence of poliovirus transmission in 2003.

Monovalent oral polio vaccine (mOPV) has recently been licensed and is being used in the final stages of eradication; mOPV types 2 and 3 will also need to be licensed, including for stockpiling in the post-OPV era

### **New influenza vaccines**

The widespread circulation of H5N1 influenza virus in birds and animals continues to pose a risk of transmitting the infection and causing a pandemic in humans.

Pilot projects are ongoing to evaluate inactivated H5N1 pandemic vaccines in clinical trials, but development of vaccines with cross-protective activity against different influenza viruses could help to revise the current vaccination strategy based on annual intervention and contribute greatly to protection against epidemics and pandemics.

### **Adjuvants and immunomodulators**

The possibility of modulating and enhancing the immune response has been known for decades, and such agents have been widely used in experimental immunology. By contrast, there has been little experience of adjuvants in humans, but we have started to understand the complex regulation of the immune responses. A possible obstacle to this development may lie in the impossibility of licensing adjuvants as such, and not as part of a specific vaccine.

There is currently a lack of public-sector knowledge and expertise in formulation, which might support the establishment of a centre of expertise in vaccine formulation. Such a facility could provide expert advice to PPPs, facilitate access to proprietary adjuvants and provide quality formulation service.

### **Burden of diarrhoeal diseases due to ETEC and *Shigella***

Although a considerable amount of data has been published on the incidence of these diseases and on their share in the total burden of enteric infections, much of this data is limited geographically and in time. Thus the current knowledge of the burden of these diseases, particularly for shigellosis, is not as good as it should be, and new epidemiological studies are called for. By contrast, it is already widely accepted that in view of the importance of ETEC as a cause of diarrhoea in young children, such a vaccination should be in place as soon as possible.

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Several candidate ETEC vaccines are available, and both encouraging and disappointing data on the protective efficacy of these vaccines have been reported from studies in Bangladesh and Egypt, respectively. With clear determination and investment in ETEC vaccines, it is thought that a vaccine could be available in five years. For Shigella, more time seems to be needed before a vaccine could be available.

### **Tuberculosis, malaria and HIV vaccine R&D**

The three major killers, HIV, tuberculosis and malaria have proven extremely difficult targets for vaccine development. For the three diseases, progress has been slow, but recent data with the RTS,S vaccine developed by GSK and WRAIR gives hope that a malaria vaccine might become available in the next 5–10 years. This vaccine is based on the circumsporozoite protein, CSP, which is produced in yeast as a fusion protein with hepatitis B surface antigen. The recombinant protein forms regular small particles which, combined with a novel adjuvant, have proven a potentially useful vaccine.

A TB vaccine developed in the United Kingdom (MVA 85A) is the first TB subunit vaccine ever moved from non-endemic to endemic setting, i.e. the Gambia, West Africa. It has been found highly immunogenic, and further clinical trials are planned in Senegal and South Africa. Other approaches in or close to clinical evaluation include adjuvanted protein subunit vaccines, recombinant BCG, rationally attenuated *Mycobacterium tuberculosis* and adenovirus vectored vaccines.

Currently, more than 30 candidate HIV vaccines are being tested in small-scale human clinical trials. Two large-scale HIV vaccine trials were completed in 2003 with VaxGen's AIDSVAX candidate, unfortunately showing no protection in the vaccinated volunteers. A third large-scale trial was initiated in 2005 to test Merck's adenovirus-based candidate.

Although it is suggested that an effective HIV vaccine will need to induce both neutralizing antibodies and cell-mediated immunity, the attention of the HIV vaccine field has focused on induction of HIV-specific cellular immune responses, based on the hypothesis that such responses would, hopefully, enable the vaccinated persons to better control virus replication following infection. Mathematical models predict that even one-log reduction in viral load levels could have a major impact by reducing the number of secondary infections, and consequently by reducing mortality from HIV-1 within 20 years after introduction of the vaccine.

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# Annex:

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The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested (*Initiative for Vaccine Research*).

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards (*Quality Assurance and Safety of Biologicals*).

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented (*Vaccine Assessment and Monitoring*).

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies (*Access to Technologies*).

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives (*Expanded Programme on Immunization*).

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