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Acronyms & Abbreviations

AE	adverse event
Aeras	Aeras Global TB Vaccine Foundation
AIDS	acquired immunodeficiency syndrome
AMC	Advanced Market Commitment
APC	antigen-presenting cell
ARI	acute respiratory infection
ARSN	Asian Rotavirus Surveillance Network
BCG	bacille Calmette-Guérin (vaccine)
BMGF	Bill & Melinda Gates Foundation
CAVD	Collaboration for AIDS Vaccine Discovery
CDC	Centers for Disease Control and Prevention (USA)
CHAVI	Centre for HIV Vaccine Immunology
CIN	cervical intraepithelial neoplasia
CIPIH	Commission on Intellectual Property Rights, Innovation and Public Health
CSF	cerebrospinal fluid
CTB	cholera toxin B chain
CTL	cytotoxic T-lymphocyte
CVD	Cardiovascular Disease Programme
CVP	Children's Vaccine Program (USA)
DALY	disability adjusted life year
DCJI	disposable cartridge-jet injectors
DCVRN	Developing Country Vaccine Regulatory Network
DEC	diethylcarbamazine citrate
DHF	dengue haemorrhagic fever
DHHS	Department of Health and Human Services (USA)
DNA	deoxyribonucleic acid
DOMI	Diseases of the Most Impoverished (Program)
DOTS	directly observed treatment short-course
DT	diphtheria-tetanus vaccine
DTP	diphtheria-tetanus-pertussis (vaccine)

EC	European Commission
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Evaluation Agency
EPI	Expanded Programme on Immunization
EPR	Epidemic and Pandemic Alert and Response
GACVS	Global Advisory Committee on Vaccine Safety
GAP	Global Action Plan
GAVI	Global Alliance for Vaccines and Immunization
GDP	gross domestic product
GIP	WHO Global Influenza Programme
GIVS	Global Immunization Vision and Strategy
GMC	geometric mean concentration
GMP	good manufacturing practices
GSK	GlaxoSmithKline
H	haemagglutinin
HAI	healthcare-associated infection
HHVI	Human Hookworm Vaccine Initiative
Hib	Haemophilus influenzae type B (vaccine)
HIV	human immunodeficiency virus
HPV	human papillomavirus
IAVI	International AIDS Vaccine Initiative
IBIS	Invasive Bacterial Infections Surveillance
ICMR	Indian Council of Medical Research
ID	intradermal
IFFIm	International Finance Facility for Immunization
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
Ig	immunoglobulin
IP/IPR	intellectual property/rights
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IVI	International Vaccine Institute
IVR	Initiative for Vaccine Research
JE	Japanese encephalitis
Mab	monoclonal antibody
MHC	major histocompatibility complex
N	neuraminidase
NCL	national control laboratory
NGO	non-governmental organization
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NIH	National Institutes of Health (USA)
NRA	national regulatory authority

OPV	oral polio vaccine
OTT	Office of Technology Transfer (USA)
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology for Health (USA)
PDVI	The Paediatric Dengue Vaccine Initiative
PEP	post-exposure prophylaxis
PPD	purified protein derivative
QC	quality control
QSS	Quality, Safety and Standards (WHO)
R&D	research and development
RIG	rabies immunoglobulin
SAPNA	South Asian Pneumococcal Alliance
SARS-CoV	SARS coronavirus
SBA	serum bactericidal antibody
SCID	severely compromised immune deficient
STI	sexually-transmitted infection
TB	tuberculosis
TOC	Test-of-Concept
TRIPS	Trade-Related Aspects of International Property Rights (Agreement)
TT	tetanus toxoid
UCLA	University of California at Los Angeles
UNAIDS	United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VLP	virus-like particule
VRC	Vaccine Research Centre
WG	working group
WHA	World Health Assembly
WHO	World Health Organization
YF	yellow fever

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

Moderators: Carlos Morel and Punnee Pitisuttithum
Rapporteur: Marie-Paule Kieny

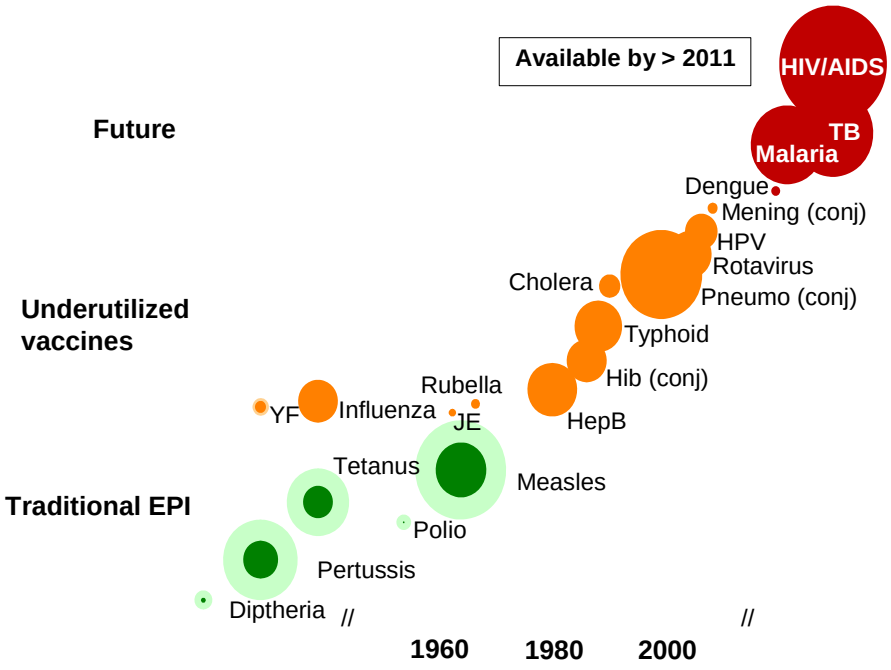
Global immunization has made considerable progress during the last 10 years. Among the indicators usually employed to assess the efficiency of immunization activities, the following two demonstrate this progress.

- The number of countries with DTP3 (third dose of Diphtheria-Tetanus-Pertussis vaccine) coverage below 50% has decreased from 19 countries in 1990, and 20 in 2000, to only nine countries in 2005.
- Global coverage with the third dose of hepatitis B vaccine in infants has increased from 19% in 1999, to 40% in 2002, and 55% in 2005.

This global progress however should not hide the fact that locally a lot of effort is still needed as, for example, DTP3 coverage in some districts in countries with high national coverage is still below 50%, and as hepatitis B vaccine coverage in south-east Asia is still less than 30%.

Fortunately, the new vaccines' pipeline has considerably expanded, giving hope that many new products will be available for introduction into immunization programmes which will be crucial for decreasing the burden of deaths due to communicable diseases (Fig 1.1).

Figure 1.1: Timescale of vaccine development



Green: traditional EPI vaccines;
Orange: available, underutilized vaccines;
Red: future vaccines.
Area of circles is proportional to the number of deaths (2002 data). Shaded areas are proportional to the number of deaths prevented by vaccination.

Of course, expanding coverage universally and introducing new vaccines will require additional resources. A global envelope to achieve the goals set for 2015 by the WHO-UNICEF Global Immunization Vision and Strategy (GIVS) goals has been estimated at around US$ 35 billion for the period 2006-2015, US$ 11 to 15 billion of which represents the expected funding gap. In this context, it is encouraging that new funding for immunization is being made available through the Global Alliance for Vaccines and Immunization (GAVI), notably through the International Finance Facility for Immunization (IFFIm) which raised more than US$ 1billion on the stock market in November 2006, and the Advanced Market Commitment (AMC) which will distribute US$ 1.5 billion to subsidize conjugate pneumococcus vaccine for developing countries.

Malaria, HIV and tuberculosis vaccines

A lot of new activities have been launched in the domain of vaccines and new results obtained against the three main poverty-related infectious diseases. Among these, a global strategy (the *Malaria Vaccine Technology Roadmap*) aimed at accelerating the development of effective malaria vaccines, was published and endorsed by major funders of malaria vaccine development. The roadmap was officially launched at this Global Vaccine Research Forum in Bangkok. In terms of malaria vaccine candidates, the most advanced candidate (RTS,S/AS02) was shown to be able to induce 50% protection against severe disease up to 18 months after vaccination. Multi-site pivotal trials of this vaccine are planned for 2007-2008. In addition, numerous other candidates are entering the Phase I or Phase I/II clinical evaluation stage, and results from "proof of concept" trials of some leading candidates are expected soon.

In the HIV vaccine field, the 2006 G8 Summit in St Petersburg in the Russian Federation reaffirmed high-level political support for global efforts to promote the development of vaccines against the pandemic. In the United States of America, NIH/NIAID have established the Centre for HIV Vaccine Immunology (CHAVI), and the Bill & Melinda Gates Foundation (BMGF) has approved the first grants for the establishment of the Collaboration for AIDS Vaccine Discovery (CAVD). Equally important is that a growing number of low- and middle-income countries are participating in preparation and conduct of HIV vaccine clinical trials, and WHO and UNAIDS are providing a forum for discussions relevant to the development of policies, norms and standards in support of HIV vaccine trials, with a special focus on developing countries. Pending efficacy data, the earliest possible licensure of an HIV vaccine is now envisaged as 2010 (for the ALVAC-gp120 candidate vaccine) or 2014 (for an adenovirus-based vaccine).

With regard to tuberculosis, the first five tuberculosis vaccine candidates have undergone Phase I clinical trials: two adjuvanted protein subunit vaccines; two live recombinant vaccines; and one recombinant bacille Calmette-Guérin (BCG) vaccine (later abandoned due to regulatory shortcomings). The most advanced candidate, MVA85A, entered Phase I/II evaluation in the Republic of South Africa, which is one of the 22 tuberculosis highest-burden countries, in 2006. Moreover, seven more products are positioned in the immediate pipeline (1-3 years before entry into clinical trials).

Influenza vaccines

Pandemic influenza preparedness is seen as one of the major global health security priorities for the World Health Organization. In this context, a consultation was held in May 2006 to put together a Global Action Plan to increase supply of pandemic influenza vaccines (See Chapter 3). WHO's contribution to the implementation of the Global Action Plan has focused on a few key activities, among which are:

- strengthening national regulatory authorities (NRAs) for licensing of influenza vaccines;
- capacity-building for H5N1 vaccine manufacturing in developing countries;
- systematic evaluation of available technologies for the production of influenza vaccines;
- contribution to the development of practical antigen dose-reduction strategies through clinical trials of intradermal jet-injector delivery methods;
- evaluation of delivery strategies;
- regular update on clinical trials of prototype H5N1 vaccines and on research and development (R&D) for influenza vaccines with broad spectrum and long-lasting immunogenicity.

Rotavirus, pneumococcus and HPV vaccines

These three new vaccines will soon be ready for introduction into the immunization programmes of both industrialized and developing countries. Notable milestones in this area have been met.

Among these, two live rotavirus vaccines have been licensed by multinational vaccine producers, and more "upstream" rotavirus vaccine candidates are undergoing development by developing-country vaccine manufacturers, often with financial support from the BMGF. WHO is collaborating with the Program for Appropriate Technology for Health (PATH), and others, to evaluate the effectiveness of the newly licensed products in Africa; Rotarix® is undergoing evaluation in the Republics of Malawi and South Africa, and RotaTeq® will soon enter clinical trials in the Republics of Ghana and Kenya.

Similarly, very important advances have been made towards the introduction of conjugate pneumococcus vaccines. On the scientific side, an 11-valent conjugate vaccine (TT/DT conjugate) was demonstrated to be effective against radiological pneumonia in the Republic of the Philippines. On the financial side, pneumococcal conjugate vaccines have been chosen to pilot the AMC process. In addition, PATH has launched a project to support the development of protein-based pneumo vaccines, with finances from the BMGF.

One human papillomavirus (HPV) cervical cancer vaccine, Gardasil®, was licensed for protection against cervical cancer induced by HPV 16 and 18 and genital warts caused by HPV 6 and 11. Another candidate vaccine, Cervarix®, is in advanced stages of development and its licensure is expected in 2007. In order to facilitate introduction of these vaccines in developing countries, WHO has established a global HPV laboratory network which will consist of sentinel centres for monitoring HPV DNA and antibody detection.

Vaccines against bacterial enteric diseases

A number of new international initiatives have been launched in the field of vaccines against bacterial enteric diseases (all of them funded by the BMGF), which should allow effective synergy of activities between interested parties. These are:

- a multi-centric study of the aetiology and burden of enteric diseases using similar techniques and methodology (CVD, Baltimore, USA);
- the Cholera Vaccine Initiative (IVI, Seoul, the Republic of Korea);
- a feasibility study for a future cholera vaccine stockpile for pre-emptive use (WHO, Geneva, the Swiss Confederation);
- the Enteric Vaccines Initiative (still to be awarded).

The WHO cholera vaccine project will be conducted in a context where the Organization currently does not recommend establishment of a cholera vaccine stockpile with the only available 2-dose international vaccine. The project intends therefore to gather the scientific evidence which will be needed for the establishment of a future stockpile of a 1-dose vaccine. It will develop tools for cholera risk assessment, and examine financing and sustainability of such a stockpile, as well as examine specific research questions such as herd protection, safety in HIV infected individuals, and possible use in endemic situations with predictable seasonal cholera outbreaks.

Dengue vaccines

In terms of global developments, a Phase II pediatric clinical trial with the yellow fever-dengue (YF-Den) chimeras has started, and clinical trials with new tetravalent dengue vaccines (live Den/Den recombinants) are expected soon. WHO emphasis has been on getting consensus on the best way to measure immunity to dengue. Moreover, the Organization is finalizing a new dengue vaccine clinical-trial guidance document and is providing support to innovative virus attenuation strategies. In spite of encouraging progress however, many challenges still lie ahead, notably the identification of approaches in managing interference in tetravalent vaccine formulations, and of strategies to demonstrate efficacy and long-term safety of candidate vaccines.

Other activities

Other WHO activities will be reviewed in the following chapters of this report, namely:

- the measles aerosol project (Michel Greco, Chapter 8.3);
- the meningitis vaccine project (Marc LaForce, Chapter 2.2)
- Japanese encephalitis (Chapter 7).

2. Update on vaccines against GAVI priority diseases

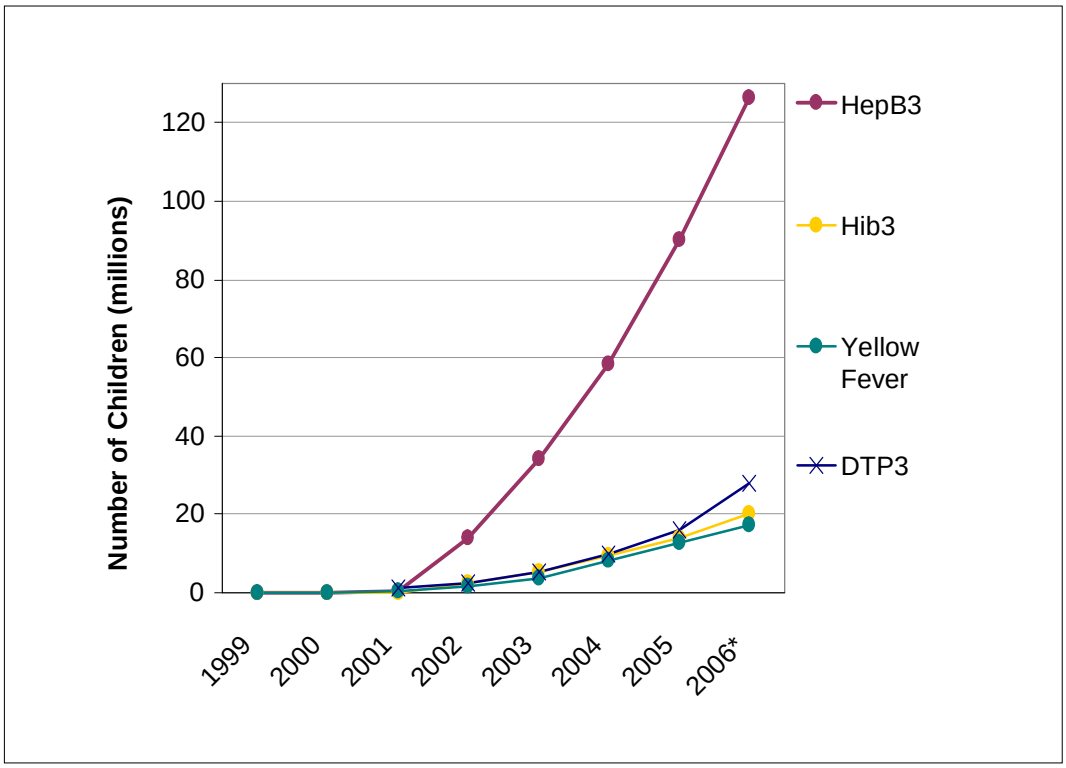
Moderator: Jan Holmgren
Rapporteur: Duncan Steele

2.1 GAVI Phase 2 - innovative financing for vaccines and immunization (*Michel Zaffran*)

During 2005 and 2006 a remarkable commitment by the international community to develop health and vaccination has occurred. The G8 countries have pledged to double their aid to Africa, and global aid is projected to increase from US$ 80 billion to US$ 130 billion by 2010. Many African countries have made substantial progress toward their 2001 commitment to raise health spending to 15% of national budgets. Greater predictability in donor financial- support is widely acknowledged to be a key factor in effective development. In this respect, innovative financing mechanisms need to be explored in order to provide sufficient, predictable and long-term financing to reach the "hard-to-reach" vulnerable populations worldwide.

Significant success has been achieved by the GAVI initiatives which highlight the contribution of GAVI to vaccine introduction and capacity strengthening. For instance, the introduction of new and under-utilized vaccines in a number of countries with GAVI support, has allowed the immunization of approximately 130 million young children with hepatitis B vaccine and 20 million infants with a conjugate Hib vaccine (Fig 2.1). DTP3 coverage has increased too, with an estimated 28 million children receiving their third vaccine dose on time. Thus, in 40 countries receiving GAVI support, DTP3 coverage has now reached >80% of infants, from an initial low of 34% in 2000, and 73% in 2005.

Figure 2.1: Cumulative number of children reached in GAVI-supported countries



The GAVI alliance, with its focus on a country-driven approach, accountability, and results, has shown that substantial new additional finances can be generated and used to deliver those results. The objectives and goals of GAVI Phase 2 are now:

- to help strengthen the capacity of the health system to deliver immunization and other health services in a sustainable manner;
- to accelerate the uptake and use of underused and new vaccines and associated technologies, and to improve vaccine supply security;
- to increase the predictability and sustainability of long-term financing for national immunization programmes;
- to demonstrate the added value of GAVI as a public/private global partnership through efficiency, advocacy and innovation.

Nevertheless, the Global Immunization Vision and Strategy (GIVS) has indicated that there will be a shortfall of between US$ 11 billion and US$ 15 billion between now and 2015 which needs to be generated by GAVI.

In November 2005, GAVI launched a pilot International Financing Facility for Immunization (IFFIm) to generate a total of US$ 4 billion through the international bond market, in support of immunization in the poorest countries of the world. The first bonds of US$ 1 billion were issued in November 2005 and were rapidly over-subscribed by 1.5 times.

After discussions within the G8, three countries (Canada, the Republic of Italy, and the United Kingdom of Great Britain and Northern Ireland) have decided to consider the joint recommendations from the World Bank and GAVI for the introduction of an Advanced Market Commitment (AMC) to accelerate the availability and introduction of new vaccines to tackle critical diseases in the poorest countries. Initial efforts will focus on a pneumococcal vaccine, and should be launched in early 2007.

These instruments reflect a new approach to financing vaccine development. An investment through the IFFIm of US$ 4 billion could prevent an additional five million child deaths by 2015. AMCs offer the real possibility, when combined with other incentives, to advance research and development for the diseases that afflict the most vulnerable. These pilot projects have the potential to pave the way for other innovative financing solutions, going well beyond vaccines and the feasibility of these new instruments to address specific issues.

GAVI has approved US$ 200 million for rotavirus and pneumococcal vaccines until 2010, to initiate negotiation for the purchase of vaccines and to finance technical activities to support their introduction.

Discussion

Questions were raised about the need to support the "pull" mechanism offered by these new instruments, with a "push" incentive or mechanism to entice industry to support upstream vaccine R&D on the diseases of interest to the international community. The answer was that it was not the role of GAVI to create a "push" mechanism, but by demonstrating the value of the vaccines, it could possibly influence industry involvement in upstream R&D in the future.

2.2 Meningitis vaccine project update and results of first clinical trials in India (*Marc LaForce*)

The meningitis vaccine programme is a partnership between WHO and the Program for Appropriate Technology in Health (PATH), which is developing an affordable conjugate serogroup A meningococcal vaccine manufactured by the Serum Institute of India, Ltd., for use in sub-Saharan Africa. The vaccine was evaluated in a Phase I, double-blind, controlled trial, to assess the safety of the tetanus toxoid-MenA polysaccharide conjugate (PsA-TT) vaccine, and to obtain preliminary information on its immunogenicity in healthy adult volunteers aged between 18 and 35 years. The study was conducted at three sites in the Republic of India between August and December 2005.

The primary objective was to evaluate the safety of a single injection of the new PsA-TT vaccine during a four week post-vaccination period, with comparison to a reference bivalent MenA/MenC polysaccharide vaccine (PsA/C) and to a control tetanus toxoid (TT) vaccine. The secondary objective was to assess the week four immune responses to the vaccine in terms of serum bactericidal antibody (SBA) activity and serogroup A-specific IgG responses, and then to determine the persistence of the immune response at weeks 24 and 48.

A single intramuscular injection of one of the three vaccines was administered to 74 healthy Indian adults (PsA-TT n=24; PsA/C n=25; TT n=25). Blood samples were collected pre-vaccination and at four weeks post-vaccination; safety was assessed according to well- established, standard criteria, using diary cards and home visits. SBA responses were measured by a standardized SBA assay using baby rabbit complement; serogroup A-specific IgG titres were measured by standardized enzyme-linked immunosorbent assay (ELISA) and anti-tetanus IgG titres by standardized ELISA using an international reference standard.

In the three vaccine groups, the local solicited reactions were similarly mild and transient. No serious adverse events were reported. Serogroup A-specific IgG geometric mean concentrations (GMCs) were higher for PsA-TT than for PsA/C. Post-vaccination titres and $\geq$ 4-fold rises pre- to post-vaccination for the PsA-TT group were the same or higher (not statistically significant) than the PsA/C group.

It was concluded that the PsA-TT conjugate vaccine is safe and immunogenic in Indian adults and that progression to Phase II trials is warranted.

Discussion

The Expanded Programme on Immunization (EPI) schedule for the use of this vaccine remains to be determined and evaluated on two fronts, namely:

- non-interference with routine EPI vaccines;
- protection against serogroup A meningitis in two year olds after early infant vaccination.

It will be important to interact with the regulatory authorities in Africa through the Developing Country Vaccine Regulatory Network (DCVRN) as this would help the national regulatory authorities (NRAs) to assess the clinical development and review process of the vaccine.

2.3 Integrating a heptavalent DTPw-HBV/Hib-MenAC combination vaccine within the current EPI in developing countries (*Abraham Hodgson*)

Meningococcal disease remains a significant cause of morbidity and mortality, including in children aged <1 year. In developing countries within Africa and Asia, meningococcal serogroups A and C (MenA,C) are the predominant causes of disease. Meningococcal polysaccharide vaccines, currently used in ad hoc immunization campaigns against epidemic outbreaks, do not offer enduring protection, and are only effective for persons aged $\geq$2 years. Currently available conjugate vaccines address these shortcomings, and suggest that new meningococcal conjugate vaccines are equally effective. Combining meningococcal MenA&C conjugate vaccines with routinely administered vaccines within the EPI schedule, would improve coverage at relatively low operational and logistical cost, and with simplicity of implementation. To evaluate the feasibility of such a strategy, a DTPw-HBV/Hib-MenAC conjugate combination vaccine was evaluated in Navrongo, in the north of the Republic of Ghana.

A Phase II double-blind, randomized (1:1) controlled study was conducted in 280 infants either primed with DTPw-HBV/Hib-MenAC (study vaccine), or DTPw-HBV/Hib (control vaccine) at 6, 10, and 14 weeks, as per the EPI schedule. A booster dose of MenA,C polysaccharides was administered at 12 months of age. Immunogenicity, persistence of antibody response, immune memory and safety were evaluated.

DTPw-HBV/Hib-MenAC priming induced bactericidal antibodies against MenA and MenC in 88% of infants one month after the 3-dose primary vaccination schedule, well above the level in the control group (< 10%). Approximately half of the infants had persisting antibodies at 12 months of age. The ability to boost the immune response and induction of immune memory by the MenA/C components of DTPw-HBV/Hib-MenAC was demonstrated. The immunogenicity of the other routine childhood vaccine antigens was similar to that in the control vaccine cohort, including at the 12 month time point. DTPw-HBV/Hib-MenAC was well tolerated and safe in all infants. None of the severe adverse events reported were related to vaccination.

This Phase II vaccine trial showed positive clinical outcome in African infants in the African meningitis belt, and in Asia, following the current EPI schedule. The vaccine thus covers seven important childhood diseases, including three of the most common pathogens causing meningitis in children.

Discussion

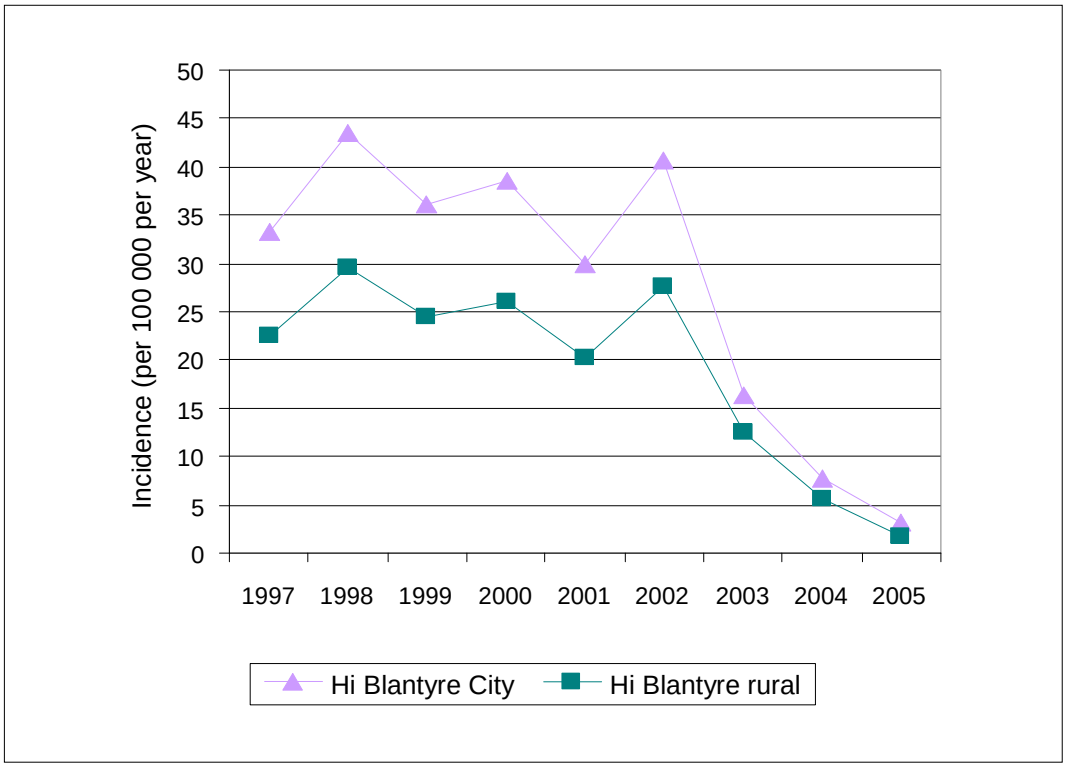
Questions were raised on the study procedures. Free health-care services were offered to the children included in the study and to their families, and an active surveillance was conducted for reactogenicity and tolerability of the vaccine at days 1, 2 and 4, followed by monthly reviews. Oral polio vaccine (OPV) was given following the normal schedule in the Republic of Ghana, which includes a dose at birth and additional doses on National Immunization Days. It was suggested that a booster dose with the polysaccharide vaccine may provide a valuable and inexpensive addition to the EPI schedule of vaccination against meningitis.

2. 4 Current status of Hib vaccines: An update from the Hib Initiative (*Rana Hajjeh*)

Only 21% of the world's children, living in 106 countries, are protected by immunization with Hib vaccine, and only 26 of the 72 GAVI-eligible countries have introduced or have approved introduction of the vaccine. Barriers to the introduction of Hib vaccine have been identified as lack of awareness at decision-making levels of the burden of disease and of the effectiveness of the vaccine.

However significant new data have been generated, including data on disease burden and the impact of vaccine programmes in the Republics of Kenya, Malawi (Figure 2.2) and South Africa, and from various studies in the People's Republic of Bangladesh, Mongolia, and the Democratic Socialist Republic of Sri Lanka.

Figure 2.2: Decline of Hib meningitis following introduction of Hib conjugate vaccines, children <5 yrs, Malawi in 1997-2005



Hib disease has been shown to be more prevalent than previously thought, through new disease burden and surveillance for invasive disease studies, and by the vaccine "probe" studies.

A WHO burden of disease project was conducted to estimate the number of cases and number of deaths averted. This led to a WHO position paper on Hib immunization which stated that:

- in view of their demonstrated safety and efficacy, Hib conjugate vaccines should be included in all routine infant immunization programmes;
- lack of local surveillance data should not delay the introduction of the vaccines, especially in countries where regional evidence indicates a high burden of disease. (*Weekly Epidemiological Record, November 24 2006, Geneva, World Health Organization*)

In addition, issues around the cost-effectiveness and financing options of the vaccine and questions of vaccine supplies and programmatic implementation, have hindered Hib vaccine introduction. New data, using the World Bank criteria, indicate that Hib vaccines are cost effective. In addition, GAVI Phase 2 has supported the introduction of Hib vaccines and the guidelines for support were sent to countries in November 2006.

Currently, there are two multivalent Hib-containing vaccine suppliers, and additional suppliers are expected by 2008. Pricing of the heptavalent vaccine will depend upon UNICEF tender information, but long-term prospects for price decline look good.

Summary

The situation for future Hib vaccine introduction looks promising. WHO has recommended the global implementation of the vaccine and disease surveillance is no longer a prerequisite to vaccine introduction, but strengthening surveillance in regions with minimal data and measuring the impact of Hib vaccine introduction both remain essential.

2.5 Serotype distribution of invasive pneumococcal isolates and anti-microbial resistance patterns in south Asian countries (*Thomas Kurien*)

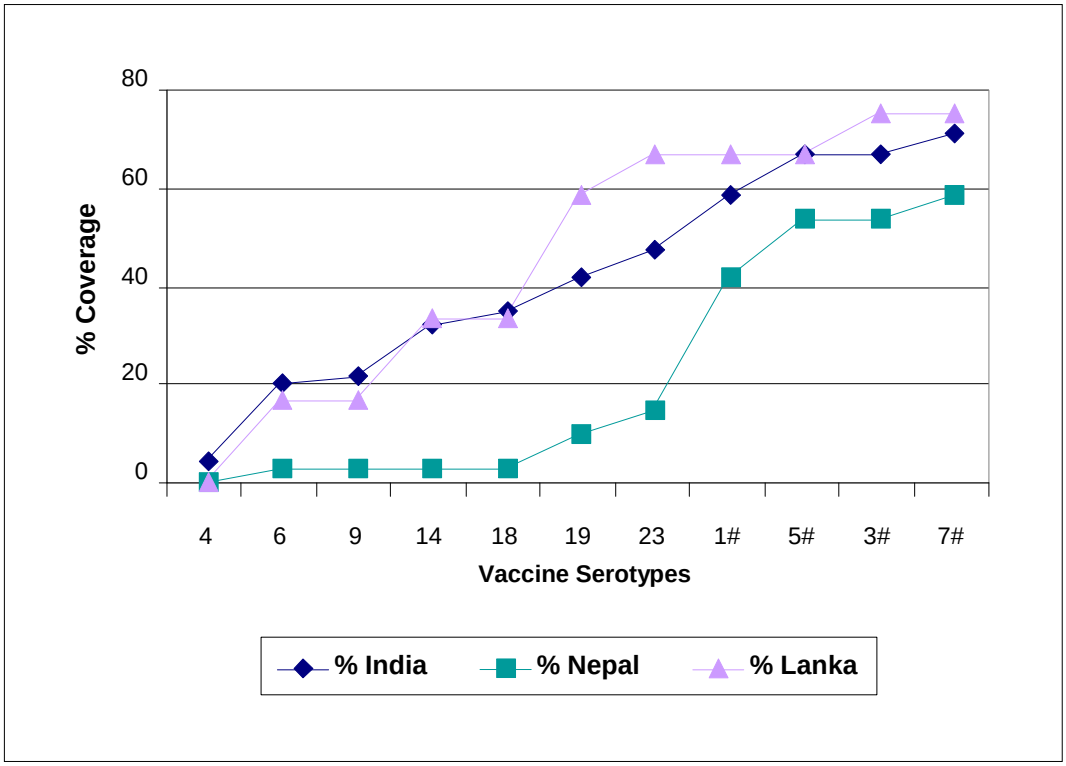
The development of a vaccine policy for *Streptococcus pneumoniae* vaccine requires data on the serotype and serogroup distribution and on the levels and indications of anti-microbial resistance patterns. The South Asian Pneumococcal Alliance (SAPNA) and the Invasive Bacterial Infections Surveillance (IBIS) in the Republic of India have been collecting data in different countries in the sub-continent for several years. The objectives of the networks are:

- to describe the distribution of bacterial serotypes and serogroups found in invasive pneumococcal disease (IPD) in children less than five years of age;
- to assess the potential effect of current 7-valent protein conjugate pneumococcal vaccine;
- to determine the patterns of anti-microbial resistance in different countries within the region.

Data on invasive pneumococcal disease have been collected from tertiary care facilities in the Republic of India, the Kingdom of Nepal and the Democratic Socialist Republic of Sri Lanka. Children between two months and five years of age, presenting with symptoms of pneumonia, meningitis and/or septicaemia were enrolled in the study. Blood, cerebrospinal fluid (CSF) or other normally sterile body fluids were collected and tested for *S. pneumoniae* by various laboratory methods including culture. *S. pneumoniae* isolates were confirmed and serotyped and the anti-microbial resistance determined.

Results showed that the prevalence of common vaccine-related *S. pneumoniae* serotypes in the three countries was found to be somewhat different, showing that the epidemiological profile of invasive pneumococcal disease in south Asia varies in different areas of the region (Fig 2.3). In the Republic of India and the Kingdom of Nepal, serotypes 1, 6 and 5 were predominant, contributing 45% and 41% respectively of invasive disease. The most common serotypes in the Democratic Socialist Republic of Sri Lanka were 14 and 19. Low levels of resistance to penicillin were seen in the Republic of India and the Kingdom of Nepal, whereas very high levels were found in the Democratic Socialist Republic of Sri Lanka.

Figure 2.3: Distribution of vaccine serotypes of *Streptococcus pneumoniae* in three countries in south Asia



Discussion

The data were considered very important although the manner in which they were presented was questioned. It was felt important to stress the overall impact of the vaccine by computing the number of cases of invasive pneumococcal disease that could have been prevented by immunization, rather than the percentage of circulating strains which are included in the vaccine. In countries where disease incidence is high, such as in the Indian sub-continent, the overall impact of immunization on invasive pneumococcal disease would be far greater than the individual protection afforded by the vaccine.

2.6 Incidence of invasive pneumococcal disease in Bangladesh (*Abdullah Brooks*)

Pneumonia is the leading cause of childhood death in the People's Republic of Bangladesh, although the contribution of invasive pneumococcal disease is unknown. The pneumoADIP programme was established to facilitate and speed up introduction of new pneumococcal vaccines in developing countries. A study was set up with the support of this programme to identify the most common serotypes and the anti-microbial resistance patterns of the *S. pneumoniae* isolates circulating in the country. In addition, the study was designed to estimate population-based incidence of laboratory-confirmed invasive pneumococcal disease in children, and to enhance the capacity of the local laboratories to isolate and characterize *S. pneumoniae*.

Approximately 5 000 young children less than five years of age living in a poor urban area called Kamalpur were selected for surveillance by a stratified cluster randomization. Weekly visits by health-care workers were conducted to screen for signs associated with invasive pneumococcal disease, and children fitting this description were referred to the local primary health-care clinic. Clinical specimens and demographic and clinical data were collected in the clinic.

In a tw- year period between 2004 and 2006, almost 4 000 cases of clinical pneumonia were identified corresponding to an incidence rate of 505.2 cases per 1 000 child years of observation. Five cases of meningitis were observed in this same population group (incidence 0,7 / 1 000 child years of observation). Altogether, 33 pneumococcal strains were isolated in association with pneumonia (n=7), upper respiratory tract infection (21), or febrile syndromes (5).

The study thus confirmed substantial rates of invasive pneumococcal disease in the People's Republic of Bangladesh (4.2-4.5 episodes/1 000 child-years) versus a 7-valent vaccine antigen-specific rate of 2.5 episodes/1000 child-years. The coverage of serotypes included in the vaccines was 41% for the 7-valent vaccine and 60% for the 9 to 13-valent vaccines.

Current conjugate vaccines should therefore have an impact on pneumonia in the People's Republic of Bangladesh. For instance, assuming a 20% vaccine efficacy, immunization would result in one million cases being averted. Even with a low 16% vaccine efficacy, more than 100 000 deaths could be averted annually.

2.7 Cost-effectiveness of pneumococcal conjugate vaccines in GAVI-eligible countries (*Anushua Sinha*)

In developing countries, routine vaccination of infants against *Streptococcus pneumoniae* would need substantial investment by governments and donor organizations. When considering these investments, policymakers require information on the projected health benefits and number of lives saved, and on the costs and cost-effectiveness of the vaccines.

Pneumococcal vaccination of infants was compared with no vaccination in the 72 GAVI-eligible developing countries using a decision-making analytic model that takes into account vaccine, demographic, epidemiologic and cost data. Pneumococcal vaccination at the vaccine coverage level of DTP vaccine in these countries was projected to prevent 262 000 deaths per year (7%) in children aged 3-29 months. This translates into 8.3 million disability adjusted life years (DALYs) averted annually.

At a vaccine cost of US$ 5 per dose, vaccination would have a net cost of US$ 838 million a year, corresponding to US$ 100 per DALY averted. At a vaccine cost of between US$ 1 and US$ 5 per dose, purchase and accelerated uptake of pneumococcal vaccine in the poorest countries of the world would substantially reduce childhood mortality and be very cost effective.

2.8 Rotavirus vaccine: experience with its introduction in the Americas (*Merle Lewis*)

Rotavirus diarrhoea among children less than five years of age is a significant public health problem in Latin America and the Caribbean region, where it is a major cause of hospitalizations, out-patient visits, and deaths, and results in substantial costs to national health systems. It is estimated that among Latin American children under five years of age every year there are 10 million episodes of rotaviral diarrhoea requiring domiciliary care; two million episodes requiring a clinic consultation; 75 000 episodes requiring hospitalization, and 17 000 deaths. The disease burden measured as DALYs and the associated direct medical costs are considerable, as for example, in the United Mexican States, where the disease accounts for over 31.7 thousand DALYs and direct medical costs of more than US$ 17.2 million annually. Rotavirus vaccines have been recommended in recognition of the fact that adequate disease control may not be achieved through improvements in water supply, hygiene or sanitation.

In keeping with its mandate to improve the health of the peoples of Latin America and the Caribbean region, and congruent with its foundation principles of pan-Americanism and equity, the Pan American Health Organization (PAHO) has worked in close collaboration with its member countries, its vaccine partners and WHO for further achievement of this public-health goal. PAHO has undertaken a series of strategic activities, including:

- increasing awareness of rotavirus disease burden and stimulating support for rotavirus vaccine introduction through advocacy;
- mobilizing technical and financial resources to extend the reach of technical cooperation activities through the creation of partnerships;
- working to develop effective epidemiologic and adverse events surveillance systems at the country level;
- engaging the rotavirus vaccine manufacturers in an ongoing dialogue, particularly in the areas of vaccine safety, costs and availability;
- collaborating with national regulatory authorities to enhance the regulatory environment for rotavirus vaccine introduction;
- providing countries with simple models and tools for economic analyses of disease burden and vaccine cost-effectiveness so as to generate evidence for rational public health decision-making regarding rotavirus vaccine introduction;
- sharing the experience generated and the lessons learned in the Americas to complete the WHO agenda regarding the vaccine.

The surveillance systems which have been implemented in six Latin American and four Caribbean countries, are functional, but there is a need for expansion of the system to include more countries and for improvement in current data quality. Of significant interest has been the detection of uncommon, non-vaccine rotavirus serotypes such as G8 P[8] and G12 P[6] in certain Caribbean countries. As of November 2006, seven countries in the Americas have introduced rotavirus vaccination, five with the human monovalent Rotarix® vaccine and two with the human-bovine pentavalent Rotateq® vaccine. One of the significant challenges associated with the Rotarix® vaccine is its cumbersome packaging.

The excessive volume of space required has negatively impacted cold-chain storage capacity and procedures at the national, sub-national and local levels of the health systems in all the countries involved. For example, the Federative Republic of Brazil has had to reduce the quantity of its orders, while increasing their frequency.

Rotavirus vaccine introduction in the Americas has taught us some key lessons, namely:

- that we have an obligation to engage manufacturers in an open and early dialogue about a product's packaging and its potential impact on national cold-chain systems;
- that in an ever-changing global marketplace early WHO vaccine pre-qualification is an important requisite for guaranteeing equity, and assuring availability and access in national public-health sectors, so that the most vulnerable populations can be protected;
- that there is a need for strong coordination and cohesive linkage between the political and technical decisions, to introduce a new vaccine and the programmatic feasibility of an actual roll-out.

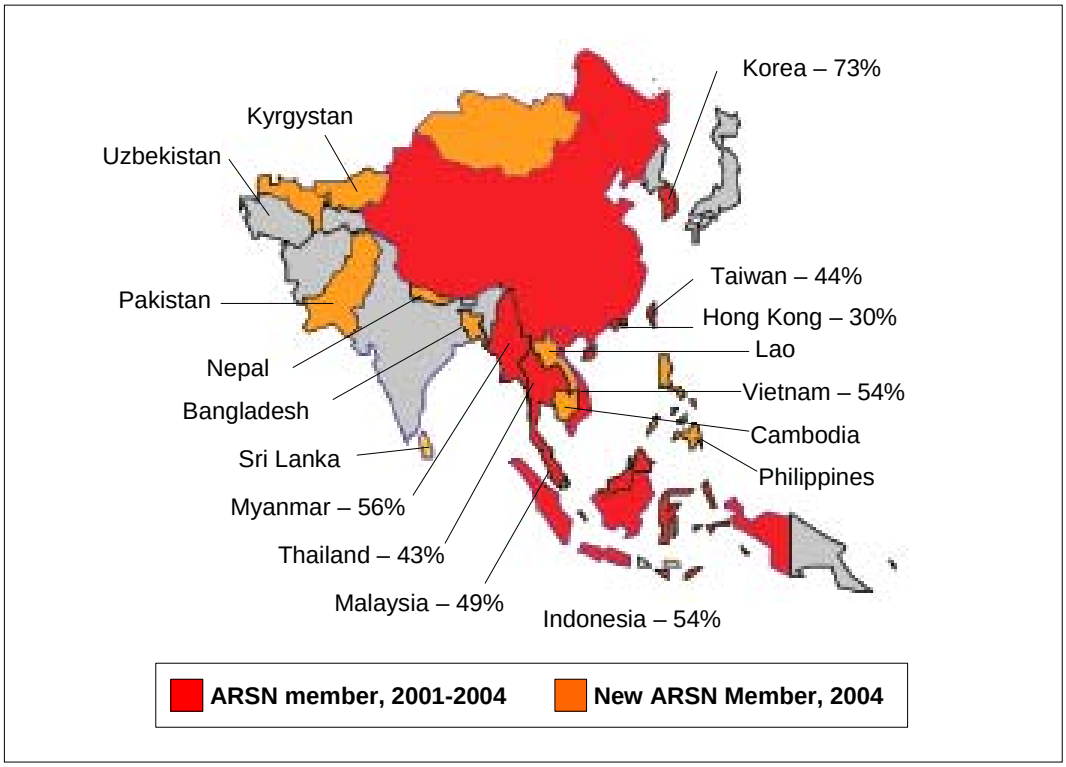
2.9 Rotavirus disease burden and potential for rotavirus vaccine introduction in the Asia-Pacific region (*E Anthony Nelson*)

Past experience has shown that there are unacceptable delays in introducing new vaccines to developing country populations. Even in industrialized countries a number of safe and effective vaccines are not routinely given to all children. To speed up the process of vaccine introduction, GAVI and other organizations have emphasized the importance of obtaining timely and reliable local data on disease and cost-effectiveness to guide decisions on whether new vaccines should be included in universal immunization programmes.

The Asian Rotavirus Surveillance Network (ARSN) was launched by WHO, Centers for Disease Control and Prevention (CDC) and the Children's Vaccine Program (CVP) in 1999 to collect such data for rotavirus disease. Nine countries participated in the first phase of the ARSN. A second phase was launched in 2003 involving 14 countries (the People's Republic of Bangladesh, the Kingdom of Cambodia, The People's Republic of China, the Republic of Indonesia, the Kyrgyz Republic, the Lao People's Democratic Republic, Mongolia, the Union of Myanmar, the Kingdom of Nepal, the Islamic Republic of Pakistan, the Republic of the Philippines, the Democratic Socialist Republic of Sri Lanka, the Kingdom of Thailand and the Republic of Uzbekistan), and funded primarily by the RVP and WHO.

Rotavirus disease burden in Asia was seen to be higher than previously reported (Figure 2.4) as an overall 45% of admissions for diarrhoea in the participating centres were rotavirus positive (Republic of Korea 73%; Japan 58%, Viet Nam 55%, Myanmar 53%, China 50%, China, Hong Kong SAR 30%, Taiwan, China 43%, Thailand 43%).

Figure 2.4 - Rotavirus burden of disease in Asia



The predominant rotavirus serotypes identified during the surveillance period were G1 (China, Hong Kong SAR, Viet Nam), G3 (China) and G9 (Republic of Korea, Taiwan, China, Thailand). Preliminary results of the second ARSN study indicate that a similar high proportion of admissions for diarrhoea (24%-57%) are positive for rotavirus. Direct medical costs of an admission for rotavirus in Japan and China, Hong Kong Special Administrative Region, were US$ 1 236 and US$ 1 868 respectively. Universal rotavirus immunization in Asia could avert 109 000 deaths, 1.4 million hospitalizations and 7.7 million outpatient visits. Cost-effectiveness of universal rotavirus immunization in Asia will depend on the individual country income level and the vaccine price.

However, in contrast to Latin America, and despite the excellent ARSN disease-burden data, no Asian country has as yet recommended rotavirus immunization. This regional difference is somewhat surprising and indicates the importance of factors other than disease burden and economic evaluation in the decision-making process. Representatives of 14 Ministries of Health in Latin America jointly declared their support for universal rotavirus vaccination in 2004. Similar high-level regional support may be needed in Asia if universal rotavirus immunization is to be recommended at an early stage.

2.10 Rotavirus vaccines: update and future directions of research (*Duncan Steele*)

Rotavirus is well recognized as the most common cause of severe acute gastroenteritis in infants and young children worldwide. In developing countries, rotavirus is estimated to cause approximately 527 000 deaths each year, accounting for approximately 21% of all childhood deaths due to diarrhoeal disease. It is estimated that over 82% of the rotavirus-associated deaths occur in infants and young children in the developing countries of Africa and Asia.

WHO has prioritized the development of rotavirus vaccines and recommended the parallel evaluation of these vaccines in developing countries. In October 2002, GAVI established a special initiative called the Rotavirus Vaccine Programme (RVP) at PATH with the specific goal of accelerating the development of new rotavirus vaccines and introducing them in the countries where they are most needed.

Two new rotavirus vaccines were licensed internationally by the multinational pharmaceutical companies in 2006, and these are currently being used in routine childhood immunization programmes. Although these rotavirus vaccines have been licensed, neither one has been evaluated for clinical efficacy in infants in developing countries in Africa or Asia. Much remains to be done to prove their effectiveness in these regions.

In addition, there are several other promising candidate vaccines which have undergone preliminary clinical evaluation. These include a human neonatal rotavirus strain (RV3), a multivalent bovine human reassortant rotavirus candidate (UK) and a naturally occurring bovine-human rotavirus reassortant (116E). A WHO meeting in March 2006 highlighted the role and importance of these alternative vaccine candidates and the role of the emerging vaccine manufacturers in the international landscape. Many emerging vaccine producers in the Federative Republic of Brazil, the People's Republic of China and the Republics of India and Indonesia are considering rotavirus vaccine production with one of the candidates listed above. This new programme, funded by the BMGF and based at PATH, will facilitate technology transfer, vaccine production and clinical evaluation of selected alternative candidates.

Experience with new vaccines, such as the hepatitis B or Hib vaccines, has illustrated the importance of the emerging vaccine producers in terms of vaccine costs and supplies of vaccine for infants in the developing world. Rotavirus vaccine development is progressing rapidly in the developing world and will support an international ability to vaccinate all the world's infants.

2.11 Cost-effectiveness of rotavirus vaccines: an evidence-based review (*Damien Walker*)

Rotavirus gastroenteritis continues to be a major cause of childhood morbidity and mortality worldwide, with the vast majority of mortality occurring in the poorest countries. In 2004, the first of the new generation of rotavirus vaccines was licensed for administration to infants in the United Mexican States, and in 2005 this vaccine was licensed in over 30 countries. In addition, other rotavirus vaccines are near licensure or in development. The promise that rotavirus gastroenteritis is a vaccine-preventable disease is now being realized, and work is underway to demonstrate the need for these vaccines in the poorest countries. Central to this work is the collection and communication of reliable data on disease burden, as well as the collection and analysis of data to estimate the economic burden of rotavirus. During the last few years, several global, regional, and country-specific studies have been conducted to evaluate the impact and cost-effectiveness of rotavirus immunization.

Following the recommendation of the Commission on Macroeconomics and Health, WHO categorizes interventions that avert a DALY for less than the country's per capita gross domestic product (GDP) as highly cost-effective. The emerging evidence-base from the People's Republic of Bangladesh, the Republic of Ghana, China, Hong Kong SAR, the Republics of Peru and South Africa, and the Socialist Republic of Viet Nam suggests that at a cost of less than US$ 15 per immunization course, rotavirus vaccines will be highly cost-effective. Furthermore, these studies illustrate that the main drivers of the cost-effectiveness are the burden of disease, vaccine effectiveness, timing of vaccination, number of doses, vaccine cost, additional immunization programme costs, model structure and study perspective. Relatively little has been done up to now to assess the impact of patients' out-of-pocket treatment expenses and indirect costs related to diarrhoeal disease, at both public and private facilities, on household expenditure and poverty levels.

Future studies would benefit from improved empirical evidence on vaccine effectiveness from a wider sample of countries; better understanding of deaths from diarrhoea in vaccinated and non-vaccinated young children; additional research on the vaccine efficacy for different dosage regimes; and improved information on introduction costs associated with training, social mobilization, awareness-raising, and changes in logistic costs related to the cold chain and transport of new vaccines. To support the comparability of results among countries, a set of guidelines to standardize cost-effectiveness evaluation methods needs to be developed, including common guidelines for presenting and interpreting results in the context of a country's ability to finance vaccines as part of their national immunisation programme.

3. Pandemic influenza vaccine research and development

Moderator: John Boslego
Rapporteur: Alejandro Costa

3.1 Avian flu in animals and humans (*Malik Peiris*)

Human as well as animal influenza viruses have a high mutation rate, leading to high genetic diversity, as seen in the haemagglutinin (H) and neuraminidase (N) genes of the viral strains that affect humans (H1N1; H3N2; H1N2), aquatic birds (H1-16; N1-9), terrestrial poultry (H9N2; H9N1; H6N1), pigs (H1N1; H3N2; H1N2; H3N1) and equines (H3N8; H7N7).

The first outbreak of H5N1 influenza in humans was reported in 1997 in China, Hong Kong SAR with 18 cases and six deaths. Since then an ever increasing number of cases has been reported from the Republic of Azerbaijan, the Kingdom of Cambodia, the People's Republic of China, the Arab Republic of Egypt, the Republics of Iraq and Indonesia, the Kingdom of Thailand, the Republic of Turkey and the Socialist Republic of Viet Nam, with more than 200 cases altogether, of which more than 100 were fatal.

H5N1 viruses can be subdivided from their nucleotide sequence into a series of clades.

- Clade 1: Vietnam, Thailand, Cambodia
- Clade 2.1: Indonesia
- Clade 2.2: Qinghai Lake, China, central Asia, Europe, Africa, India
- Clade 2.3: Anhui/Fujian-like sub-lineage

A pre-pandemic human vaccine should have broad H5 cross-reactivity to provide cross- immunogenicity and to be effective against all current H5 clades. It is envisaged that the development of an effective vaccine which is able to provide broad protection may take several years.

Meanwhile the recommended strategy to minimize the risk of human infections is to control H5N1 transmission in poultry. Increased surveillance and early detection of animal cases have allowed the eradication of the virus in countries like China, Hong Kong SAR, the Republics of India and Korea, Japan and Malaysia. In still endemic countries/areas, it is necessary to enhance surveillance and thereby early detection. Currently two types of intervention have been successful in effectively controlling virus transmission, namely:

- surveillance, detection and culling of poultry as done in the Kingdom of Thailand;
- vaccination of poultry, as in the Socialist Republic of Viet Nam.

3.2 Pandemic flu vaccine regulatory preparedness (*David Wood*)

WHO and the national regulatory authorities are working together to develop regulatory tools for the rapid approval, licensure and release of influenza vaccines in the event of a pandemic. Two workshops to harmonize criteria and regulatory requirements were held in 2006 - one in Ottawa, Canada on 9-11 March 2006 and the other in Bethesda, MD, USA on 12-13 June 2006.

An international consensus emerged regarding the need for a full regulatory submission for licensure, but with an expedited regulatory process, including:

- a flexible approach for the reception and review of data;
- reliance on post-approval efficacy studies;
- requirement for providing post-approval safety data;
- emergency-use options in case the vaccine was needed before the completion of the regulatory process.

WHO is working to develop standard processes. One of the challenges is to set up general immunogenicity criteria to evaluate candidate pandemic vaccines. Efficacy criteria currently used are based on the European Medicines Evaluation Agency (EMEA) recommendations for the evaluation of seasonal flu vaccines. The healthcare-associated infection (HAI) antibody titre is the commonly accepted correlate of immunity, but there are instances when this criterion appears unsatisfactory, in particular for assessing live attenuated vaccine immunogenicity. The NRAs agreed that WHO should convene a group of influenza immunology experts to help develop an authoritative position on the immunogenicity criteria that could be used to evaluate pandemic vaccines.

Another challenge would be the quality control (QC) test, and capacity to release vaccine lots during a pandemic. WHO is evaluating global requirements for batch release, reagent preparation and QC test capacity, and also how this capacity could be increased. This evaluation has led to the development of a contact list for National Control Laboratories (NCLs) worldwide, and a questionnaire on global needs which was approved at the Bethesda meeting and is being distributed to NCLs. An assessment of the results is pending.

There was also a consensus during the Global Advisory Committee on Vaccine Safety (GACVS) meeting on 27-28 November 2006 for a rapid alert system for the notification of adverse events with pandemic vaccines during pandemic as well as pre-pandemic phases. This implies the enhancement of existing national and global networks sharing vaccine safety information and the increase of current evidence on seasonal influenza vaccine safety that could be used as proxy for future pandemic influenza vaccines.

WHO is currently working to develop guidelines and regulatory tools, such as:

- guidelines on regulatory preparedness for pandemic vaccines - regulatory pathways; Q,S,E specifications; QC preparedness; safety monitoring;
- updated Q,S,E guidance for live attenuated flu vaccines;
- anti-H5N1 standard serum.

3.3 The possible use of H5N1 vaccines in the pre-pandemic period (*David Salisbury*)

One of the greatest challenges in responding to an influenza pandemic will be to develop an effective vaccine. Rapid deployment of a vaccine is a key goal in responding to an epidemic. Ideally, vaccination would have to begin within the first two months of the initial global outbreak. A delay of more than four months from the start of the pandemic would mean that the initial epidemic would be largely extended worldwide. However, the vaccine will need to match the pandemic strain of virus and as it takes from four to six months to prepare a batch of a new vaccine, no vaccine will be available during the first wave of the pandemic.

Some countries are considering that one of the possible strategies would be to stockpile pre-pandemic vaccines prepared against the currently circulating avian flu strain. However, this vaccine should provide cross-immunity to have an impact on the eventual pandemic strain. There is currently little evidence that a H5N1 vaccine will effectively provide cross-protection against an eventual pandemic strain, although recent evidence suggests that H5N3 or H5N1 whole virus vaccines with new adjuvants (squalene-based - MF59 or ASO3) may induce adequate responses against all H5 strains, but not against strains other than H5 strains.

Another possible strategy would be to prime the population with one dose of a currently available H5N1 vaccine and, after a pandemic is declared, to administer a booster dose of vaccine with a vaccine closely matching the pandemic strain. However, time frame for the second dose, availability of the pandemic vaccine, licensing criteria for an adequate level response, costs and replenishment are important issues to be addressed.

In the United Kingdom, the Department of Health has purchased 3.5 million doses of H5N1 vaccine from two manufacturers. One manufacturer makes an egg-based second generation vaccine adjuvanted with MF59, whereas the other makes a cell culture-based vaccine adjuvanted with alum. These vaccines will only be used if the risk of a pandemic was to increase significantly.

Summary

Efforts should be made to develop pre-pandemic vaccines rather than pandemic vaccines, including cross-protective vaccines (e.g. H5N3, M2 protein, nucleoprotein). The use of new adjuvants could allow considerable antigen-sparing (3.75 or 7.5 µg doses of HA), thereby expanding vaccine production capacity. However, obtaining an efficacious cross-protective vaccine will take time, perhaps as much as another 10 years.

3.4 Update on clinical trials with H5N1 vaccines (*Linda Lambert*)

In response to the concern of several countries facing simultaneous appearance of avian influenza virus, NIAID/NIH/DHHS decided in 2004 to initiate a number of clinical trials with H5N1 vaccines. The main objective of these trials was to obtain an H5N1 vaccine from manufacturers with licensed products (with and without adjuvants) and to evaluate their safety and immunogenicity in human volunteers.

The following clinical trials were undertaken.

- Sanofi-pasteur inactivated subunit vaccine produced in eggs, using 7.5, 15, 45 or 90µg HA per dose. The vaccine showed a clear dose-response curve, with two doses of 90µg HA being optimal.
- Sanofi-pasteur vaccine, intradermal (ID) versus intramuscular administration with a 2- dose schedule. The study showed no clear advantage of the ID route at 3 and 9µg HA per dose.
- Clade 3 vaccine as primer and a 2-dose of Sanofi-pasteur Clade 1 vaccine at 90 µg HA/dose. The results demonstrated higher responses in subjects primed with the Clade 3 vaccine than in unprimed subjects, even after two doses of 90 µg Clade 1 vaccine.
- Inactivated H5N1 vaccines with adjuvants. These are still ongoing studies, but preliminary results show that low dose formulations adjuvanted with an oil/water emulsion achieved high immune responses (Novartis MF59: as low as 7.5µg HA; GSK AS03: as low as 3.75µg).
- Live attenuated H5N1 vaccine (MedImmune): NIAID initiated a Phase I trial of a live attenuated (LAIV) H5N1 vaccine. Results are pending.

Summary

There are currently several ongoing clinical trials with split virus or whole virus, added or not with an adjuvant (Alum, ASO3, MF59) and using from 3.5 to 90µg HA. Some candidate vaccines and formulations were demonstrated to be safe and immunogenic. Several are in Phase III and should be licensed soon. However, there are few clinical trials looking for cross-protection, with the exception of MedImmune with their LAIV and by Novartis with adjuvant MF59.

3.5 Global pandemic influenza action plan to increase vaccine supply (*Alejandro Costa*)

A Global Action Plan (GAP) document was developed in response to World Health Assembly (WHA) Resolution WHA58.5, which requested the WHO secretariat to seek solutions to reduce the potential global shortage of influenza vaccines. WHO organized three working group meetings with several experts from the NRAs and from the vaccine industry, scientists, virologists, experts in immunization programmes, and donors, on the following topics:

- WG1: Immunization and vaccine demand;
- WG2: Vaccine production capacity;
- WG3: New vaccine research and development.

The objective was to facilitate discussion on these three areas of work and identify strategies and activities aimed at increasing vaccine supply. Each working group (WG) had an external facilitator and a rapporteur, and a WHO focal point to develop the action plan. Over two months the WGs debated by e-mail the strategies and activities in their domain of the action plan, after which they met in Geneva, Switzerland to hear the other WGs present their action plan and to consolidate all strategies into a single comprehensive GAP.

The participants drew up an action plan with strategies for the short, mid and long term, aiming to increase influenza vaccine production and surge capacity before and during an influenza pandemic. Their principal recommendations were:

- to increase the seasonal influenza vaccine coverage so as to provide protection against influenza in the general population, and at the same time to use the increased demand to stimulate industry to expand capacity in order to meet a potential demand for a pandemic vaccine;
- to increase the vaccine production capacity through the establishment of new vaccine production-capacity by direct investment and by facilitating technology transfers to developing/middle-income countries, as well as by improving current vaccine production technologies to obtain better yields;
- to continue efforts in research and development and design more potent and effective vaccines that would induce protection after only one dose, and/or could elicit broad spectrum and long-lasting immunity.

Conclusion

An effective partnership and a commitment to sustain efforts over 5-10 years are judged indispensable for the success of this endeavour. Implementation of the global pandemic influenza action plan to increase influenza vaccine supply will require substantial funding - preliminary budget estimates indicate a need of between US$ 3 billion to US$ 10 billion. International organizations, including the WHO, need to take an active role in coordinating and streamlining many of the planned activities. Most importantly, none of these strategies will be able to fill the gap in the immediate short term but, starting now, first results may be visible in three to five years.

After the GAP was approved, WHO started implementing its proposals by:

- mapping the landscape of demand and supply of influenza vaccines by initiating a global survey to estimate the vaccine demand for seasonal and pandemic vaccines;
- stimulating the WHO collaborating centres to improve production yields with H5N1 vaccines;
- reviewing current technologies and discussing with manufacturers possible production technology transfers to developing country manufacturers;
- exploring the establishment of new capacity in developing countries;
- developing adjuvanted vaccines, whole virus vaccines, and intradermal delivery of influenza vaccines.

4. Development of vaccines against HIV, malaria and tuberculosis

Moderator: Fred Binka
Rapporteur: Saladin Osmanov

4.1 Phase IIB "Test of Concept" HIV vaccine clinical trials: advantages and limitations (*Patricia Fast*)

Traditionally, Phase I and Phase II clinical trials are concerned with safety and immunogenicity of candidate vaccines respectively, while Phase III pivotal trials are intended to assess the protective efficacy and safety of the vaccine in populations for which the vaccine was designed, and to provide the basis for regulatory rulings concerning licensure, or approval to market the vaccine.

The major scientific challenge for most vaccines under development is, however, the lack of knowledge of the qualitative and quantitative immune responses against infection that the vaccine ought to elicit to be effective in preventing infection or controlling the development of the disease. In addition, the conduct of a licensure trial requires major investments of time and resources, the development of definitive manufacturing processes, full validation of methods, and the establishment of extensive trial-site infrastructures. There is, therefore, an understandable reluctance to embark upon pivotal Phase III trials without supportive evidence that the vaccine is likely to demonstrate a most significant level of efficacy.

In an attempt to overcome some of these challenges, an intermediate vaccine evaluation step, referred to as Phase IIB "Test-of-Concept trial" (Phase IIB-TOC) has been proposed for evaluation of HIV vaccine candidates. In the past, a similar step was used to estimate preliminary efficacy of drugs and of some non-HIV vaccines (e.g. rotavirus, HPV, malaria). However, concerns relating to definition and potential usefulness of this type of trial for evaluation of candidate HIV vaccines remain, and this prompted WHO, UNAIDS and the International AIDS Vaccine Initiative (IAVI) to convene a consultation from 31 January-2 February 2006 in New York, NY, USA to discuss the definition of Phase IIB-TOC trials, and their place in the overall pathway of HIV vaccine research and development.

The panellists were asked to make recommendations concerning:

- situations in which such trials may be of greatest (or lowest) utility;
- the preparation for, and the conduct of IIB-TOC trials, particularly with respect to conveying the correct message to governments, NRAs, communities and participants;
- implications for product development, manufacturing, and potential licensing.

The consultation proposed a working definition of Phase IIB-TOC, which clarified some of the key elements of this type of trial.

- Phase IIB-TOC trials are designed to provide a hypothesis-driven evaluation of potential HIV vaccine efficacy. These trials are intended to inform the "stop-go" decisions in the development of a candidate HIV vaccine. A Phase IIB-TOC trial is designed to test a carefully defined concept or research question, which should be clearly formulated. These trials will therefore be conducted in populations at higher risk for HIV infection.
- Phase IIB-TOC trials are not designed to independently support licensure, but rather to identify relatively rapidly vaccine candidates that merit further testing in pivotal licensure trials, and those that should be reformulated or abandoned as unlikely to show significant levels of efficacy in a Phase III trial.
- A Phase IIB-TOC trial may share some design elements with Phase III efficacy trials, but Phase III trials are more likely to have clinical end-points that require longer follow-up, as compared to IIB-TOC trials where end-points are selected to obtain rapid answers.
- The overall product development plan incorporating one or more Phase IIB-TOC trials might not be necessarily cheaper or faster than a plan that progresses directly from Phase II to Phase III trials, but it may be more useful in furnishing essential information that will help in the overall development process.

An important clarification was made relating to the fact that Phase IIB TOC trials do not represent a licensure trial, due to a number of important limitations, namely:

- unlike pivotal Phase III efficacy trials, the product being tested in a Phase IIB-TOC trial could be a prototype or in the early stage of development;
- the trial is hypothesis-driven and can be designed for testing a candidate vaccine in a restricted population based on the use of shorter-term non-validated end-points and biomarkers;
- the statistical power is less than required for typical Phase III trials (VEs +/- 30% rather than +/- 15%);
- incidence estimates would exclude a lower confidence limit of zero efficacy, rather than 30% or greater efficacy that is more likely to be required for regulatory approval.

On the other hand, Phase IIB TOC trials may have clear advantages in:

- identifying whether there is any observed "non-zero" protective efficacy of the vaccine against acquisition of HIV infection, even if the magnitude is not precisely characterized;
- evaluating the vaccine impact on the viral load set-point in vaccinees who become infected, which may be predictive of a slowing-down or a modification in the natural history of the disease;.

- providing evidence for design of subsequent pivotal Phase III trials by helping in choosing the most appropriate study design, end-points and sample size, and looking into potential population-based benefits of the vaccine, such as the reduction of post-infection viral load and secondary HIV transmission;
- generating preliminary evaluation data on current or novel biomarkers as potential end-points or correlates of protection for future studies and subsequent, more rigorous testing.

Finally, it was recognized that the application of different novel vaccine evaluation strategies will require considerable discussion with national and international research and development agencies, including in particular NRAs. It was also emphasized that WHO/UNAIDS should play a role in promoting effective exchange of information on issues surrounding Phase IIB-TOC trials in order to help NRAs, ethics committees and trial investigators in making rational decisions concerning such trials, especially in resource-poor settings.

4.2 Update on new HIV vaccine candidates (*Ann Duerr*)

The importance of developing a safe, effective and affordable HIV vaccine is emphasized by the fact that, to date, almost a quarter of a century into the HIV pandemic, we are still facing a growing number of HIV infections and AIDS-related deaths. The global HIV vaccine research and development effort has been continuing over the past two decades resulting in the development and evaluation of more than 30 candidate vaccines in more than 85 human clinical trials involving thousands of volunteers and investigators, and staff from 25 nations from developed and developing countries. The global financial investment in HIV vaccine R&D has exceeded more than US$ 3 billion. However we still do not have an HIV vaccine.

The major obstacles in HIV vaccine R&D come from the lack of basic scientific knowledge of protective immune responses. However, some progress has been made in this field, allowing the following general conclusions.

- Most of the efforts to elicit broadly-reactive HIV neutralizing antibodies have met with failure, and none of the vaccine candidates based on this concept have thus far been able to confer protection.
- Vaccine candidates that elicit cellular immunity against HIV have shown promising results in animal experiments, in particular in controlling the rate of virus replication after challenge. However most of these vaccine candidates are still in the early stages of development.
- The results from testing T-cell based vaccines have given rise to a new dilemma, namely, will the vaccine-induced reduction of the virus load have a significant impact on the clinical course of the disease and/or on reducing secondary transmission in humans?

To date, there are three ongoing larger efficacy trials: *Canarypox*/rgp120 in the Kingdom of Thailand, the Merck Ad5 candidate vaccine in the Americas (protection against subtype B) and in the Republic of South Africa (protection against subtype C). A fourth trial is planned to start in 2007 with an NIH/VRC multi-clade/multi-gene DNA/Ad5 prime boost combination. These trials are meant to: (a) evaluate the vaccine efficacy in inducing protection against infection versus control of virus replication; (b) assess the impact of pre-existing anti-vector immunity on the vaccine's immunogenicity and efficacy; (c) define the breadth of potential cross-protection against different HIV genetic subtypes. The results from these trials are expected in 2009-2011.

4.3 Update on Phase III HIV vaccine clinical trial in Thailand (*Supachai Rerks-Ngarm*)

This trial was conducted under multiple sponsorship by the Thai Ministry of Public Health, Royal Thai Army, Mahidol University, Thailand, Sanofi-Pasteur, Walter Reed, NIH/NIAID, Henry Jackson Foundation and VaxGen Inc.

The primary objective of the trial was to determine the efficacy of the ALVAC vCP1521/AIDSVAX BE rgp120 prime-boost combination regimen in a general population in the south-eastern provinces of the Kingdom of Thailand in preventing HIV infection, and controlling virus replication. The secondary objectives included: the evaluation of the vaccine impact on CD4 counts after inter-current infection; the confirmation of vaccine safety; and the evaluation of the potential for increased risk behaviour of volunteers in an HIV vaccine trial.

The trial was started in September 2003. From an initial 60 000 interested individuals who were interviewed, more than 26 000 volunteers were screened and 16 402 volunteers were enrolled. By 31 July 2006 all vaccinations had been completed.

The results that are available to date provide detailed information on the demographic characteristics of the enrolees, assessment of reasons and motivation for participation, estimate behavioural risks, and participation impact. No adverse events have been documented so far and there have been no concerns about the retention and follow-up rates in the trial. The final results from the trial are anticipated in Q3/2009.

4.4 Clinical trial end-points for evaluation of malaria vaccine efficacy: results of a WHO consultation (*Vasee Moorthy*)

WHO convened a study group to address the question of the "*definitions and methods for the measurement and analysis of clinical outcomes in malaria vaccine trials*". The main objectives of this meeting were to develop and harmonize case definitions and optimize trial designs and methods of measurement and analysis, while fully respecting regulatory standards, in order to support licensure.

The WHO advisory role is particularly relevant in the context of clarifying the licensure pathway, defined by Article 58 of the EMEA constitution, which permits the EMEA to consider products not otherwise targeting European markets for licensure, and to deliver an opinion that would be equivalent to a market authorization or licensure of the product.

The study group recommended that a key regulatory expectation to keep in mind when selecting a primary end-point in a clinical trial is that it must be sufficient to demonstrate a "clinically relevant impact of the vaccine on malaria". Two primary end-points were discussed, clinical malaria and severe malaria, both of which were likely to satisfy this requirement.

For a case definition of clinical malaria, the three elements that should be considered are the definition of morbidity, the parasite density threshold and the case-detection system. Although malaria results in non-specific symptoms, the morbidity parameter of measured fever, with an axillary temperature >37.5°C, was recommended based on studies looking at groups with significant morbidity attributable to the disease in stable malaria transmission settings.

The parasite density threshold was shown to increase the specificity of the clinical diagnosis. The consultation agreed that standard methodology (i.e. the Smith and Schellenberg Test) should be used to derive and calculate the threshold in the area using recent appropriate historical data. A threshold with >90% specificity should be chosen, using the same age group and case-detection system. Given the influence of the case-detection system on the severity distribution of detected malaria cases, the consultation agreed that a case-detection system should be included in the primary objective of the trial, considered in the calculation of sample size, and used for the preparatory longitudinal epidemiological studies. The choice of a case-detection system depends upon the level of parasite density threshold, access to health-care facilities and the stage of development of the vaccine.

For the definition of severe malaria, criteria had been defined previously by WHO, but these criteria addressed treatment and not the need for a specific diagnosis required for pivotal trial of a preventive vaccine. A key rationale in the development of this definition is that it should identify a group of patients with malaria illness with one or more criteria associated with poor outcome, at several centres in endemic countries, and by several groups of investigators. The definition must be standardizable over time and across sites, and should balance pragmatic considerations in terms of performing the assessments and measurements in the field research settings in sub-Saharan Africa.

A major consideration was that undetected co-morbidity can decrease the specificity of the severe malaria case definition. An approach for measuring and analysing these interactions therefore needs to be formulated. Another major issue which needed to be addressed was uncertainty about estimates of the incidence of severe disease.

Discussion

The group agreed on the importance of standardization and harmonization of case definitions to be used as end-points in Phase III malaria vaccine trials.

- There was agreement on a primary case definition for *clinical malaria* and on principles for that for *severe malaria*.
- It was recognized that there was a need to address multiple transmission settings, and it was recommended that pivotal trials be performed across the range of settings, and that trials be empowered to detect variation in clinical malaria efficacy at different sites.
- It was recommended that, despite the possibility of vaccine licensure based on a duration of efficacy of 12 months, safety as well as efficacy considerations should require a minimum follow-up of two years, and ideally of up to five years.
- Regarding the choice of primary end-point, there was strong consensus that the public health burden of *clinical malaria* justified its use as a primary end-point for licensure. It was recognized that introduction of the vaccine could be accelerated by the use of a *severe malaria* end-point.
- For facilitating introduction of the vaccine, it was felt that data on duration of efficacy and efficacy in multiple transmission settings, were equally important, and that pivotal trials should be designed to generate such data whenever possible.
- Vaccine delivery was another key introduction issue and it was agreed that generating data to support the integration of the malaria vaccine within EPI was clearly needed.

Conclusion

The group agreed that a Phase III trial programme should generate information on:

- time to the first or only episode of malaria end-point;
- occurrence of multiple episodes of malaria;
- duration of efficacy for at least two years;
- variation in efficacy between different sites in multi-site trials;
- efficacy in infants;
- safety and non-inferiority of the vaccine when administered with EPI vaccines.

4. 5 Update on new tuberculosis vaccines (*Yasir Skeiky*)

Despite vigorous implementation of a highly successful public-health tuberculosis (TB) control strategy known as directly observed treatment short-course (DOTS), it will probably be impossible to contain the TB pandemic with drugs alone. New, deadlier TB strains carrying resistance mutations against first-line drugs (MDR-TB) or against first and second-line drugs (XDR-TB) are on the rise. The goal of eliminating TB as a public-health problem by the year 2050 is out of reach in the absence of a more effective vaccine than the current BCG vaccine, which, although most useful against childhood manifestations of TB, is largely ineffective in protecting adolescents and adults against pulmonary disease. The current research and development approaches to improve vaccine protection against TB rest on two pillars: improving BCG itself, and combining it, in a prime-boost vaccination paradigm, with a variety of subunit vaccine-delivery systems.

Improving BCG involves two principal strategies, namely:

a) (over-) expression of proteins that have been shown to be protective in animal models;

b) modification of the antigen presentation pathways, such as introduction of endosome escape mutations.

While earlier versions of re-engineered BCG vaccine candidates only carried one extra gene insertion, such as BCG30, which over-expresses Ag85B (UCLA, Los Angeles, USA) or the listeriolysin-expressing BCG:*ΔureC-Hly* (MPI Berlin, Germany), the Aeras Global TB Vaccine Foundation (Aeras) has now developed a double insertion mutant, AFR-01, which expresses TB stress proteins as well as perfringolysin, a protein that forms pores in the endosomal membrane and thus allows mycobacterial proteins to enter the major histocompatibility complex (MHC) Class 1 ($CD8^+$) presentation pathway. The vaccine has been shown to be as least as immunogenic and protective as wild-type BCG in animal models, and safer than BCG in severely compromised immune deficient (SCID) mice. While BCG30 has already been tested in clinical Phase I trials and shown to be safe and immunogenic, vaccine candidates BCG:*ΔureC-Hly* and AFR-01 were not expected to enter clinical trials until mid-2007.

A special case of live TB vaccines is represented by rationally attenuated *Mycobacterium tuberculosis (M. tuberculosis)* strains, of which there are at least two strains under study, an auxotrophic mutant and a regulatory mutant, which currently are in preclinical development respectively at the Albert Einstein College of Medicine, New York (NY, USA), and at the University of Zaragoza (Spain).

BCG or recombinant derivatives are likely to be required in all new TB vaccine regimens, so it is timely to consider new approaches to produce the vaccine. Since BCG is an old vaccine with over 85 years of use in humans, its current production procedure and quality-control technology is outdated. Aeras has risen to that challenge by building its own vaccine production plant, where a fermentation process to replace traditional shake flask culture is being developed. At the same time, WHO/IVR and QSS are collaborating with TB researchers and vaccine producers to replace phenotypic and morphologic criteria in BCG quality-control procedures with better defined molecular criteria.

Development of TB vaccines to be used for booster immunization after BCG is an empiric process, with numerous vaccine-delivery systems being tested for induction of optimal protective vaccine responses. Thus, new TB subunit vaccines, composed of one or several *M. tuberculosis* antigens are being developed either as adjuvanted protein subunit vaccines, DNA vaccines, or live recombinant vaccines using viruses or bacteria as vectors.

Among the adjuvanted protein subunit vaccines, two have entered clinical evaluation in humans: Mtb72F (Aeras and GSK), a fusion protein of TB antigens Mtb39 and Mtb32 formulated in a GSK proprietary adjuvant and Hybrid-1 (Statens Serum Institute, Copenhagen, Denmark and EC), a fusion protein of secreted *M. tuberculosis* antigens ESAT-6 and Ag85B in adjuvant IC31. In order to avoid conflict with the ongoing use of ESAT-6 as a diagnostic antigen, it is likely that the Hybrid-1 vaccine development will be discontinued in the future to the benefit of HyVac-4, a similar construct in which the sequence of ESAT-6 has been replaced by that of *M. tuberculosis* antigen TB10.4.

The most advanced of all the new TB vaccines is a live recombinant vaccine, MVA85A, which consists of a modified vaccinia virus Ankara vector (MVA) expressing Ag85A. The vaccine is being developed at Oxford University in the United Kingdom and is currently in Phase II clinical trials in the Republic of South Africa. This vaccine was found to be safe in adults independently of their purified protein derivative (PPD) or HIV status, and was demonstrated to boost pre-existing antimycobacterial memory decades after BCG vaccination. Another prominent virus-vectored approach in late preclinical development is represented by a recombinant adenovirus vector (Ad35) which expresses multiple TB antigens, the product of collaboration between Aeras and Crucell Inc. The advantage of this expression system consists in the simultaneous induction of $CD8^+$ and $CD4^+$ T-cell immune responses. Due to the choice of Ad35, a low prevalence virus strain, as the vector, this vaccine is unlikely to be affected by pre-existing anti-adenoviral immunity, which is a major concern with "conventional" Ad5-based recombinant vaccines.

The initial goal of all these approaches is to have at least one safe, efficacious and affordable new TB vaccine by 2015. Many promising approaches have emerged over the last few years. However, due to the lack of relevant animal models and the absence of a surrogate marker of protection, only clinical efficacy trials, which are not planned to start before 2009-2010, will show whether this goal can be achieved.

5. Rabies, an unrecognized health priority in Asia

Moderator: Henry Wilde
Rapporteur: François Xavier Meslin

5.1 Epidemiology of rabies in Asia (*Elizabeth Miranda*)

Rabies is a viral zoonotic disease for which there is no effective treatment and which is responsible for an estimated 55 000 human deaths every year in Africa and Asia alone. It is also estimated that at least 40% of these deaths occur in persons less than 15 years old. Most deaths follow bites from rabid dogs. In 2005, more than 10 million people received rabies post-exposure prophylaxis (PEP) in Asia alone. Human rabies has recently been re-emerging in countries where it had been brought under control, such as the People's Republic of China and the Socialist Republic of Viet Nam. During the past 10 years it has also emerged and become entrenched in islands historically reported as rabies-free, such as the Flores and the Moluccas in the Republic of Indonesia. Most of the countries reporting the highest rabies death rates also harbour the largest population of stray and poorly-controlled dogs.

Rabies is a vaccine-preventable disease in both humans and animals, and many human deaths could be avoided by the appropriate application of vaccines to exposed people and dogs. Effective, safe and relatively inexpensive animal vaccines are manufactured in many countries, but the 70% vaccine coverage of canines which would be needed to control animal rabies is seldom met. Similarly, effective cell culture rabies vaccines for human pre- and post-exposure prophylaxis are available in most large cities in the developing world but animal brain tissue-derived rabies vaccine is still produced and used for PEP in some developing countries, mostly in Asia. Some 12 million people receive PEP each year, which saves about 275 000 lives. In the Kingdom of Thailand, the number of human deaths due to rabies has been drastically reduced during the past 20 years, mainly through improving health staff ability to deliver appropriate PEP and making modern cell culture vaccines available throughout the country. Rabies vaccine has also been used for preventive immunization of schoolchildren in limited clinical trials in rabies hyperendemic areas of the Republic of the Philippines, the Kingdom of Thailand, and in the Socialist Republic of Viet Nam in a trial in young infants in association with EPI vaccines.

It is sad to realize that rabies kills more people than dengue, Japanese encephalitis, meningococcal meningitis or yellow fever, yet it has received much less attention from governments and non-governmental organizations (NGOs), and rabies vaccines have not yet received support from an international funding agency.

5.2 Introduction of intradermal rabies vaccination: A success story in Sri Lanka (*Omala Wimalaratne*)

While human rabies vaccines remain costly for those who need it most, alternative economic pre- and post-exposure regimens using a fraction of the intramuscular dose have been shown to be safe and efficacious when administered by multi-site intradermal (ID) injections. ID multi-site regimens, first used in the Kingdom of Thailand in 1987, have been successfully introduced in other Asian countries such as the Republic of the Philippines, the Democratic Socialist Republic of Sri Lanka, and more recently in the Republic of India. In the Democratic Socialist Republic of Sri Lanka, an ID vaccine administration regimen was first used in 1997 in two teaching hospitals in Colombo which conducted several comparative immunogenicity studies. The technique is now applied in all teaching, general, base and district hospitals on the island, and involves 85% of all patients seeking PEP. Since the introduction of ID vaccination as a part of PEP, only two treatment failures have been reported, in spite of a chronic shortage of rabies immunoglobulin (RIG) products. Better patient compliance with PEP requirements as well as fewer adverse events following vaccine administration have been reported. The shift to ID PEP in the Democratic Socialist Republic of Sri Lanka was shown to be cost effective and is receiving continuous support from health policymakers.

5.3 Monoclonal antibodies as a replacement for polyclonal rabies immunoglobulins (*Richard Franka*)

There is a critical shortage of rabies immunoglobulins (RIG) in all the countries where canine rabies is a problem. New immunoglobulin manufacturers are emerging in the People's Republic of China, the Republic of India and the Kingdom of Thailand. However, questions have been raised regarding the safety and efficacy of the new RIG products and unfavourable reports of lesser activity have been made on the occasion of PEP failures when everything seemed to have been done according to WHO PEP guidelines. Research on RIG alternatives is progressing, and it is hoped that more effective and affordable monoclonal antibody (MAb) products will replace RIG in the future. Anti-rabies MAbs are proposed as a safe, efficient and cost-effective replacement for equine and human RIG products. They can be produced on a large scale with high batch-to-batch consistency, lack of health risk associated with blood-derived products, and the possibility to manipulate Fc fragments to induce minimal adverse effects and prolong half-lifes in the case of murine MAbs. Similarly to polyclonal RIG products, no single MAb is pan-reactive with the global spectrum of Lyssaviruses. Given the diversity of the latter, a cocktail of at least two MAbs is recommended for PEP. A WHO coordinated multi-centre study concluded that a cocktail of two MAbs of human or murine origin represents a promising, safe and efficacious biological for use in PEP as a replacement for equine and human F(ab)2 fragments.

5.4 The global control of rabies (*Thiravat Hemachudha*)

Progress has been recorded in rabies prevention and control during the past 15 years. Many countries have stopped using brain tissue-derived rabies vaccines and are now using modern cell culture vaccines administered intramuscularly or intradermally for human PEP. The annual number of human rabies deaths has decreased markedly in many countries during that period, particularly in Asia (e.g. the People's Republic of China, the Republics of India and the Philippines, the Democratic Socialist Republic of Sri Lanka, the Kingdom of Thailand and the Socialist Republic of Viet Nam). During the past few years, more than 10 million PEPs have been administered annually, thereby preventing an estimated 280 000 deaths a year. However resources are urgently needed in a number of African and Asian countries to improve health-staff skills in the proper use of rabies biologicals, particularly that of vaccines by the ID route, as well as raising public awareness regarding rabies prevention and control. International support is required to facilitate access to modern vaccines, particularly in Africa, and to alternative technologies for the replacement of RIG to satisfy the need of the developing world for effective and affordable products for passive immunization in cases of severe exposure. Control and elimination of rabies animal reservoirs also need to be further promoted in most countries. Candidate countries have been identified in Africa and Asia where "proof of concept" national comprehensive projects for the elimination of canine and human rabies may be implemented in the near future. Support for these projects is urgently required to demonstrate the cost-effectiveness of a rabies elimination "package".

6. Human papillomavirus (HPV) vaccines

Moderator: Helen Rees
Rapporteur: Teresa Aguado

6.1 Epidemiology of cervical cancer in Asia (*Corazon Ngelangel*)

Approximately 15% of human cancer incidence can be attributed to virus infections, i.e. viruses represent the second most important risk factor of cancers in humans after tobacco consumption. Cancer of the uterine cervix is the second most common cancer in women worldwide and actually ranks number one in a large number of developing countries. Incidence and mortality vary among the four Asian subregions, south and central Asia accounting for about 26% of the cases, south-eastern Asia for 19%, eastern Asia for 7% and western Asia for 6%, the highest figures in these subregions being found in the Kingdom of Cambodia, Georgia, and the Republics of India and Korea respectively.

The etiological cause of cancer of the cervix has been demonstrated to be infection by a high risk, oncogenic HPV, but several other factors also play a role, such as high parity, use of some contraceptives and consumption of tobacco, as well as precocity and degree of sexual activity.

There are more than 100 known HPV types, with about 40 types infecting the genital tract. Out of these, only a few are carcinogenic. Genital HPV types can be classified into two categories, "high risk" and "low risk" viruses, that cause cervical cancer or genital warts respectively. The DNA of a high risk HPV type can be recovered from virtually all invasive cervical cancers, from about 80% of anal cancers, and from 30% of cancers of the vulva, vagina, penis, and oropharynx. The most common types of HPV worldwide are HPV 16 and 18, which are found on average in about 70% of cervical cancer cases, and HPV 6 and 11, which are recovered from 90% of genital warts cases.

Reasons to justify the prevention of HPV infection and cervical cancer are overwhelming, as about 50% of sexually active adults contract a genital HPV infection in their lifetime and as rates of both cervical cancer ("high-risk" HPV) and genital warts ("low-risk" HPV) are rising in young women. Prevention has relied so far on screening methods (cytological-pap test, visual inspection followed by acetic acid-VIA and HPV DNA detection). Two vaccines will soon be available that are active against HPV 16 and 18, and HPV 16, 18, 6 and 11, respectively. While these vaccines appear to be very effective against the two most common HPV types, HPV 16 and 18, screening and treatment will need to be maintained for a long time, as the vaccines do not contain all high-risk HPV types and as the effect of vaccination on the number of cancer cases will not be visible for many years. It will therefore be important to keep strengthening screening programmes while at the same time pushing for the introduction of the vaccine.

6.2 Update on clinical trials on the efficacy of HPV vaccines (*Lauri Markowitz*)

Results of clinical trials have been made available for both the quadrivalent HPV vaccine, Merck's Gardasil® which is already licensed and for the bivalent HPV vaccine, GSK's Cervarix® which is currently still a candidate. Both vaccines are based on the use of the HPV major capsid protein L1, which is expressed through recombinant technology. The L1 protein spontaneously self-assembles into virus-like particles (VLPs) that are then purified and made into a vaccine.

The quadrivalent HPV vaccine contains type 6/11/16/18 VLPs, is produced in yeast, adjuvanted with alum and given on a 0, 2 and 6 months schedule. The Phase II and III trials have been conducted in 16-26 year old females and additional immunogenicity and safety were studied as a bridging study in 9-15 year old adolescents. The vaccine was safe and well tolerated with no side-effects except local reactions. A 99% seroconversion rate was observed in 9-26 year old persons. Remarkably, antibody titres were substantially higher after vaccination than after natural infection. The longest the antibody titres have been followed is over five years, showing constantly high levels. The bridging studies also demonstrated very high antibody titres in adolescents, even higher than in adult women.

The vaccine showed a 100% efficacy against HPV 16 and 18 related cervical intraepithelial neoplasia (CIN)-2/3 lesions, and a 95% efficacy against HPV 6,11,16,18 related CIN-1 or external genital warts in 16 to 26 year old HPV-naive females over a mean follow-up of 1.5 years. In the Phase II study, prevention of HPV 16 persistent infection in the vaccinated group was 100% over a five-year follow-up. In contrast, no evidence of therapeutic efficacy of the vaccine could be demonstrated on pre-existing HPV infections.

The bivalent HPV vaccine from GSK contains HPV types 16/18 VLPs, is produced in baculovirus-infected insect cells, adjuvanted with AS04 (alum and monophosphoryl lipid A) and given on a 0, 1 and 6 months schedule. Phases II and III have been/are being conducted in a population of 15-25 year old females, and additional immunogenicity and safety studies were done in 10-14 year old female adolescents. No vaccine-related serious adverse events were reported.

The Phase II results showed 100% prevention of HPV 16 and 18 persistent infection, 95% protection against incident infection and 100% protection against HPV 16 and 18 CIN end-points. Antibody levels have been followed for over four years and appear relatively constant for both HPV 16 and 18 throughout the follow-up period. Vaccine-induced antibody titres were substantially higher than after natural infection and, as with Gardasil®, highest in those vaccinated at younger ages.

Another extremely encouraging result is the preliminary indication of possible cross-protection against infection with other HPV types. As expected, the more closely related, the higher seems to be the cross-protection, with a value of 94% for HPV 45.

Summary

Results for both vaccines were broadly similar.

- Both vaccines showed high efficacy against end-points associated with the vaccine HPV types. Efficacy against moderate-severe CIN due to HPV types 16 or 18 was close to 100%, but no data are available for efficacy in men.
- HPV vaccines induced systemic virus-neutralizing antibodies in virtually all vaccinated individuals at titres several-fold higher than those seen after natural infection.
- Antibody titres were higher after vaccination of young adolescents (<15 years old) than adult women. Note however that the minimum protective antibody threshold is not known.

6.3 Introducing HPV vaccines in adolescent populations: update on the PATH Project (*Robin Biellik*)

PATH is in charge of a major pilot HPV vaccine introduction project, related to both acceptability and socio-cultural issues as well as to programmatic aspects. HPV vaccines provide a unique opportunity to implement widespread primary prevention of cervical cancer and other HPV-related diseases through immunization. There are, however, multiple challenges to widespread vaccination, including: poor general knowledge and understanding of the link between HPV infection and cancer; socio-cultural barriers and issues related to an "STI vaccine"; logistic issues - such as lack of established vaccination programmes for pre-adolescents and adolescents, cost of the vaccine, requirement for three immunizations, cold chain implications, etc.

In industrialized countries, HPV vaccination ought to be facilitated by factors such as: the demand among young women; minimal perceived societal and parental barriers; clinical experience with young adolescents; endorsement of the vaccine by influential organizations; perception of early age of sexual debut; proportion of young females likely to be sexually active. Although many parents are less informed than their children, and some are likely to be very concerned about possible increased risky sexual behaviour after vaccination, a good proportion will trust health-care providers and be willing to appreciate the benefits of vaccination.

The situation is quite different in developing countries, due to lack of information at all levels, so that working up conditions for vaccine acceptance, delivery and use is urgently needed prior to any possibility of successful vaccine introduction. In view of this situation, PATH, in collaboration with other partners, has launched a project whose goals are:

- to generate critical data and experience for evidence based decision-making, strengthening essential health-system capabilities, and creating a supportive social and political environment for national readiness in four countries - the Republics of India, Peru and Uganda, and the Socialist Republic of Viet Nam;

- to increase country experience to promote favourable global HPV vaccine policy, regional HPV vaccine strategies and government introduction plans;
- using strategic forecasts, investment cases and decision-making tools, to inform and influence industry supply and pricing decisions, international agency financing decisions, and government introduction plans.

Major outcomes expected depend on key questions that vary from country to country.

- **In India**: what is the best age for community-based delivery?
- **In Peru**: what is the best strategy for school-based delivery: girls only or girls and boys?
- **In Viet Nam**: what is the best delivery strategy for reaching 14 year old girls?
- **In Uganda**: what is the feasibility of delivering HPV vaccine through school-based strategies to 10-12 year old girls, and could an additional strategy be to reach girls out of school, possibly in synchrony with semi-annual Child Health Days?

In addition, two pre-licensure studies are planned, one in the Republic of Uganda and one in the Socialist Republic of Viet Nam, to assess immunogenicity of alternative schedules and to facilitate delivery strategies.

6.4 The epidemiological impact and cost-effectiveness of HPV vaccination (*Ruanne Barnabas*)

A model has been worked up to help perform a cost-effectiveness analysis of the introduction of the newly-developed HPV vaccines in two situations - availability or unavailability of organized screening. A specific example of the major impact of good screening coverage in England on the incidence of cervical cancer between 1971 and 1995 was taken as a reference.

Early indication of cost-effectiveness of the vaccine was illustrated by a specific analysis for the Federative Republic of Brazil (Garnett et al., *Vaccine*, 2006, 24(Suppl.3):178-186) where it has been shown that the most cost effective-strategy will depend on the cost of the vaccine and the cost of its delivery. Vaccination alone, assuming 70% coverage, will reduce overall cervical cancer incidence by 48%. If vaccination was supplemented by screening three times per lifetime, the figure would increase to 66%.

Conclusions

- HPV vaccination will significantly reduce deaths from cervical cancer both with and without formal screening in place.
- Vaccination of boys can add significantly to protection of women if vaccine coverage of girls is low (30%) but not if coverage is higher (70%).
- The cost-effectiveness of HPV vaccination will mostly depend upon the cost of the vaccine and of its delivery.

7. Satellite symposium on Japanese encephalitis and dengue vaccine research

Chair: Supamit Chunsuttiwat

The satellite meeting on flavivirus vaccine development was opened by Dr Joachim Hombach (WHO) who welcomed participants and presented the meeting agenda. The inclusion of both Japanese encephalitis (JE) and dengue in the agenda reflected the strong interest in both diseases in the South-East Asia Region. To cover both diseases the agenda had to be selective, emphasizing with JE the recent experience with the JE vaccine campaigns in the Republic of India and other preparatory measures to introduce the vaccine, and with dengue the considerable research efforts made in the Region in preparing for vaccine evaluation. Dr Supamit Chunsuttiwat (Ministry of Public Health, the Kingdom of Thailand) chaired the meeting, highlighting the public-health importance the two diseases have for his country.

7.1 JE transmission patterns and epidemiology (*Zhi-Yi Xu*)

While JE disease burden and transmission patterns have traditionally been investigated in countries with a temperate climate (the People's Republic of China, Japan, the Republic of Korea and the Kingdom of Nepal) or subtropical climate (the Republic of India, the Kingdom of Thailand and the Socialist Republic of Viet Nam), much less information has been gathered from countries in tropical areas. Several studies from tropical countries (the Kingdom of Cambodia, the Republic of Indonesia and Malaysia) now suggest that these zones can also be favourable for JE transmission. As the disease shows less seasonality and cyclic epidemics in tropical countries than in temperate climate zones, it is more difficult to identify. Careful regional assessment is required as socio-cultural practices may influence JE transmission, as shown in the relatively high prevalence of JE in Bali, a Hindu area, versus low prevalence in Java, which is accounted for by the relative absence of pig breeding in Java, a predominantly Muslim island.

With vector control not being feasible in most rural areas, the most promising long-term and sustainable control strategy for JE is immunization. Routine childhood JE immunization with either inactivated, mouse-brain vaccine, or live, attenuated vaccine is highly cost-effective and may still be cost-effective for low-incidence areas. Widely-distributed flaviviruses (JE, dengue, West Nile and others) in tropical regions, immunologically cross-react with each other. Therefore, an unresolved question to be answered is whether pre-existing antibody to other flaviviruses interferes with the immune response to the live JE vaccine.

7.2 Japanese encephalitis associated morbidity (*Tom Solomon*)

The *Liverpool Score* is designed to be a simple tool to assess long-term morbidity in survivors of JE. Such a tool should be helpful to quantify the disease burden, but may also help target patient management more appropriately. The score is based on 10 questions to be asked and five behaviours to be observed. A first assessment of the current score system shows high sensitivity and specificity, as well as high inter- and intra-observer consistency. It is a simple tool that can predict dependency as reliably and exhaustively as the broad range of neuro-psychiatric and development measures that are currently recommended as standard procedures to assess neuro-psychiatric disability in a child following illness.

The ultimate aim is to make this tool accessible and usable by peripheral health workers in rural settings in developing countries where diseases such as JE are endemic. Questions to be explored further are whether the score is able to discriminate other neuro-psychiatric conditions, including autism, from disabilities that may result as sequelae of JE infection.

7.3 The live attenuated JE vaccine (*Mansour Yaïch* and *Julie Jacobson*)

The live, attenuated JE vaccine strain SA14-14-2 has been used in the People's Republic of China since 1988. In recent years it has been licensed in several Asian countries, and was extensively used during 2006 in mass immunization campaigns in the Republic of India. While the product is currently not WHO prequalified, much investment and effort has been made to bring production and quality control to international standards.

Several studies were undertaken during 2006 to confirm that a one-dose immunization at the age of nine months, in co-administration with the measles vaccine, conferred lasting protection. The long-term effectiveness of a single dose of SA14-14-2 was demonstrated in 2001 in a case-control study of Nepalese children. The vaccine effectiveness was corroborated by persisting high neutralizing antibody titres, even though these titres may have been influenced by occult, natural boosting. Recent studies from the Republic of the Philippines have demonstrated the safety and efficacy of the vaccine in co-administration with the measles vaccine at nine months of age. Further studies are planned in the Republic of Indonesia and the Democratic Socialist Republic of Sri Lanka to confirm these findings in other Asian settings. Other studies need to address vaccine immunogenicity against a background of JE immunity induced by vaccination with the inactivated vaccine. Post-marketing surveillance in the Republic of India following the recent introduction of the vaccine, as well as data from the Republic of Korea, failed to demonstrate any serious adverse events directly attributable to the live attenuated JE vaccine, although the total sample size remains somewhat limited. Fever was the most common adverse effect, occurring in some 10% of vaccine recipients.

While the introduction of a new vaccine is a complicated process, strong political and trustful collaboration of partners can make that process successful. This was considered the driving force behind the successful introduction of the SA14-14-2 JE vaccine in the Republic of India. Starting in May 2006, India vaccinated 9.3 million children in 11 districts scattered in four states where JE is considered highly endemic. Selection of districts in the four states was based on the assessment of historic data on acute encephalitis syndrome. Analysis of these data also revealed that previous efforts to control disease through vaccination with mouse-brain vaccine had shown substantial impact, while vector control measures had not shown any measurable impact.

The decision to introduce the live attenuated vaccine on a special license followed a careful assessment of all vaccine options, including supply, cost and operational aspects. The time from making the decision to the start of the campaign was only eight months. The experience and the infrastructure of polio eradication in the Republic of India clearly contributed to the success of the JE vaccination campaign. Some 504 adverse events were reported within the immediate period following the beginning of the mass campaign, including 66 severe cases, of which 22 were lethal. An expert review committee concluded, while criticizing the quality of the investigations, that none of the deaths were attributable to the vaccine, and thus recommended its continued use. This did not stop the press from speculating on the lack of safety of the vaccine and voicing allegations which had an immediate negative impact on vaccine acceptance, as seen for instance in the poor vaccine coverage in West Bengal.

Although the mass campaign was quite successful in reaching the majority of the target children, the real challenge in the future is to ensure high coverage in the routine vaccination programme. In many of the states where JE vaccine has been introduced, routine immunization coverage has remained as low as 26%. Without achieving higher coverage, a sufficient number of susceptible children will build up, and new outbreaks might occur again.

7.4 Serological interaction between dengue and JE (*Sutee Yoksan*)

The possibility of cross-reactivity between dengue and JE is an important question to consider when immunizing against JE in dengue-exposed populations, and is an equally important question for future dengue vaccines being introduced in JE endemic regions. Interaction between the two pathogens may theoretically impact vaccine-conferred protection, but also disease outcome. To address some of these questions, cross-neutralizing antibody titres were determined in samples from previous vaccine trial participants who had received live-attenuated dengue vaccine. Upon JE infection, there was no indication of a boosting effect on dengue titres.

Similarly, when analysing flavivirus immunity in recipients of the JE inactivated vaccine, no cross-reacting antibodies could be found to dengue, even though the antibody response to JE broadened over time. Preliminary data using the JE live attenuated vaccine seem to corroborate these findings. These data therefore, based on neutralization assays, do not support previous observations suggesting that JE immunization had a beneficial effect on dengue disease severity. Clearly, more research needs to be conducted in this area.

7.5 Dengue immunopathology (*Prida Malasit*)

Dengue biomedical research has recently benefited from increased interest that has led to a surge of publications. With regard to severe dengue, there is no test available to predict the course of the disease, and in particular pleural effusion, a hallmark of dengue pathology. A combination of NS1 antigen and complement factors might have predictive value, an hypothesis to be confirmed. With regard to the virus, the relationship between genotype and virulence remains ill-defined. Antibody characterization needs to be improved to better predict protection from pre-infection antibodies, and to differentiate protective from potentially enhancing antibody types. Mapping of antibody epitopes might shed some light on this issue in the near future. However, the possibility exists that immune enhancement might occur through different mechanisms. Innate immunity, shown to be of great importance in early responses to infection or vaccination, also needs to be further studied in this respect.

7.6 Dengue vaccine development (*Alan Barrett*)

The four dengue viruses, although normally referred to as four serotypes, actually are genetically as different from each other as JE, West Nile and St Louis encephalitis viruses are different from one another. This leads to a major challenge when developing a tetravalent dengue vaccine. Other obstacles to the development of a dengue vaccine are the lack of a suitable animal model mimicking human pathology, the poor characterization of virulence factors, incomplete understanding of protective immune mechanisms, and the possibility of immune enhancement of disease. While virtually any vaccine technology has been applied to dengue vaccine development, which is still mostly at a preclinical level, the more advanced vaccine pipeline is dominated by live vaccines.

Classical live attenuated vaccines show great promise but require careful formulation to obtain balanced immune responses against all four strains. Long-term safety follow-up of recipients of such vaccines do not show adverse outcomes subsequent to dengue exposure. Live, recombinant candidate vaccines also have entered advanced clinical evaluation, but tetravalent formulations show similar signs of strain interference. More research is needed into this phenomenon. The definition of correlates of protection will require a systematic study of the immune responses to the vaccine in the course of vaccine trials. While neutralizing antibodies are the primary correlate of protection, other effector mechanisms are likely to play a supportive role and should also be studied.

To compare data, assays will need to be harmonized and reference reagents produced to correct possible inter-laboratory variations. Field evaluation will require multicentre studies to take into account various epidemiologic backgrounds of dengue and other flavivirus transmission. Finally, in due course, a discussion on optimal vaccination strategies needs to be held to assure that vaccines will be used in an optimal fashion in endemic countries.

7.7 New dengue vaccine candidates (*Nopporn Sittimsombut*)

New live attenuated dengue vaccine candidates have been developed by modifying the prM-E cleavage site through mutagenesis of the dengue virus genome. Incomplete cleavage led to partially immature viral particles with a reduced number of EE protein homodimers, which was associated with reduced virulence. A systematic analysis of the prM-E junction using site-directed mutagenesis led to the identification of critical amino acid residues modulating the efficiency of protein cleavage. Different mutants were generated and assessed for phenotypic properties. Promising candidates have been transferred to the Mahidol Centre for Vaccine development for Vero cell adaptation and further characterization. So far, three mutants have been identified with a phenotype of pinpoint plaque formation and reduced neurovirulence in suckling mice. However, they also show reduced immunogenicity in mice, as compared to the parent virus.

7.8 The Paediatric Dengue Vaccine Initiative (PDVI) (*Harold Margolis*)

The overall scope and strategic orientation of the initiative, which has been established to accelerate and facilitate the development and introduction of paediatric dengue vaccines, includes strategic partnerships with vaccine developers, supportive research and development, and vaccine evaluation and vaccine access. In relation to vaccine evaluation, PDVI has taken the initiative to establish and link field sites in several dengue endemic countries both in Asia and the Americas that should serve to conduct epidemiologic studies, possibly host future population-based vaccine trials, and act as sources of well characterized clinical specimens for diagnostic and research purposes. Key to all sites is a sensitive prospective febrile illness surveillance, while the epidemiologic design can be cohort- or community-based. All sites are currently focussed on paediatric populations, but adults may be added at a later time point. Challenges relate to the management and evaluation of large numbers of febrile illnesses, laboratory proficiency, harmonized case definitions and other operational issues. It is expected that some sites will host dengue vaccine trials in the near future.

7.9 The dengue research platform at Mahidol University (*Arunee Sabchareoan*)

The dengue research platform at Mahidol University, Bangkok, Thailand, was created in order to bring under one roof and to better coordinate research teams working on clinical trials, cohort studies, clinical pathology and diagnostics, as well as eco-bio-social and vector control research. Research highlights include the development and clinical evaluation of the live, attenuated dengue vaccine, whose vaccinees are still being followed up for long-term safety, plus research into the decay of maternal antibodies in infants born to dengue-immune mothers, and their possible linkage to severe disease. In contrast to previous publications, no indication was found that pre-existing maternal antibodies were harmful to infants when exposed to dengue. New studies are ongoing in relation to liver involvement in dengue haemorrhagic fever (DHF).

Recently, the Ratchaburi dengue epidemiological cohort study has been set-up, covering some 3 000 elementary schoolchildren who will be actively followed up for febrile illness. During the first 11 months of the operation, more than 6 000 cases of school absenteeism have been followed up, including some 1 500 cases of febrile illness. It is expected that the site will host a Phase III study in due course.

7.10 Conclusions and general recommendations

- There is a remaining research agenda to improve the assessment of JE disease burden, in particular in tropical countries and in different socio-cultural settings.
- A systematic assessment of the lessons learned from the Indian JE mass immunization campaign should be made.
- More research is needed to improve understanding of JE vaccine efficacy/safety in dengue immune individuals.
- Improved dengue case classification is urgently needed.
- Dengue vaccine field sites should be more tightly linked to biomedical research on dengue pathogenesis, an area that deserves continued investment.
- Guidance on clinical dengue vaccine evaluation and stepwise introduction strategies is greatly needed.

8. New vaccine presentations and delivery

Moderator: Claire Broome
Rapporteur: Martin Friede

8.1 Sublingual immunization as a vaccine strategy (*Cecil Czerkinsky*)

The sublingual route has been utilized for many years to present small peptides and drugs to the body, and several drugs are now licensed for delivery via this route. Surprisingly, the potential of this route for the delivery of vaccines has received little attention, yet it appears to meet ideal criteria as a site for immunization that is not met by the oral or nasal route. In the nasal passage the lymphoid tissue is anatomically isolated (nasopharyngeal tonsils) and cilliary action serves to continuously remove antigen from the mucosa, whereas the sublingual route is richer in lymphoid tissue and does not have active removal of antigens. The oral route has anatomically isolated lymphoid tissue and is further hampered by enzymes, acid pH, intestinal flora and food. There is a precedent for the use of the sublingual route for immunization, as small lipidated peptides were shown to induce cell-mediated immunity via this route. To date, however, nobody has investigated the sublingual route for larger antigens.

The mouse sublingual mucosa has a structure similar to that of the human mucosa, but the human mucosa is non-keratinised and therefore more likely to permit transport. The mouse sublingual mucosa is enriched in dendritic cells with a massive presence of Langerhans-type cells whose phenotypic pedigree resembles that of skin Langerhans cells, and hence are likely to be excellent antigen-presenting cells (APCs). Delivery of antigen to these cells could therefore be expected to induce a strong immune response.

Proof of concept was obtained in the mouse and hamster models using ovalbumin as a model antigen. In preliminary studies, fluorescent ovalbumin administered sublingually was found to be taken up within two hours into the mucosa epithelium. Both IgGs and IgAs were induced, at a level comparable to that obtained by intranasal immunization. Surprisingly, cytotoxic T-lymphocytes (CTLs) were also induced with this non-replicating antigen, and CTLs could be recovered from cervical lymph nodes, lung and spleen, suggesting that the sublingual route of administration may somehow be able to induce a cellular immune response which cannot normally be induced by non-replicating antigens without the addition of specific adjuvants.

Sublingual vaccination of mice with inactivated influenza virus (H1N1) resulted in partial protection of the animals against lethal virus challenge, which could be converted to complete protection by the addition of cholera toxin as an adjuvant. Protection was also seen following the sublingual or nasal administration of live attenuated influenza virus. The presence of viral antigen and signs of viral replication could be seen in the central nervous system following nasal administration, but not sublingual administration of the virus. This suggests that the sublingual route is safer than the intranasal route. This safety advantage was also observed using a replication deficient adenovirus expressing the spike protein from SARS coronavirus (SARS-CoV).

A Phase I clinical study has now been completed using recombinant cholera toxin B chain (CTB) as an adjuvant. Serological responses to the antigen were observed in 14 of 15 volunteers. The sublingual route thus appears to be safe and offers a viable alternative for non-invasive delivery of vaccines, leading to broad immune responses that may enable the induction of protective immunity.

8.2 Dose sparing by intradermal immunization (*Martin Friede*)

Administering vaccines into the dermis for a number of antigens has been shown to be able to induce an immune response with less antigen than that required for intramuscular or subcutaneous delivery. This dose-reduction phenomenon is generally explained by the skin's richer endowment with antigen-presenting dendritic (Langerhans) cells, which upon activation migrate to deeper lymphoid tissues to initiate the first steps in the immune response. Dose reduction through intradermal delivery has been demonstrated for rabies, for which it is now the recommended route of administration, as well as for hepatitis B, where it is also used to induce immunity in immunosuppressed individuals, influenza and inactivated polio vaccine (IPV). Despite the cost savings and capacity enhancement that could be achieved, this route has not been widely used (except for rabies) because reliable intradermal immunization is not easy with needle-and-syringe.

Several new technologies are under development that claim to permit reliable intradermal delivery, including syringes fitted with short intradermal needles, disposable cartridge-jet injectors (DCJI), microneedles, patches and ultrasound-driven injectors.

WHO has undertaken the evaluation of DCJI for the intradermal delivery of reduced doses of vaccines. This technology was chosen because it is in late development and approved devices are available for study, but also because the ability to administer vaccines without needles offers the potential of greater safety and hence of improved access. These devices also have the potential of offering needle-free delivery of vaccines by the IM and SC route if needed.

WHO has initiated Phase I/II clinical trials to evaluate the dose sparing potential of intradermal delivery of influenza vaccine to naive toddlers (a study conducted in the Dominican Republic in collaboration with the CDC) and of IPV to infants (one study conducted in the Republic of Cuba and another to be conducted in the Sultanate of Oman). The two vaccines were chosen because of the public-health advantages that could result from dose sparing, including capacity enhancement and cost reduction. Initial results indicate that this route of delivery is safe, equally well accepted by the health-care workers, the parents and the infants, and reliably induces a wheal indicative of successful intradermal delivery. Immunological data will be available by mid 2007.

Despite the attractiveness of this approach, several unknowns relating to the response to intradermal injection still need to be evaluated, including the tolerability for vaccines containing aluminum adjuvant, the comparative duration of the immune response, the various delivery devices, and how factors such as skin type, exposure to sunlight, etc. could affect the response. Further studies will be required before this route can be broadly recommended, and it may be necessary for the public sector to choose one intradermal delivery method and stick with it, since regulatory approval for the administration of a vaccine with an ID device may not be transferable to another ID device. Further work on evaluating the potential of the various devices is clearly needed.

8.3 Update on the measles aerosol project (*Michel Greco*)

The existing measles vaccine has an excellent track record of safety, proven effectiveness, good heat stability before reconstitution, and a low cost (approximately US$ 0.26 for the vaccine plus safety equipment, i.e. a total cost of US$ 0.8 per child immunized in a mass vaccination campaign). Administration by syringe and needle however presents risks in terms of sharps handling. A non-invasive method of delivery would permit safer and easier administration and a potential to facilitate mass vaccination in low-resource environments.

The aerosol route of delivery appears appealing - this route has been used for measles vaccine delivery in the United Mexican States. Numerous studies here and elsewhere have reported it to be safe and to induce a level of immunity that is equivalent to, or better than that induced by subcutaneous delivery. These studies have not however been undertaken under conditions that would permit licensing of the vaccine for delivery by the aerosol route.

The WHO measles aerosol project was initiated to collect data that would permit such licensing. Its goal was to develop a measles vaccine that is safe, immunogenic, inexpensive, easier to administer than by injection, using the same dose of the EZ strain vaccine, same vaccination schedule, and same recommendations for use as the current vaccine. The project is a partnership between the WHO, the CDC and ARC, the Serum Institute of India which produces the vaccine, and the device companies Omron, Nektar and Trudell, with funding from the Bill&Melinda Gates Foundation.

Preclinical studies were undertaken to select an aerosol delivery device and to assess its safety, immunogenicity and local and systemic toxicity. This enabled device selection, identification of optimal dose and analytical assays, and preparation of an IND which has been approved.

Phase I studies are currently underway on 100 volunteers in the Republic of India. Only a few mild adverse events (AEs) have been reported so far, with recovery within a few days. In one site, there was an observed transient rise in eosinophil levels in the volunteers. The relevance of this is not known and the parameter is being further investigated. There are reports of this event occurring following subcutaneous measles vaccination. Analysis of the immunological parameters is in progress with preliminary indications of a good immunological response.

A Phase II study involving 3 750 children is planned in the United Mexican States that will be followed by a pivotal trial in the Republic of India. It is anticipated that within two years licensure might be obtained in India. In parallel, studies are being done to identify an optimal device-design and to select the best device, considering parameters such as weight, energy source, robustness, consumables and waste.

The safety of the aerosol route of delivery needs to be thoroughly demonstrated to overcome concerns. The potential for cross-contamination between vaccinees has been eliminated by the use of one-way valves and the selection of a device to prevent re-use of the potentially contaminated component. Other safety concerns are being addressed, including the risk of brain exposure to the vaccine virus, risk of environmental spread to vaccinators or contacts, risk for people with asthma, and risk for HIV-infected persons.

This new delivery route, if successful, could potentially be used for other vaccines such as rubella, mumps or influenza, and could enhance vaccine acceptability in areas with low disease incidence.

9. Keynote address: neglected tropical diseases

Update on new interventions against neglected tropical diseases (*Peter Hotez*)

Numerous parasitic diseases, while not causing significant mortality, are endemic in poor areas of the world where their very significant morbidity hinders the economic and social development of the country and hence actually promotes poverty. In addition, these diseases can contribute to the transmission and fatal progression of diseases such as malaria, TB or HIV. They are not emerging diseases but are the most common infections of poor people in the world and are prevalent in populations currently living on less than US$ 2 per day.

These diseases include the following.

- **Protozoan infections**: African Trypanosomiasis, Chagas disease and Leishmaniasis.
- **Bacterial infections**: Buruli ulcer, Leprosy, Leptospirosis, Trachoma and Treponematoses.
- **Ectoparasitic infections**: Scabies.

Helminth infections: Ascariasis, Hookworm, Trichuriasis, Strongyloidiasis, Schistosomiasis, Trematodiases, lymphatic Filariasis, Onchocerciasis, Dracunculiasis and larval Cestodiases.

As so little attention is paid to these diseases, it is fitting to call them "neglected diseases", and as they do not directly cause much mortality, it is difficult to attract the attention of policymakers so as to make them no longer neglected. Actually, analysis of the disease burden using DALYs (disability adjusted life years, or the number of years of healthy life lost to premature death or disability) shows that the combined effects of this disease family are comparable to that of heart disease and greater than that of malaria. Developing vaccines, therapies and other disease controls against neglected diseases should therefore be a priority, and could lead to reduced morbidity from other diseases. For example, malaria infection is more severe and leads to more severe anaemia in people infected with hookworm; schistosomiasis infection appears to facilitate HIV infection, possibly through loss of T-cells or genital lesions; parasitic infections lead to impaired immune responses, increased viral loads in HIV-infected persons and increased mother-to-child transmission of the virus.

Chemoprophylaxis plays a major role in the control of parasititic diseases. Diethylcarbamazine citrate (DEC), which was administered as a supplement to table salt, successfully eliminated lymphatic filariasis in the People's Republic of China. Similarly, ivermectin was succesfully used in the Kingdom of Morocco and Zanzibar to eliminate trachoma. Since multiple co-infections exist in many places, there is a great economy of scale to deliver a package of drugs. This has resulted in the development of a "rapid impact" drug package which combines drugs such as albendazole, praziquantel, DEC/Ivermectin and azithromycin. These drugs are mostly provided for free (from GSK, Merck and Pfizer) so that they cost roughly US$ 0.5 per person which is significantly less than the cost of treatment for HIV, TB or malaria. A new Global Network for Neglected Tropical Disease Control is now helping to coordinate the major public/private partnerships devoted to controlling these conditions through chemotherapy packages.

Chemotherapy does however have drawbacks: after controlling hookworm with a mebendazole treatment, the disease often comes back within 4-12 months. There are also data suggestive of emergence of anti-helminthic drug resistance. There is therefore a need to develop vaccines against these diseases, but it has been difficult so far to get vaccine development undertaken by major pharmaceutical companies. Several product development partnerships have therefore been created to facilitate the development of such vaccines.

One example is the Human Hookworm Vaccine Initiative (HHVI), based at the Sabin Vaccine Institute with partners at George Washington University, Fundaçao Oswaldo Cruz (FIOCRUZ) and Instituto Butantan, Brazil, London School of Hygiene and Tropical Medicine, and the Queensland Institute of Medical Research. It has been known since the 1960s that protective immunity against human hookworm is possible, since irradiated larvae induced protection in a veterinary model. From these studies, several protective antigens have been identified including a 21 kD Na-ASP-2 protein. Yeast (*Pichia*) -produced GMP lots of the protein have been prepared in the USA and formulated with alum as an adjuvant, and Phase I clinical trials are in progress. A pipeline of new hookworm antigens has now been developed for the purpose of vaccine development, with plans to conduct clinical trials on several antigens in the coming years. Technology transfer to the Brazilian manufacturer, Instituto Butantan, is currently underway.

There are homologues of the hookworm antigen that also work for onchocerciasis, and protective antigens have been identified for numerous other diseases in this family including: leptospirosis (leptospira proteins); schistosomiasis (sh28GST and smTSP-2 proteins which are in clinical trials); and leishmaniasis (Leish-111f protein, also in clinical trials). If these vaccines were provided with the chemotherapy drugs as an integrated package, the total cost would be less than US$ 1 per dose.

The lessons learned from the development of these anti-poverty disease vaccines can be summarized as follows.

- The vaccines need to be **affordable**, so the process absolutely requires high-level expression systems and cheap purification and downstream processing.
- The vaccine must be **thermostable**, which may be achieved though site-directed mutagenesis in the early stages of development .
- The need to achieve high levels of immunity with little antigen and few immunizations implies access to a platform of **adjuvants**.
- The production of the antigen needs to be done in developing countries, so that contact with and engagement of **developing country vaccine manufacturers** must be done at an early stage.
- Efforts also need to go into **community preparedness**. These vaccines will probably not be delivered to infants as part of EPI but possibly to children in and out of school.
- Vaccine **financial support** needs to be found and organized.

To promote this topic and to facilitate knowledge dissemination, a new open access journal has been launched that focusses on neglected tropical diseases: *http://www.plosntds.org/*.

10. Keynote address : The Diseases of the Most Impoverished (DOMI) project

The DOMI project: achievements and prospects (*John Clemens*)

The DOMI Program, funded by the Bill&Melinda Gates Foundation and coordinated by the International Vaccine Institute (IVI), Seoul, the Republic of Korea, was initiated against a backdrop of a high continuing disease burden from enteric infections, estimated at about two million childhood deaths per year. To take advantage of the fact that licensed, effective vaccines were available for typhoid and cholera, but were not being used in developing countries, and of the fact that promising vaccine candidates were available for cholera, typhoid, and shigellosis, the DOMI Program was launched in 2000. The programme had as its goals to provide needed evidence to accelerate the rational introduction of already licensed vaccines and to conduct clinical trials in developing countries of promising candidate vaccines against cholera, typhoid, and shigellosis. The geographic focus was primarily on Asia, although as the programme evolved, work was also undertaken in East Africa.

To guide the design of the DOMI Program, at its inception, DOMI conducted face-to-face, semi-structured interviews with nearly 200 policymakers and opinion leaders in DOMI's partner countries: the People's Republics of Bangladesh and China, the Republics of India and Indonesia, the Islamic Republic of Pakistan, the Kingdom of Thailand, and the Socialist Republic of Viet Nam. Cross-cutting findings of this survey were that vaccines were judged to be potentially important tools for the control of typhoid, shigellosis, and cholera; vaccines would be widely used in these countries for shigellosis and typhoid, and would be deployed for circumscribed populations defined to be at high risk for cholera; and that for a vaccine to be an effective tool, it would have to be available for less than US$ 1 per dose, and ideally produced by local vaccine producers. Moreover, respondents felt that vaccine introduction would require, at the country level, a body of evidence on disease burden, including: economic costs of disease; economic evaluations of vaccine cost-effectiveness; and demonstration projects of vaccines in real-life public health programmes. The respondents also emphasized that, to be successful, the DOMI Program should be broadly inclusive, including international organizations such as WHO; Ministries of Health and research institutions in partner countries; technical experts from industrialized countries; and vaccine producers, both from developed and developing countries. These views guided both the design and conduct of the DOMI Program over the ensuing years.

Following the advice of expert advisory committees, DOMI's work on already licensed vaccines focused on killed oral vaccines against cholera and on Vi polysaccharide vaccine against typhoid fever. A translational research agenda was formulated for each of these vaccines to provide evidence at the country level for each of the seven DOMI partner countries in Asia. In addition, evidence for the rational introduction of killed oral cholera vaccine was generated for the Republic of Mozambique, a country with regions which are hyperendemic for cholera. This translational research was designed to provide, at the country level, a complete array of studies needed by policymakers to make an informed decision about vaccine introduction: studies of disease burden; studies of the feasibility, acceptability, and impact of the vaccines when administered in demonstration projects; studies of the cost of illness, the cost of vaccination, and the cost-effectiveness of vaccination; studies of population demand and willingness to pay for vaccine; and policy analyses of options for financially sustainable vaccine introduction. For shigellosis, for which there was no acceptable licensed vaccine available, a similar matrix of studies was constructed, but without vaccine demonstration projects or evaluations of vaccine costs and cost-effectiveness.

Beyond collecting evidence and presenting it to policymakers for their consideration, DOMI has incorporated this evidence into policy analyses of options for financially-sustainable vaccine introduction. An interesting example of these data syntheses concerned Vi polysaccharide vaccine, for which it was found that the cost of vaccine was low enough (under US$ 0.50 per dose), and demand for vaccine was high enough, that it was possible to consider cross-subsidization schemes as possible ways to ensure financially-sustainable vaccine introduction. Two of the DOMI partner countries (the Republic of Indonesia and the Islamic Republic of Pakistan), are now planning to pilot such schemes, whereby free vaccine for poorer people is subsidized by users's fees from the more affluent.

Because evidence per se cannot motivate vaccine introduction without an adequate and cost-competitive supply of vaccine, the DOMI Program also devotes considerable attention to working with both international and local suppliers of killed oral cholera and Vi polysaccharide vaccines. IVI's technology transfer division, which has experts in vaccine process development and production, is transferring the technology for production of both vaccines to emerging producers. An interesting example of these technology transfer activities is a two-way transfer of oral killed whole cell-only cholera vaccine from VaBiotech in the Socialist Republic of Viet Nam on the one hand, to Shantha in the Republic of India and BioFarma in the Republic of Indonesia on the other hand. In addition to assisting with technology transfer, IVI is assisting both companies with the clinical studies needed for licensure, including a large-scale, randomized, placebo-controlled trial now being conducted in nearly 70 000 persons in urban Kolkata in India. Beyond being the first example of south-south technology transfer of a new generation vaccine, this partnership will enable international use of the killed whole cell-only vaccine produced by companies (Shantha and BioFarma) in countries with WHO-approved NRAs. Because the Vietnamese NRA is not yet WHO-approved, the use of the Vietnamese vaccine has to date been limited to that country.

DOMI's upstream work on newer vaccine candidates against these three diseases has focused on support for evaluation in the People's Republic of Bangladesh of a live oral vaccine candidate against *Shigella flexneri* 2a (SC602); for evaluation in Bangladesh of a live oral vaccine candidate against cholera (Peru-15); and for evaluation in the Republic of India of a live oral vaccine candidate against typhoid fever (ZH09). Work on Peru-15 is continuing under a follow-up grant from the BMGF (Cholera Vaccine Initiative), which aims to license this vaccine in both Bangladesh and India. In addition, in collaboration with the laboratory of Dr John Robbins and Dr Shousun Szu at NICHD/NIH (USA), IVI has successfully co-developed a Vi polysaccharide-protein conjugate vaccine which will soon be transferred to one or more developing-country producers.

In summary, the DOMI Program is a multi-country, multidisciplinary programme designed to accelerate the rational introduction of new generation vaccines against cholera, typhoid, and shigellosis into public-health programmes for the poor in developing countries. The research of DOMI has been carefully constructed to create a matrix of evidence that allows policymakers to make judgements about whether it makes sense to introduce these vaccines into their programmes. The DOMI Program is also facilitating transfer of vaccine technologies in order to help create an adequate and cost-competitive supply of vaccines, and has conducted pre-licensure trials to help accelerate the pipeline of promising new vaccine candidates. The combination of translational studies, technology transfer, and clinical trials for licensure, provides a model for programmes designed to accelerate introduction of needed vaccines into developing countries.

11. Panel discussion on innovation, intellectual property rights (IPR) and new vaccine production in the South-East Asia Region

Moderator: Carlos Morel
Rapporteur: Miloud Kaddar

Members of the panel were representatives from BioFarma (Indonesia), CIGB (Cuba), Fiocruz-Biomanguinhos (Brazil), Serum Institute and Shanta Biotechnics (India), Institut Pasteur (Dakar-Senegal), the Office of Technology Transfer at the NIH (USA) and IFPMA.

Although intellectual property rights (IPRs) have not so far proved a major obstacle to the access to vaccines, they may play a more important role in the future, especially for the production of new vaccines and technologies in developing countries. The world of vaccines is operating in a changing context, including: product divergence across markets and continents; increasing role of emerging manufacturers in the global supply of vaccines; new arrangements being made between the research and development based industry and developing country vaccine manufacturers; and increasingly complex regulatory requirements and liability concerns which are raising production costs and level of investments. Patent portfolios are becoming a more important component of company assets, even in emerging economies where stronger IPR regimes have been adopted in compliance with the TRIPs Agreement. The objectives of the round table were thus to update information and discuss views on how to move forward in two critical areas, namely:

- impact of IP protection on production of new vaccines and access to such vaccines in developing countries;
- principles and practices for an appropriate balance between stimulating innovation and R&D, and enhancing access to priority vaccines.

A first contribution was made to the debate by Luis A Salicrup, Senior Advisor for the International Activities Office of Technology Transfer (OTT) at the NIH. The NIH run on an annual budget of US$ 28 billion, most of which goes to extramural projects. The primary aim of OTT is to benefit public health worldwide. Early stage technologies have been transferred to public and private institutions in developing countries, after efforts were made to ensure that participating institutions had at least some level of R&D capability. Examples are: the transfer of the polysaccharide conjugation technology to WHO and PATH for the production of a serogroup A meningococcal vaccine in partnership with the Serum Institute of India, for eventual distribution in sub-Saharan Africa; transfer of biological materials for conjugated vaccines to the International Vaccine Institute (IVI), in partnership with Shanta Biotech in the Republic of India and BioFarma in the Republic of Indonesia; and transfer of the human-bovine reassortant rotavirus vaccine to multiple public and private institutions in, the Federative Republic of Brazil, the People's Republic of China, the Republic of India and the United States of America.

The NIH strategy for licensing is traditionally based on the delivery of non-exclusive licenses to meet global public-health needs, often using a multi-prong or geographically regional approach. Whenever a "worldwide" license is granted, it contains both milestones and diligence requirements in the USA. Licenses often contain a "White Knight" clause requiring efforts from the licensee in the fields of public education, indigent patient programme, or distribution in developing markets. More recently, with products that have a worldwide market, NIH required submission of commercialization plans for other countries upon first regulatory approval in the USA or in the European Union.

The NIH are also promoting an active knowledge-sharing and capacity-building effort by creating and maintaining a "database of technologies for neglected diseases" and an "information bank" about technology transfer programmes, IP training, fellowships, and opportunities for cooperation available to managers and scientists worldwide. Moreover, OTT has implemented an International Technology Transfer Training Programme which has already trained more than 15 scientists and technology managers from institutions in the Argentine Republic, the Republic of Chile, the People's Republic of China, the Republic of India, the United Mexican States, and the Republics of the Philippines and South Africa, and in areas related to licensing negotiations, public/private partnerships, and evaluation and marketing of technologies and IP policy.

The representatives of the emerging manufacturers expressed their views on IPRs and new vaccine productions. They all agreed on the importance of innovation, R&D and compliance with international regulations, but they all insisted that the priority was to provide a consistent and sustainable supply of quality vaccines at an affordable price to developing countries. Most of the companies in the Federative Republic of Brazil, and the Republics of Cuba, India and Indonesia, are already able to produce high quality vaccines suitable for local markets as well as for sale to UN agencies including UNICEF, PAHO's Revolving Fund, WHO and GAVI. Most of them are expanding their capacities and adding new technologies, including DTwP based combination vaccines and *Haemophilus influenzae* type b (Hib) vaccine, and have initiated efforts for the development of rotavirus, pneumococcus, and other vaccines.

Stronger IP laws have been adopted in compliance with the TRIPS Agreement, which raises new challenges and obstacles. The impact of patents on access to technology will progressively affect developing countries as they join the World Trade Organization and agree to respect the TRIPS Agreement. It is not possible to predict the full impact of the latter on the cost of vaccines. However of real concern to the emerging manufacturers are the unknowns and in particular so-called "immoral" patents and practices, such as a recent patent on the use of aluminum phosphate as an adjuvant for combination vaccines, even though this adjuvant has been used for decades; or a recent patent on cross-flow filtration for a concentration step in the manufacture of the Hib vaccine. The "evergreening" practice and the tendency to patent all components and aspects of a vaccine production chain is of major concern, as IP is a complex field which is particularly difficult to deal with for many developing country vaccine producers and can be very costly to manage and challenge.

Manufacturers have identified specific general assistance from which all could benefit, including access to unbiased legal review, assistance in the writing of patent applications, and training on how to better detect and understand infringements. Some suggested more flexible interpretation of IP rules and were also in favour of the creation of a sort of global fund on vaccine technology and IP, to promote research, development and production of priority vaccines of global importance.

The representative of the IFPMA emphasized that IP protection is absolutely critical to innovation and R&D effort. IP is also valuable to the vaccine industry because it allows for the recovery of investment necessary for innovation. Under the current system, IP provides protection to investors who are willing to provide the funds necessary to bring a product through the regulatory process up to licensure and market. These costly investments are of great interest and value to the concerned parties and also to the public sector. Furthermore, patents have not been shown to impede access to existing or new vaccines; in many developing countries, vaccine coverage is still very poor for non-patented vaccines (e.g. EPI vaccines). Rather, impediments to access to vaccines in developing countries include a range of issues related to infrastructure, such as finances, political choices, capacity building, etc. Industry also faces impediments relating to increased regulatory review times and increasingly complex requirements for compliance with safety and efficacy standards, as well as global variations in regulatory approval requirements, and increasing R&D costs. Minimum conditions for consideration of technology transfer include compliance with GMP standards, existence of a strong and independent local regulatory authority, and full respect for current trade and IP agreements.

The Immunization, Vaccines and Biologicals Department of WHO, 19-20 April 2004, organized a workshop on "Intellectual Property Rights and Vaccines in Developing Countries" and their report can be seen at: *http://www.who.int/intellectualproperty/events/vaccines_meeting/en/.*

The WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) published its report in April 2006 (*http://www.who.int/intellectualproperty/en/*).

A special issue of the WHO Bulletin (May 2006) that includes an article on IP and vaccines is available at *http://www.who.int/bulletin/volumes/84/5/360.pdf.*

Following the May 2006 World Health Assembly resolution, a WHO IP Working Group was set up to develop a global framework for essential health research and development (EBB117 R13), and a global strategy and plan of action based on the recommendations of the WHO Commission [CIPIH].

12. Satellite symposium on standards of care and treatment in vaccine clinical trials

Moderator: Daniel Tarantol
Rapporteur: Zarifah Reed

Following a series of consultations in this area convened by the World Health Organization Initiative on Vaccine Research (WHO/IVR) in 2005-2006, a process for deciding on the standards of care and treatment has been formulated and proposed. The symposium was aimed at discussing issues relevant to the standards of care provided in the context of vaccine trials, particularly in resource-poor countries. Perspectives from the diverse stakeholders who are key participants in the conduct of clinical trials were discussed: funding agencies who sponsor trials; trial investigators who conduct trials; countries that host trials; and the community from which the target populations of the trials are derived.

The Vice-Chairman of the National Ethics Committee of The Ministry of Public Health of Thailand, Dr Vichai Chokevivat, provided a summary of ethical guidance on the issue, and emphasized the important role that ethical review committees had in the process of both ensuring that the defined standards of care, and the care and treatment package, were appropriate, available and accessible in different settings.

Dr Tonya Villafana described the efforts of the Malaria Vaccine Initiative of PATH to involve the site investigators, community, and local and national administration in deciding on appropriate standards of care to offer in the multi-site, multi-national Phase III vaccine trials of a malaria vaccine candidate in sub-Saharan Africa. Investigating the background standard of care at the different sites, investing in upgrading the necessary research infrastructure (both in facilities and capacities), and developing partnerships with local health delivery systems, are part of these ongoing efforts to both ensure a safe and ethical conduct as well as to strengthen and enhance local standards of care.

Dr Atif Habib described the conduct of typhoid vaccine trials meant to provide evidence of feasibility of mass typhoid vaccination. Each of the centres involved had teams on the project which provided training and guidance according to the International Vaccine Institute (IVI) specifications that all appropriate investigations and medicines were made available, and a proper level of clinical care provided to the trial participants and communities in the context of relevant acute conditions such as fever of unknown origin.

Dr Vasantha Muthuswamy described the evolution of the Indian Council of Medical Research (ICMR) guidelines on ethical conduct of vaccine trials. She highlighted the variability of "background standards of care" in a country like the Republic of India where there was a tremendous disparity between what was available on the open market and what was available through government-based systems. The latest recommendation of the ICMR was to provide the best possible nationally-available care in the public-health system to participants.

Ms Nusara Thaitawat discussed the community perspective of vaccine trials. In particular she highlighted the possible discordance between sponsors and participating communities in terms of expectations from trials, such as high level of care at any cost, post-trial access, and treatment for a lifetime for some communities. She emphasized that a shift in attitude was needed to promote and develop a community perspective that would be engaged and informed about the trial and product development, so as to be able to make informed decisions. Finally, she highlighted that perhaps the way forward was to no longer consider community engagement as an option, but to consider the responsibilities of key stakeholders in engaging the relevant communities.

On behalf of WHO, Dr Daniel Tarantola presented the proposed decision-making framework for formulating care and treatment plans in vaccine trials. This approach is documented in a working paper that was made available to the participants of the symposium. The approach proposed a framework which considers concerned populations in the specific categories with regard to specific diseases, and determines the standards of care for the related and non-related diseases and conditions. A list of questions aimed at acquiring the necessary background elements of information relevant to the trial and site for local decision-making accompanies the framework. It is an attempt to ensure that the key issues in determining appropriate care and treatment for trial participants are considered in a defined process that is structured, participatory and transparent.

It was emphasized that in most situations, no one country, industrial partner, sponsor or agency will or should bear the entire burden of providing treatment. Sponsors and investigators may have to seek partners that can share in the effort to provide care and treatment for eligible participants. Public/private partnerships are also growing in number, diversity and commitment towards provision of enhanced care and treatment. Exploring and developing these ad-hoc partnerships could further strengthen local research as well as health delivery infrastructures, mechanisms and expertise towards the provision of care and treatment for and beyond the disease under study.

General feedback from the participants was positive to this approach. The recommendation was made that groups involved in the conduct of trials should consider this approach and adapt it to their particular needs. Feedback from testing this framework in the field would help further disseminate, as well as improve, its basic concept.

13. Satellite symposium on perspectives on immunization schedules for conjugate vaccines

Moderator: Marc LaForce, Rana Hajjeh
Rapporteur: Marie-Pierre Preziosi

Background

Conjugate vaccines have proven to be excellent tools to control diseases caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, while producing effects both at the individual and at the population level. In countries where these vaccines have been introduced, schedules vary, and optimal strategies have not been clearly defined. Fitting them into the current EPI schedule as established in the 1970s might not be the most appropriate strategy to maximize the effects of these powerful vaccines. The purpose of the symposium was to provide a forum for discussion on potential strategies for introduction of such vaccines, particularly in developing countries.

Presentations

A series of eight presentations outlined the general framework of vaccine effects, the experience with the use of conjugate vaccines in developed as well as developing countries, and the potential implementation issues.

1) Perspectives on direct and indirect effects of vaccination (Betz Halloran).
2) Experience to date with introduction of Men C conjugate vaccination in Europe and in Canada (Caroline Trotter).
3) Epidemiology and control of meningococcal disease in Africa: recent experiences and future challenges (William Perea).
4) Cross-cutting issues with introduction of Hib in Africa (Richard Adegbola).
5) Experience and cross-cutting issues with introduction of Hib in Europe (Mary Ramsay, and presented by Marie-Pierre Préziosi on her behalf).
6) Epidemiology of pneumococcal disease and main results of clinical trials with conjugate vaccines (Ron Dagan).
7) Cross-cutting issues with introduction of pneumococcal conjugate vaccination (Claire Broome).
8) Overview of schedules for introduction of conjugate vaccines: presentation of cross-cutting issues (Draft WHO concept paper) (Caroline Trotter).

Due to dependent happenings in infectious diseases, where the number of individuals becoming affected depends on the number of individuals already affected (Ross 1916), vaccination can produce several kinds of effects at the individual level (direct, indirect, total) and at the population level (overall effects). All these effects, and in particular indirect effects (carriage and transmission reduction), and overall effects (herd immunity), have been well documented for all three conjugate vaccines. The immune response to a conjugate vaccine is only one component contributing to the protection of an individual by such a vaccine. Catch- up campaigns contribute to control of the disease. Thus if immunology can help define relevant formulation and schedule issues, understanding and taking into consideration both direct and indirect protection will help utilize these highly efficacious vaccines in the most sensible fashion.

Discussion

In terms of vaccine schedules, key questions comprise the number of doses required for primary immunization, the timing and age at primary immunization, the need for a booster dose or that of a single later dose in the second year of life, and the duration of protection. The purpose of the current effort is geared towards reviewing evidence documenting these points, and identifying gaps to be filled.

Vaccine effect on carriage and on induction of herd immunity was thought to require further study, in particular to define the optimal target age groups and to measure how much population vaccine coverage is needed to raise herd immunity and reach an overall reduction of cases. Extrapolating results from one setting to another or from one conjugate vaccine to another requires caution. This is particularly true with the pneumococcal conjugate vaccine because of the number of different serogroups for each of which these parameters may vary, and which are still largely unknown. Strategies need to be evaluated in the long-term to monitor eventual serogroup or serotype replacements. Complexity also lies in the fact that schedules optimal for individual protection might not be optimal for herd immunity. Catch-up campaigns are a powerful tool to bring a disease under control, and there could be mixed strategies including initial catch-up campaigns followed by schedules with administration of vaccines at an older age when the response would be more robust. The role of combination formulations and the interactions with vaccines given in combination or concomitantly need to be carefully assessed and taken into account in terms of how many immunizations can be administered in a single visit.

Resistance to any change to the EPI schedules is a reality, and sound preparatory research including programmatic feasibility and cost-effectiveness is needed before this happens. There still is a lot of work to be done to improve current awareness and coverage while keeping a continuous and open dialogue on optimal schedules. This requires innovative and courageous proposals. The principal driver for the EPI schedule as established in the 1970s was pertussis. In the light of more recent studies on pertussis vaccine effects in populations, the schedule could be made more flexible. However, the reflexion should not be restricted or tied to traditional schedules. While there are established schedules in developing countries, many vaccines are actually not given on time but are often given much later.

Preliminary analyses from ongoing surveys looking at actual age at vaccination, and real schedules in countries, show that there are certain ages at which timely compliance is much higher, such as at birth or at one year of age. Linking the results of such surveys with disease data will indicate whether the timing of vaccination is actually appropriate to prevent the disease through direct or indirect effects of vaccines. An example is that of the Republic of the Gambia, where the benefit of the Hib vaccine was largely due to indirect effects. Efforts should be undertaken to try to incorporate age at immunization in all surveillance and case- control studies. Studies on population value and demand for what the vaccine might do are also warranted (e.g. to better convey information to the communities on potential remaining disease after vaccine introduction, e.g. acute respiratory infection (ARI) or meningitis).

The issue of potential alternative schedules for conjugate vaccines is not going to wane soon, and there is now a chance to do it right, i.e. to design the most effective strategy for each country, provided an open dialogue is maintained and the appropriate research is conducted.

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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