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Proceedings of the fifth Global Vaccine Research Forum

Montreux, Switzerland 7–10 June 2004

Immunization, Vaccines and Biologicals

World Health Organization

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

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

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

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

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

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

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

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Contents

Abbreviations and acronyms

Ad5	Adenovirus 5
ARF	acute rheumatic fever
ARI	acute respiratory infection
BCG	bacille Calmette–Guérin (vaccine)
BPL	beta-propiolactone
CAIV	cold-adapted influenza vaccine
CDC	Centers for Disease Control and Prevention (United States)
cDNA	complimentary deoxyribonucleic acid
CIGB	Centro de Ingeniería Genética y Biotecnología
CL	confidence limits
CNIC	Centro Nacional de Investigaciones Científicas
CoV	corona virus
CRS	congenital rubella syndrome
CS	circumsporozoite
DCVMN	Developing Country Vaccine Manufacturers Network
DT	diphtheria–tetanus (vaccine)
DTwP	diphtheria–tetanus–wholecell pertussis (vaccine)
EC	European Commission
EDCTP	European and Developing Country Clinical Trial Partnership
EDSR	end-stage renal disease
EPI	Expanded Programme on Immunization (WHO)
FAO	Food and Agriculture Organization of the United Nations
FP9	Fowlpox 9
GAS	group A streptococcus
GAVI	Global Alliance for Vaccines and Immunization
GMO	genetically-modified organism
GMP	good manufacturing practice
GSK	GlaxoSmithKline Biologicals
HA	haemagglutinin
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HBV	hepatitis B virus

IPR	intellectual property rights
IVR	Initiative for Vaccine Research (WHO)
MCC	meningococcal conjugate vaccine
MDCK	Madin-Darby canine kidney
ME	pre-erythrocytic antigen
MMR	measles–mumps–rubella (vaccine)
MRC	Medical Research Council
MUNJI	multi-use-nozzle jet injectors
MVA	Modified Vaccine Ankara (non-replicative vaccinia virus strain)
MVP	Meningitis Vaccine Project
NA	neuraminidase
Nm A	*N. meningitides* serogroup A
NIH	National Institutes of Health (USA)
NRA	national regulatory authority
OECD	Organisation for Economic Co-Operation and Development
OMP	outer-membrane proteins
OMV	outer-membrane vesicle
OPV	oral polio vaccine
ORS	oculo-respiratory syndrome
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health (USA)
RIVM	Dutch National Institute of Public Health and the Environment
RSV	respiratory syncitial virus
RTS,S	malaria vaccine candidate based on a fusion of circumsporozoite protein (CSP) with hepatitis B surface antigen
SAGE	Strategic Advisory Group of Experts
SBA	serum bactericidal activity
TB	tuberculosis
TRAP	thrombospondin-related adhesion protein
TRIPS	Agreement on the Trade-Related Aspects of Intellectual Property Rights
TT	tetanus toxoid (vaccine)
UNICEF	United Nations Children's Fund
USFDA	United States Food and Drug Administration
VAR	vaccine attributable reduction
Vero	continuous cell line, derived from African green monkey kidney, accepted for vaccine production
WHO	World Health Organization
WTO	World Trade Organization

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Preface

Co-chairs Drs Stanley Plotkin and José Ignacio Santos warmly welcomed the participants and thanked them for attending this gathering of specialists in vaccine research and development (R&D). The Fourth Global Vaccine Research Forum (GVRF) is the ninth meeting in a series previously referred to as the Montreux meetings, and it is the fourth joint WHO/GAVI meeting on global vaccine research.

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

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

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

The global vaccine market is worth US$ 6 billion dollars, and although 85% of its consumers live in developing countries, 82% of its profits come from sales in industrialized countries. It is no surprise, then, that 90% of the industry's vaccine R&D efforts are focused on vaccines for industrialized countries, while 10% of R&D efforts are focused on vaccines needed in developing countries. Indeed, while developing countries have far and away the most to gain from vaccines that address health problems in developing countries, pharmaceutical companies have the most to gain from producing vaccines that address health problems in industrialized countries.

WHO's Initiative for Vaccine Research is involved in vaccine R&D as a facilitator, developer and watchful attendant. A vaccine R&D programme will be integrated into IVR's portfolio when the disease that the vaccine tries to prevent has the following characteristics:

- the disease has a public health importance;
- there is currently no vaccine available, or an existing vaccine is not suitable for large scale use in developing countries;
- there is no alternative, easy-to-implement treatment;
- there is not enough industry involvement to meet developing country needs;
- a vaccine appears feasible.

If any of these factors are not met, if other players are more suited to the role, or resources do not exist within IVR because of higher priorities, then IVR will take the decision not to include the disease in its portfolio.

The Global Vaccine Research Forum aims to stimulate R&D efforts on new vaccines, especially those needed to fight infectious diseases in developing countries. This years' agenda will focus on the following topics:

- the GAVI vaccine R&D projects
- new vaccines for old bacteria
- vaccine manufacturing
- emerging acute viral respiratory infections
- new methods for vaccinating against measles and rubella
- progress in HIV/AIDS, malaria and TB vaccines.

The meeting co-chairs and secretariat wished all participants an interesting and productive meeting.

1. The GAVI vaccine R&D projects

1.1 Pneumonia surveillance *(Rosanna Lagos)*

Pneumonia is still listed as the leading cause of childhood mortality in developing countries, and is associated with 3.5 million deaths annually (WHO report, 1999). The major etiological agents of pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).

Pneumonia is one of several diseases that result in acute respiratory infection (ARI). ARI mortality rates are primarily generated through verbal autopsy reports. Verbal reports are generally used because:

- there are unspecified and inconsistent clinical definitions of ARI and pneumonia;
- there is virtually no information of specific etiology of ARI and pneumonia; and
- there is poor diagnostic yield of microbiological investigations for ARI and pneumonia.

As a result, estimates have become more and more imprecise, creating a worst-case scenario for advocating and introducing a new and expensive vaccine.

To address the problem, WHO convened a working group of Hib and *S. pneumoniae* investigators and vaccine trialists to develop a common definition of bacterial pneumonia for use in vaccine trials and epidemiological studies of pneumonia burden. The goal was to make it possible to estimate the potential impact of a vaccine on local and regional pneumonia burden.

The group decided that definitions for bacterial pneumonia should have the following attributes:

- imply an objective, verifiable proof of the anatomopathological lesion that distinguishes pneumonia from other ARIs (i.e. inflammation of the lung parenchyma);
- have high sensitivity and specificity to capture the actual bacterial pneumonia cases and avoid underestimating the impact of vaccination and the efficacy of the vaccine, respectively;
- be reproducible (low inter-observer and intra-observer variability); and
- be suitable and accessible for use in field conditions in developing countries.

The working group defined a "likely bacterial pneumonia" which could be a suitable endpoint: **a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air-brochograms and sometimes associated with pleural effusion.**

Potential radiological categories include:

- endpoint consolidation;
- other consolidation or infiltration; and
- no consolidation, with infiltrate or pleural effusion.

Due to intra-observer variability, WHO's quality control helped develop and evaluate standardization through a system using definitions, calibrations, workshops and training.

After evaluating the results in different settings, WHO developed a standardized method of chest radiographs for pneumonia and disseminated it into the Latin American Region. Thus far, four regional working groups have been held (in Chile, Costa Rica, Mexico and Panama).

WHO standardized procedures can and should be used for burden of disease and vaccine trial studies. The WHO definition should allow for adequate evaluation of vaccine impact on *S. pneumoniae* and Hib pneumonia.

In summary, under the leadership of WHO, pneumonia vaccine investigators and Expanded Programme on Immunization (EPI) investigators developed and agreed to use a common, standardized tool to assess the impact of pneumonia vaccines and to measure the burden of pneumonia in children. This tool will allow comparisons of vaccine efficacy across trials, and will make it possible to estimate the reduction of pneumonia burden that could be attainable by use of pneumonia vaccines in areas where there will be no local vaccine efficacy data. The tool is being disseminated and adopted by investigators other than those who participated in its development.

1.2 Update on the conjugate pneumococcal vaccine efficacy studies *(Anne Schuchat)*

The capsular polysaccharide of *S. pneumoniae* is considered a critical virulence factor in developing pneumococcal conjugate vaccines. Antibodies against this antigen have been shown to be protective; however, there are more than 90 capsular polysaccharide serotypes and the protection is serotype specific – this means that the vaccines should contain multiple polysaccharides. Fortunately 7 to 12 serotypes account for most paediatric invasive infections worldwide, which has led to the development of polyvalent conjugate vaccines with these common serotypes. Current and candidate pneumococcal vaccines are conjugate vaccines that include between 7 and 11 serotypes. The polysaccharide or oligosaccharide serotypes include the same serotypes in all vaccines, with additional serotypes to produce a 9-valent or 11-valent vaccine.

The 7-valent vaccine has shown to be very effective against invasive disease in the United States of America (USA) (more than 95%) and among native Americans (more than 75%). Importantly, strain replacement with non-vaccine serotypes did not occur in invasive disease in these populations. Also, the 9-valent vaccine candidate showed good protective efficacy against invasive disease in HIV-positive (65%) and HIV-negative (83%) infants in South Africa. Efficacy against radiologically-confirmed pneumonia was also good in these trials; in South Africa it was 20–25% among HIV-negative and 9–13% among HIV-positive people; and in the USA it was 20.5%.

There are several ongoing trials and studies that have yielded interesting results. Updates are provided below.

Two large vaccine efficacy trials are ongoing in Gambia and the Philippines.

- In the Gambia, a 9-valent vaccine is being administered at 6, 10 and 14 weeks. The primary endpoint is radiologically confirmed pneumonia. Follow-up is ongoing and should be complete by end 2004 with results published in 2005/06.
- In the Philippines, an 11-valent vaccine is being administered at 6, 10 and 14 weeks of age. The primary endpoint is radiologically confirmed pneumonia. The trial will be complete by end 2004, with results expected in 2005/06.

Another trial is ongoing in South Africa; indications of the results so far are outlined below.

- In HIV-negative children, the vaccine showed 19% protective efficacy with the WHO case definition (2.2 VAR – vaccine attributable reduction – per 1000 person years) and 10% against the clinical definition of pneumonia (4.0 VAR).
- In HIV-positive children, the vaccine showed 13% efficacy using the WHO case definition (24 VAR) and 12% using the clinical definition of pneumonia (47 VAR).

The trial has also shown that burden of disease is higher in HIV-positive children, and vaccine efficacy is highest in children aged 6 to 12 months.

A probe study (Madhi SA, Klugman KP, The Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat. Med*. 2004;10(8):811–813) to evaluate the efficacy of the pneumococcal conjugate vaccine against viral pneumonia yielded surprising results:

- 31% protective efficacy against any virus detected in patients with pneumonia;
- 45% efficacy against influenza and 44% against para *influenzae* isolation;
- 22% efficacy against respiratory syncitial virus (RSV) isolation; and
- 7% efficacy against adenovirus isolation.

A post-licensure study in the USA provides a real-life assessment of the 7-valent vaccine when used on a large scale, including insight into partial immunization due to vaccine shortages, herd immunity in young and old people (outside optimal vaccine group), and replacement of invasive disease with other serotypes. The study results are outlined below.

- The vaccine had direct effects on the immunized group (whether with full or partial immunization) and showed substantial decline in invasive pneumococcal disease in children under age 5 (80% in infants under 1 year).
- The direct effect on infants under six months was similar whether obtained with three or two doses (95–96%), although efficacy of a single dose drops to 67%.
- Herd effects were evident among the very young and the elderly, showing a 50% drop in strain-related pneumococcal disease in children under two months and a 31% drop in adults over age 65.
- Replacement of invasive pneumococcal disease with non-vaccine serotypes was seen, although low compared to the beneficial effects.
- Replacement of invasive pneumococcal disease with non-vaccine serotypes in HIV-infected adults was high, about 50%.

1.3 Rotavirus surveillance *(Joseph Bresee)*

The global burden of morbidity and mortality of rotavirus infection is well recognized. An estimated 480 000 to 600 000 deaths in young children under 5 are attributable to rotavirus annually. All children will get at least one rotavirus infection early in life. So why should we do more surveillance?

The three most commonly heard complaints against doing more rotavirus surveillance are:

- there is no need to better define the global importance of rotavirus – we know it already!
- vaccines will be accepted by local decision-makers based on global or regional data;
- there are too many studies already – local decision-makers have plenty to work with.

However, each of these complaints has a counter argument. For example, there is still a need to track global rotavirus disease burden over time. Studies on diarrhoeal mortality rates show that diarrhoeal mortality has shown a significant drop over the past two decades (4.6 million deaths in 1982 to 1.6 million deaths in 2003). However, the proportion of these deaths due to rotavirus infection has also changed.

Earlier studies of rotavirus epidemiology showed that about 20–25% of hospital diarrhoea admissions were due to rotavirus. This was regarded as the likely proportion of diarrhoeal deaths due to rotavirus. Recent studies by the Asian Rotavirus Surveillance Network have shown that the average number of hospital admissions due to rotavirus has risen and is actually 45% and over 50% in some locations. Therefore the proportion of diarrhoeal disease hospitalizations due to rotavirus has

increased while the total diarrhoeal cases has declined. Therefore, the absolute number of rotavirus deaths in children under 5 may not have changed as dramatically as once thought.

Second, it is generally believed that global or regional data is enough to convince local decision-makers to accept a new vaccine such as rotavirus. However, audience research by the McKinsey Group with policy-makers in several settings showed unanimously that *local* burden of disease was a priority for any government to decide on adoption of a new vaccine.

Finally, although there seems to be a significant body of knowledge about rotavirus epidemiology and rotavirus vaccines, the number of sound, scientific studies with appropriate population-based information is limited (some seven studies have been done globally and only one in a developing country).

Therefore, by continuing to expand rotavirus surveillance, countries can:

- refine disease burden data and epidemiological data on rotavirus;
- make informed decisions about vaccine use and composition;
- provide current quality data for advocacy;
- develop local and national champions; and
- set up systems to monitor vaccine impact.

This need for continued rotavirus surveillance has led to the following recommendations from the GAVI R&D Task Force.

- Create a simple, generic protocol for country-specific surveillance studies.
- Provide protocols for intussusception surveillance in any country interested in conducting rotavirus vaccine studies.
- Establish regional networks for rotavirus strain surveillance and characterization.
- Work with advocacy groups to ensure that data generated are useful.

Using the Asian Rotavirus Surveillance Network as an example, WHO and the Centers for Disease Control and Prevention (US CDC) have developed simple generic protocols for strain surveillance, hospital-based burden of disease studies, health services utilization studies, cost estimation of diarrhoeal disease, and intussusception surveillance. Similar networks are in place in Africa and Latin America and will, hopefully soon, also be in place in the Eastern Mediterranean Region.

The next challenge is to find the correct channels to communicate the available data with policy decision-makers and ensure that rotavirus vaccines are available in developing countries as quickly as they are in more developed countries.

1.4 Update from rotavirus vaccine trials *(Kong Boo Phua)*

The high global morbidity and mortality due to rotavirus infections and the likelihood that improved sanitation, water supply and quality, and improvements in hygiene will not decrease the overall incidence of rotavirus infections, have stimulated the development of rotavirus vaccines. Several rotavirus vaccine candidates are under development, as discussed below.

Two rotavirus vaccines are currently licensed:

- RotaShield® (reassortant rhesus rotavirus) is a vaccine that has been licensed by the US Food and Drug Administration since 1998. However, reported association of RotaShield with intussusception in 1999 has resulted in the manufacturer, Wyeth Ayerst, withdrawing this vaccine from the market. Now, a small biotech company has plans to acquire the license and master-vaccine seed lots from Wyeth and reproduce RotaShield, probably outside the United States.
- A lamb rotavirus strain manufactured by Lanzhou Institute of Biological Products is used only in China.

Two other live, oral attenuated vaccines are in late stage clinical development. These include the bovine reassortant vaccine developed by Merck & Co. and the human monovalent vaccine being developed by GlaxoSmithKline (GSK) PLC.

Merck's bovine reassortant vaccine, RotaTeq™ has been shown to have low reactogenicity, very low shedding, and good immunogenicity (88%) in quadrivalent form (serotypes G1, G2, G3 and P1a[8] gene). The quadrivalent vaccine showed 100% protective efficacy against severe rotavirus disease requiring hospitalization. Merck's pentavalent vaccine, containing the human rotavirus VP7 genes for serotypes G1 through G4 and the VP4 P1a[8] gene has also shown good immunogenicity and protective efficacy in clinical trials in Finland. A large phase III safety and efficacy trial is currently ongoing in Europe and the USA to evaluate the safety of the vaccine against intussusception in approximately 65 000 children and the clinical efficacy of the vaccine in a large subset of these children.

The monovalent vaccine Rotarix™ against one rotavirus strain, by GSK, is currently under clinical evaluation in a similar, large phase III safety and efficacy trial in Latin American countries and in Europe. Recent results of phase II and III clinical trials in Asia, Europe, Latin America and the USA have indicated good immunogenicity of the vaccine as well as good protective efficacy against severe rotavirus disease. The protective efficacy in the Latin American trials showed not only clinical protection against severe rotavirus disease with G1 (71–86%) but also a similar level of clinical protection against non-G1 strains (65–83%). Phase III efficacy trials in Singapore showed that there was no interference with concomitantly-delivered routine childhood immunizations.

There are several other rotavirus vaccine candidates under development – including other bovine reassortant strains – by the National Institutes of Health (NIH) and neonatal human strains in Australia and India. However, none are as close to licensure as the vaccines by Merck and GSK.

Discussion

Two important questions were raised in the discussion.

- How do the vaccines affect shedding and transmission to others? Merck indicated that shedding does not occur with their vaccine. GSK has seen anecdotal cases of transmission in sets of twins and is examining this more fully.
- What about intussusception? Both companies have seen isolated cases of intussusception in the large safety and efficacy trials (those with over 60 000 infants) which are designed to determine if there is an increased risk of intussusception with the administration of rotavirus vaccine. Neither company has reported intussusception cases in these large safety studies within the high-risk window of 3 to 14 days after any dose. The large safety trials by both companies are still blinded and have been examined by independent Data Safety Monitoring Boards; neither have indicated any perceived increased risk of the vaccine administration.

1.5 Update on GAVI activities to introduce new vaccines *(Tore Godal)*

GAVI has outlined a list of qualities for effective aid. These qualities have guided GAVI's decision-making, organization, and funding strategy with The Vaccine Fund to:

- focus on the poorest countries and the poorest groups within countries;
- increase predictability and reduce transaction costs;
- build on country priorities and harmonize with other types of health funding and programmes;
- scale up with the most cost-effective interventions and easy-to-use technologies;
- tie funding to performance;
- include a strong monitoring and evaluation component; and
- promote sustainability.

GAVI's core work focuses on:

- reversing the downward trends in immunization coverage that have been noted;
- reducing the delay in introducing new vaccines – hepatitis B (HepB) vaccine and Hib; and
- accelerating the development and introduction of new vaccines that are currently in late-stage development, such as multivalent pneumococcal conjugate and rotavirus vaccines.

By the end of 2003, GAVI and The Vaccine Fund approved immunization support for 69 of 75 eligible countries. Today, close to 8 million additional children are receiving routine childhood vaccinations (measured by the third dose of diphtheria–tetanus–pertussis vaccine [DTP3]). In addition, about 30 million doses of hepatitis B vaccine, 7 million doses of Hib vaccine, and 5.6 million doses of yellow fever vaccine have been introduced in developing countries, and 496 million auto-disable syringes have been provided in 37 countries for all routine childhood immunizations.

Along with the success of this effort, some lessons have been learned. Not surprisingly, easy-to-use technologies lead to faster results. For example, combination vaccines have resulted in a rapid increases in coverage rates. But this is balanced against the increased cost of combination vaccines.

There are several major challenges that remain to be addressed including financial sustainability after the five-year Vaccine Fund support period, vaccine availability, and country-level barriers to increasing vaccine coverage.

Financial sustainability requires countries to share the responsibility for financing vaccine programmes along with partners and donors. The poorest countries are not expected to become self-sufficient until economies improve; however, all countries that receive support from GAVI and The Vaccine Fund are expected to use financial planning tools and submit financial sustainability plans. Major challenges to financial sustainability include convincing governments to increase funding for health; getting firm, long-term commitments from donors and partners; and reducing programme costs (increasing efficiency) by improving resource management and programme efficiency in a real-world setting.

Thus far, 12 countries have received approval for their financial sustainability plans and an additional 22 countries have submitted plans for review.

Regarding vaccine availability, most countries applying for new HepB and Hib vaccine introduction indicated a strong preference for combination vaccines. Although there is an overall sufficient global supply of vaccines containing HepB and Hib, the availability of combination vaccines containing those antigens remains limited. As a result, some countries had to opt for alternative product selection or decided to wait until their preferred product becomes available. These combination vaccines have also remained at prices substantially higher than traditional vaccines.

There also remain many barriers to increasing vaccine coverage. These barriers can include a lack of political will and commitment by countries, the absence of physical infrastructure and equipment to deliver the vaccines, the lack of monitoring systems to evaluate disease burden, poor immunization performance and planning, as well as the gap in human resources for improving immunization delivery and social mobilization.

GAVI is working closely with WHO to help countries that have not yet applied for support or that require assistance with their financial sustainability plans. Investments are strategically offered to be time-limited, front-loaded (early targeted investments to reduce costs over time), and performance-based (stressing outcomes, not process). In the long term GAVI will seek to invest in:

- improving immunization services;
- completing the introduction of current vaccines (HepB, Hib, yellow fever);
- improving strategies for currently available vaccines (measles, tetanus, rubella);
- introducing new, near-term vaccines (rotavirus, pneumococcal, meningitis) and long-term vaccines (AIDS, malaria, tuberculosis [TB]).

1.6 Meningococcal meningitis enhanced surveillance in Africa
(Denis Kandolo)

Epidemic meningitis remains a major public health problem and challenge in Africa. An estimated 700 000 cases occurred over the last 10 years with about 70 000 deaths. Epidemics in the Meningitis Belt are usually associated with *Neisseria meningitides* (*Nm* A), which includes 12 serotypes.

After the emergence of *Nm* W135 meningitis epidemics in 2000, WHO developed a protocol for the enhanced surveillance of meningitis in three African countries (Burkina Faso, Mali, and Nigeria) during 2001 and 2002. W135 was identified as the major cause of the outbreak in Burkina Faso in 2002. However, a lack of a W135 vaccine meant that case management was used to control the outbreak. Enhanced surveillance, which included investigations for W135, was extended to 13 countries in the African Meningitis Belt in 2003 and 2004.

Enhanced surveillance requires early outbreak detection, rapid laboratory confirmation, and prompt implementation of control measures. Significant challenges remain in collecting and transporting the clinical specimens (e.g. cerebrospinal fluid [CSF]) to the laboratory. A regional surveillance team has been established in Burkina Faso.

In response to the perceived need for a polysaccharide meningitis vaccine including the A, C and W serogroups in Africa, proactive steps were taken.

- In 2004, 6 million doses of trivalent (ACW) vaccine were made available at about €1 per dose for the International Coordinating Group (ICG) for vaccination provision for epidemic meningitis control.
- Bivalent vaccine (AC) was largely made available at US$ 0.28 for ICG, and a 3.5 million dose revolving stockpile was made available.

The enhanced surveillance in 2004 detected large outbreaks (mainly caused by *Nm* A) in Burkina Faso, Democratic Republic of Congo and Niger with high case-fatality rates. However, a reactive immunization campaign was launched and quickly brought the outbreak under control without the usual rise in case-fatality rates seen previously. Furthermore, the enhanced surveillance demonstrated that there was substantially less W135 seen in 2004, and that A was again the predominant circulating strain seen.

Despite this apparent success, several challenges remain.

- Enhanced surveillance is more effective in some countries than in others.
- Many countries have weak laboratory systems and need support to develop national laboratory networks.
- Data transmission to WHO needs to occur more regularly and be more complete.
- There are inadequate resources to support surveillance and laboratory activities in many countries.

Some of these issues can be resolved by providing additional surveillance support to countries and requiring them to follow timelines and provide complete data. Standard operating procedures would help laboratories harmonize their data reporting and allow comparisons between countries.

1.7 Conjugate meningococcal vaccines for Africa *(Marc La Force)*

Epidemic meningitis is associated with great morbidity and mortality in sub-Saharan Africa and across the African Meningitis Belt with an estimated 250 million people at risk. Children and young adults up to 29 years of age constitute the most vulnerable age group. The Meningitis Vaccine Project (MVP) is a partnership between WHO and the Program for Appropriate Technology in Health (PATH), funded by the Bill & Melinda Gates Foundation. The MVP was created after all the major manufacturers had suspended their development projects of group A meningococcal conjugate vaccines. Although the primary objective of the MVP is to develop a safe and efficacious vaccine against meningitis, it has defined three guiding principles:

- the project is about public health impact and not simply about making a vaccine available;
- decisions about the future candidate vaccine are linked to introduction strategies and likely financial constraints;
- African public health officials are closely involved with the MVP.

Discussions with African public health officials have shown that the most important factor for introducing the vaccine is cost. The Meningitis Belt countries are amongst the poorest in the world and the vaccine prices should therefore not exceed US$ 0.50 per dose.

Despite the outbreak in 2001/02 of *Nm* W135 in Burkina Faso, it was decided to move ahead with the development of monovalent A vaccine candidate, with a back-up strategy allowing the development of an A/W vaccine. Careful monitoring of epidemic meningitis will determine if W135 is to become a major strain in the Region. The main reason for developing a monovalent A vaccine is that the vast majority of meningococcal isolates in Africa are still type A. Also, the lower price of a monovalent vaccine will allow the greatest public health impact.

MVP and its partners have developed an ambitious timetable of clinical trials to anticipate the production of clinical vaccine lots in 2004, with phase I and II trials starting by 2005. It is hoped the vaccine could be licensed for use by 2008.

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

1.8 New developments in meningitis vaccines in industrialized countries *(Elizabeth Miller)*

In the United Kingdom, the majority of meningitis cases seen consist of serogroups B (56%) and C (38%). In 1999, meningitis B was associated with more deaths in children under age 5 and meningitis C with a peak in deaths in adolescents.

There are currently three meningococcal C conjugate vaccines available. The strategy for the development and introduction of meningococcal vaccines in the United Kingdom (UK) is outlined below.

- Work in partnership with vaccine manufacturers to accelerate availability of meningococcal conjugate vaccine (MC*conj*) for the UK population.
- Provide the Department of Health with information needed to formulate Mc*conj* policy. Relevant questions include:
  - can MC*conj* vaccines be introduced in the accelerated primary schedule in the United Kingdom (administered at 2, 3 and 4 months)?
  - is one dose enough in children over 12 months?
  - will carrier protein interfere with DT booster doses in older children?
  - what is the safety profile in UK school children?

In addition, cost-effectiveness analyses are essential in the UK, as vaccines are provided free-of-charge by the National Health Service and limited resources have meant that policy decisions are increasingly based on economic analysis.

In conclusion:

- MC*conj* vaccine was introduced in mid-2000 and coverage quickly resembled that for routine DTP3 in children under 12 months. Meningitis C vaccine coverage is close to that of DTP4 booster doses in 5 and 6 year olds.
- Laboratory-confirmed diagnoses of meningitis C cases showed a clear decrease (90%) in cases within one year.
- Vaccine efficacy is 90% in children under 1 year of age.
- Reduction in carriage has been seen (66%) and herd immunity effect has been shown in unvaccinated children.

There has been a reported absence of serological markers of protection after approximately two years in children who received routine childhood vaccines. The long-term implications of this result remain to be investigated.

2. New vaccines for old bacteria

2.1 Group A streptococcal vaccines – an update *(Jonathan Carapetis)*

An examination of the current burden of streptococcal disease and potential control strategies clearly underlines the need for a group A streptococcal vaccine. Group A streptococcal (GAS) diseases can be divided into direct infections (superficial or invasive) and subsequent infections such as acute rheumatic fever (ARF), rheumatic heart disease, and post-streptococcal glomerulonephritis. Disease burden data are difficult to compile because case definitions vary widely from region to region, particularly in developing countries. However, it is currently estimated that there are 18 million persons with severe cases worldwide, with 1.78 million new cases and 517 000 deaths occurring each year. Most of the estimated burden is found in developing countries, which host 79% of the persons with rheumatic heart disease, 95% of those with acute rheumatic fever, and 97% of those with invasive GAS. There is no effective primary prevention, and current control measures focus on secondary prophylaxis such as that for rheumatic heart disease.

Human immunization with GAS began in the late 19th century with heat-killed and UV-killed strains, or with M-protein fragment or purified M-protein (the most virulent factor). However, vaccine development has been slowed by the fear of an increased risk of ARF following vaccination, mostly based on results from a single study published in 1969. The subsequent USA regulation, banning the use of group A streptococcus organisms and derivatives, has been an obstacle to developing a new vaccine. A better understanding of ARF pathogenesis has gradually eroded these safety concerns. Candidate vaccines are now being developed, although the lack of well-established correlates of protection and an absence of good animal models remain obstacles.

There are currently two approaches to potential vaccine candidates – using either the M-protein or non-M-protein (conserved) antigens. M-protein candidates are developed with type-specific determinants (multivalent, N-terminal) or with conserved epitopes (C-repeat region). A type-specific 26-valent M-protein-based vaccine that targets the most common invasive diseases has been tested in 30 adults in a three-dose schedule. No severe adverse event was recorded and the immunogenicity was high with the induction of bactericidal antibodies except for two serotypes. A phase II study of the vaccine is under way; however, the bactericidal activity induced is very specific to the M-protein, a highly variable antigen. Thus, this vaccine approach might not be appropriate in highly endemic regions where a rapid turnover of M serotypes has been observed and C-repeat region vaccines have been developed using various protein carriers. Some of these C-repeat vaccines are planned to enter phase I trials soon.

The US National Institutes of Health held a workshop in March 2004 with the following goals: to define priorities for GAS vaccine-development activities, to better coordinate efforts, and to define endpoints for different countries, particularly for developing countries where vaccines will have to be tested prior to policy-making. Meeting recommendations were three-fold:

- to improve documentation of disease burden particularly in developing countries;
- to define end-points for clinical trials of GAS vaccines; and
- to determine factors which will increase awareness, investment and acceptance of GAS vaccines.

Among those factors, defining the optimal age for vaccination is paramount: a compromise has to be found between missing early diseases and fitting the vaccine into an infant schedule, this will, in turn, raise concerns over the duration of protection.

2.2 The development of vaccines against *S. aureus* for prevention of nosocomial infections *(Ali Fattom)*

Staphylococcus aureus is the first cause of nosocomial infection in hospitalized patients, accounting for 20% and 24% of all such infections in Canada and the USA, respectively. In a large survey conducted between 1997 and 1999 within sentinel clinical sites located throughout Canada, Europe, and the USA, *S. aureus* accounted for 22% of all blood infections, 23% of all lower respiratory tract infections, and 39% of all skin and soft tissue infections. Mortality rates are high. For example, recently a 24% mortality rate was reported among patients with an *S. aureus* bacteraemia followed prospectively for 12 weeks in a medical centre in the USA. Resistance is a major problem; reports of multidrug-resistant *S. aureus* have augmented considerably since the 1960s. Among hospital-acquired infections, 50–60% are now caused by strains resistant to methicillin. In 2002, the first two truly vancomycin-resistant strains were reported. They had acquired a van A gene identical to that found in vancomycin-resistant enterococci. In 2004, another such strain was isolated, but found to be unrelated to the first two.

Immunotherapy for *S. aureus* began in 1879. However, uncertainties regarding immunity to the organism delayed the development of vaccines against *S. aureus* until the early 1980s when clinical isolates were found to possess capsular polysaccharides. Capsular polysaccharides help the bacteria evade opsonophagocytosis, a major line of defence against this pathogen. Current vaccine candidates target various surface components of the bacteria and are all in pre-clinical development stages except for a capsular polysaccharide conjugate vaccine currently in phase II.

The vaccine in phase II trials includes the two most prevalent *S. aureus* capsular polysaccharides—types 5 and 8—covalently bound to a carrier protein: a recombinant *P. aerations* serotoxin. Out of 13 identified capsular types, two types (5 and 8) were shown to represent over 80% of the clinical isolates. These two polysaccharides are very similar except for two sites, which naturally led to the development of a bivalent vaccine.

Conjugating bacterial capsular polysaccharides to carrier proteins increases their immunogenicity and confers T-cell dependent properties on their immune responses. Thus, the poor immunogenicity of polysaccharides among immunocompromised patients particularly susceptible to *S. aureus* infections led in turn to the development of conjugate vaccines. These conjugates elicited a high antibody response in mice and rabbits. All antibodies were opsonophagocytic and protected mice from lethal and sub-lethal *S. aureus* challenges. In mice injected subcutaneously and challenged intraperitoneally, 50% of the antibodies were still present four years later, indicating a long-lasting immune response. Types 5 and 8 capsular polysaccharide conjugates, evaluated separately, were highly immunogenic, inducing antibodies that mediated an opsonic activity in healthy human adults. The bivalent conjugate vaccine conferred a similar response in healthy adults, with an excellent safety profile.

The choice was then made to evaluate the vaccine among a target population: persons living with end-stage renal disease (EDSR), prone to *S. aureus* infections. The paradigm behind this choice was that, if efficacy could be demonstrated in this worst-case population, it should occur in immune-competent individuals as well. The vaccine was formulated to contain 100 micrograms of each capsular polysaccharide type, a higher dose than previously used in healthy volunteers, and was tested among 1800 EDSR patients in a double-blind, randomized, placebo-controlled efficacy trial with *S. aureus* bacteraemia events as a primary end-point. Vaccination reduced the number of bacteraemias by 57% for up to 40 weeks post vaccination with a good safety profile. After four weeks, protection fell off to approximately 25%. A very high antibody response was observed with a fast decline at six months. Administration of a booster dose in a small sample of patients showed that a high and sustained antibody response was elicited after the booster. A booster will be administered eight months after the first dose in a currently planned larger efficacy study.

The vaccine may have the potential to prevent infections with a higher and more durable efficacy among immunocompetent people in short-term risk groups, such as surgery patients. Vaccine licensure will be targeted to specific populations with the following potential schedules: for patients with a scheduled surgery, one week before, with a booster at one or two years as appropriate; and for patients with a chronic exposure, yearly boosters. A hyperimmune immunoglobulin derived from plasma donors previously immunized with this vaccine will be proposed for licensure with an indication in the following populations: non-vaccine responders, such as neonates with boosters every two weeks; and emergency patients (shock, traumas, etc). The use of such a vaccine in “normal communities”, e.g. local outbreaks of multi-drug resistant *S. aureus* in paediatric wards could be possible, as long as there is enough data to show efficacy and correlates of protection.

2.3 Meningococcal disease in New Zealand: epidemic control may be in sight at last *(Diana Lennon)*

New Zealand used an old approach based on epidemiology to try to control a large outbreak of group B meningococcal disease. More than 5000 cases and 200 deaths have occurred countrywide since 1991. Incidence rates in recent years were twice those observed in the UK when the MC*conj* vaccine campaign was launched. In 1998, 12 cases per 100 000 were reported in New Zealand versus 5 per 100 000 in the UK. In 2001, up to 17.4 cases per 100 000 total population were recorded in New Zealand. The rates were extremely high in young, underprivileged children, reaching 100 to 500 cases per 100 000 in 2003 among children under 5 of Maori or Pacific origin. Indeed, whereas 1 out of 3 children in New Zealand is of Maori or Pacific origin, 61% of the cases of meningococcal disease reported between 1999 and 2003 in individuals under 20 years were observed among these groups. The majority of isolates from cases with meningococcal disease between 1990 and 2002 belonged to the same serogroup B, subtype P1.4.

B polysaccharide is not immunogenic in humans and no serogroup B polysaccharide vaccine actually exists. In group B infections, bactericidal antibodies are directed against non-capsular surface antigens (i.e. the outer-membrane proteins [OMPs]). Strain-specific protein-based outer-membrane vesicle (OMV) vaccines are the only current response to group B epidemics. Thus, a proposal to develop such an OMV vaccine for New Zealand was launched as a public–private partnership between the New Zealand Ministry of Health, the University of Auckland and Chiron Corporation. Antigens on the class 1 OMP were shown to induce a serum bactericidal activity immune response following carriage, invasive disease and immunization with a serogroup B OMP vaccine at all ages.

A phase I study conducted in adults in 2001 followed by phase II studies in infants, toddlers, and school children in 2002–2003, led to provisional licensure of the vaccine. Serum bactericidal activity (SBA), a functional assay, was used here as a correlate of protection largely based on the experience gained from group A and C vaccines, where this correlation was used for licensure. Among infants, this correlation is less certain but group B OMV meningococcal vaccines have an established efficacy in older age groups and elicit a strain specific immunogenicity in infants largely induced by class 1 OMP. The New Zealand outbreak was highly strain-specific. In the phase II study among toddlers with a 3-dose schedule, 75% of the children exhibited a fourfold rise or more in serum bactericidal antibodies, and reactogenicity was similar to that observed with the wholecell pertussis vaccine. Percentages of sero-responders as measured by SBA after the third dose were around 75% in all age groups, and over 90% in individuals over 18 years of age. Immunogenicity, defined as a fourfold antibody rise, was used here as a surrogate of efficacy for vaccine licensure. It is likely to mirror efficacy, particularly because of the very clonal nature of the outbreak. However, efficacy and serogroup disappearance are still the gold-standard measures.

A phase III/IV trial aimed at epidemic control with a sequential nationwide vaccine introduction in the under-20 age group is currently ongoing (2004–2005) with intensified safety monitoring. Vaccine effectiveness will be estimated using a case–control design and a Poisson regression model: a standard method for modelling occurrence of discrete events over time, such as cases here. Risk of disease and risk of not getting the vaccine are linked in New Zealand, and this will be carefully considered in conducting the analyses to minimize interpretation biases. In an attempt to predict the progress of the epidemic in New Zealand, the numbers of reported cases have been plotted against those notified in Norway for the corresponding epidemic years. Building on the Norwegian experience, New Zealand hopes to avoid another five-year lag before vaccine introduction by using this rapid clinical development approach. This approach has been carefully monitored through multiple and international peer reviews. An Independent Safety Monitoring Board has been set up for independent evaluation of safety and effectiveness data, and close monitoring for any antigenic variation in epidemic strain is ongoing.

2.4 Meningitis B: development of the Cuban vaccine
(Concepción Campa Huergo)

In the early 1980s, Cuba experienced a nationwide outbreak of meningococcal B disease with annual incidence rates reaching 14.4 cases per 100 000 total population. A group of scientists started working on the development of a meningitis B (MenB) vaccine. Subsequently, a meningococcal BC vaccine, produced by the Finlay Institute, was licensed in Cuba in 1987 and has now been approved for licensure in 14 countries with an indication in infants, children, adolescents and adults. The vaccine is constituted of purified protein-based OMVs of serogroup B strain B:4:P1.19,15 and purified serogroup C capsular polysaccharide, with aluminium hydroxide gel as an adjuvant and thiomersal as a preservative agent.

The initial pre-licensure phase III study was carried out in Cuba in the seven provinces that had the highest incidence at that time, and was designed as a double-blind randomized placebo-controlled trial. The vaccine was administered in a two-dose schedule, randomization was done at the school level, and 105 251 adolescents included in the study were followed up for 16 months. Vaccine efficacy was estimated to be 83% with 4 out of 52 966 cases found in the vaccinated group and 21 out of 53 285 found in the placebo group. An estimated 56.2% of responders showed serum bactericidal activity versus 18.6 % in each respective group. The vaccine was found to be safe and well tolerated.

As of today, this vaccine has been used in mass campaigns in countries such as Argentina, Brazil, Colombia, Cuba and Uruguay. More than 50 million doses have been administered overall in subjects between 3 months and 24 years of age. In all studies conducted in these countries, the estimated vaccine effectiveness was 74% among subjects 48 months of age and over. In Brazil, where the outbreak was somewhat less clonal than in other places, evidence suggested that the estimated protective efficacy was independent of serotype and subtype. However, among young children less than 48 months of age, protection against homologous strains was observed while cross protection was not.

Post-licensure immunogenicity studies were conducted in Chile and Iceland. In a study conducted among young adults in Iceland, two vaccination schedules (two versus three doses) were compared for immunogenicity, measured as the percentage of responders with serum bactericidal activity (SBA) against the vaccine strain and three heterologous strains. The third dose induced an anamnestic response with SBA against all strains, thereby suggesting that using SBA as measured after two doses as a surrogate-of-protection might actually underestimate the true protection provided by the vaccine. Similar studies were conducted in Chile among infants, children two to four years of age, and adults. SBA was measured against the vaccine homologous strain and two other strains: the Chilean and Norwegian epidemic strains. A third dose increased the percentage of responders with SBA against the homologous strain in all three age groups, and against heterologous strains in children and adults but not in infants. Post-licensure safety studies conducted in Brazil, where an overall total of nine million subjects were vaccinated, confirmed the good safety profile of the vaccine.

An agreement was signed in July 1999 between the Finlay Institute and GlaxoSmithKline to develop an improved meningococcal B vaccine technologically derived from the B component of the original Finlay vaccine. Major modifications have included the addition of OMVs from a major European serogroup B strain (P1.4,7) and the removal of thiomersal. Safety and immunogenicity studies of this MenB vaccine have been conducted in Belgium, Colombia and Spain in adults and adolescents with a three-dose schedule, and have shown that the vaccine was safe and induced antibodies with both specific and cross-SBA.

3. Round-table discussion on vaccine manufacturing in developing countries

3.1 The Developing Country Vaccine Manufacturers Network *(Suresh Jadhav)*

The Developing Country Vaccine Manufacturers Network (DCVMN) was formed in 2000 to provide quality vaccines at affordable prices to the developing world, including vaccines that are in need in developing countries and vaccines that are of limited interest to industrialized nations. The Network seeks international recognition that developing country vaccine producers have an essential role in ensuring that lifesaving vaccines are available for every child.

The objectives of DCVMN are to:

- act as a source of information: e.g. inventory of production capacities;
- facilitate information exchange among members;
- provide training on vaccinology; and
- act as a facilitator for technology transfer.

Full DCVMN members are WHO prequalified manufacturers located in countries with a fully functional national regulatory authority (NRA). Prospective members are manufacturers working towards WHO prequalification, located in countries with a functional NRA. Associate members have neither a functional NRA nor prequalification, but are committed to achieving both. Institutions that can provide resources or technical support are also members. These include the International Vaccine Institute, PATH, US National Institutes of Health (NIH), and Research for Man and the Environment (RIVM, Holland).

Prequalified vaccines available from DCVMN include BCG, tetanus toxoid (TT), diphtheria–tetanus (DT), Td (tetanus–diphtheria for adults) diphtheria–tetanus–wholecell pertussis (DTwP), oral polio vaccine (OPV), measles, measles–rubella (MR), measles–mumps–rubella (MMR), HepB, yellow fever and rabies. These vaccines are made available through UNICEF and PAHO and through private export markets.

DCVMN is represented on the GAVI Board and the Strategic Advisory Group of Experts (SAGE), and is invited to attend UN agency meetings. Some members have collaborated with industrialized-country manufacturers such as Wyeth Pharmaceuticals and GSK, as well as with institutions such as PATH and NIH.

DCVMN is concerned about intellectual property rights (IPR) issues and the potential impact of these rights to prevent or limit the ability of DCVMN groups to manufacture and sell vaccines.

The Network proposes that template IPR agreements be created for developing and middle-income country vaccine manufacturers. Network members also need access to unbiased legal reviews, assistance in writing patent applications, and training on how to better detect and understand infringements.

DCVMN expects WHO and other UN agencies to come out with a white paper explaining details of IPR on vaccines and how DCVMN may continue to make vaccines available at affordable prices.

3.2 Patent issues arising from transfers of technology *(Miloud Kaddar)*

Technology transfer refers to any process by which any party gains access to another's technical information and successfully learns and absorbs it into its production process. Agreements on intellectual property and technology transfer are generally confidential, hence it is difficult to provide cases, examples and lessons learned on technology transfer. However, some issues relating to technology transfer were discussed at a WHO meeting on intellectual property in vaccines held in Geneva in April 2004.

From this meeting it became clear that technology transfer players can be divided into two groups: those who are business oriented and those who are public health oriented. With developing country vaccine manufacturers, the distinction is not always clear, as some are both business and public health oriented.

The objectives of these players can be quite different.

- *For the recipient firm*: to expand technological base and acquire know-how, produce and sell vaccines, and secure national vaccine supply.
- *For the business-oriented originator*: to gain market access and reduce costs.
- *For the public-health oriented originator*: to expand global supply of vaccines and develop vaccines which are of little interest to big pharmaceutical companies.

Currently, emerging manufacturers are producing basic vaccines whereas OECD manufacturers are producing most new vaccines. The ability of DCVMN members to manufacture new vaccine depends on a number of parameters including intellectual property, know-how and sharing.

Intellectual property

The environment around intellectual property is changing. In 2005, the World Trade Organization (WTO) agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) will be enforced in developing countries and will impact DCVMN manufacturers. In addition, the "TRIPS-Plus" agreement and bilateral agreements are being implemented, which further reduce the flexibility under TRIPS.

TRIPS contains two clauses that promote technology transfer.

- **Article 7:** The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.
- **Article 66.2:** Developed country Members shall provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to least-developed country Members in order to enable them to create a sound and viable technological base.

However it is not clear what incentives or mechanisms will enforce these clauses and promote technology transfer.

With new vaccines, intellectual property can be very complex. For example, many components of a vaccine may be covered by intellectual property including the antigen, the method of producing the antigen, the adjuvant, formulation method, or delivery device, etc. The result is that one must have access to every piece of intellectual property in order to make vaccine.

With regard to technology transfer there are three main methods of dealing with intellectual property.

1. **Territorial escape**. Go somewhere where the intellectual property is not valid. This route will become increasingly difficult after 2005.
2. **Licence from R&D-based industry**. Because R&D-based industry is not in the business of transferring technology, the licensor needs to bring something to the table, such as exclusive territorial marketing rights.
3. **Licence technology from universities**. Public health-oriented entities often do not own intellectual property. Plus, a third party often owns a relevant piece of intellectual property. The resulting technology transfer is therefore difficult and mired in third-party negotiations, making this option time consuming and costly.

New approaches are needed to solve intellectual property issues, such as patent pooling in cases where too many patents on a topic are preventing development. A discussion on these and other aspects of IP on vaccines is available on the following web site: ***www.who.int/intellectualproperty/events/archive/en/***

Discussion

- Much of the intellectual property in the USA originates in universities. How does one begin to put a framework around how universities think about intellectual property and technology transfer to developing country vaccine manufacturers? This was discussed at an NIH meeting. Examples were described where university sites receiving public support should provide intellectual property (voluntary) to the DCVMN. It was recognized that a change in practices and ethics of universities and funding agencies is needed, rather than hard and fast laws. The existence of university spin-offs creates additional complexity, as patent pooling dealing with spin-off IPR will be difficult.
- Are there any existing vaccine products that are threatened by the enforcement of TRIPS? Not currently, but there may be in the future.

3.3 Example of successful south-to-south technology transfer project: hepatitis B vaccine from Centro de Ingeniería Genética y Biotecnología to Panacea *(Yair Quinones Maya)*

Cuba has a scientist-to-population ratio similar to industrialized countries, yet the gross national product (GNP) of a developing country. Thanks to a large investment in biotechnology by the Cuban Government, Cuba has a strong biotechnology sector based on a philosophy of collaboration rather than individual competition, with solid capacity in R&D, production and marketing.

Cuba created the West Havana Scientific Pole comprising more than 58 institutions in west Havana, including Centro Nacional de Investigaciones Científicas (CNIC). With the main goal of meeting the human resource needs of the biotechnology sector, CINC encompasses facilities, diagnostic developers, etc. Collaboration between these institutes is part of their strategy for technology transfer.

Cuba is committed to ensuring intellectual property protection for the products of the Cuban biotechnology sector. Intellectual property on products from Cuba is covered by 150 patents in Cuba, 66 in other countries, and more than 500 applications.

In the early 1980s, Cuba had only three main biotechnology products. Now it expects to have over 30 commercial products in the Cuban biotechnology portfolio.

The Cuban biotechnology sector follows several principles regarding technology transfer.

- Technology transfer must be seen as a win–win approach.
- Each case is unique and requires a lot of analysis before signing a contract.
- There is a need to establish a strong relationship with the partner.
- The main goal of technology transfer is to produce the drug in the receiving territory, with the same quality and productivity, as agreed.

The main steps of technology transfer are outlined below.

- Produce a technical report, including a quotation of the offered technology (transparently shows what is offered, costs, etc).
- Sign technology transfer contracts.
- Exchange technical information between both parties involved in the project (this can be very complex for biotech products).
- Train the receiving workers.
- Provide technical assistance.
- Procure equipment and systems.
- Install, start up and commission the facilities, if required.

Information should be organized as "technological packages", which permit the flow of information. This has been shown to be very useful and enables one to disclose information and include timeline and milestones. The speaker described five technical packages covering finished-form technology, process technology, production technology, installation technology, and quality control and assurance.

Technology transfer alone is insufficient for sustainable product manufacture; therefore as part of the technology transfer package, Cuba offers training in biotechnology and technical assistance in equipment procurement and in projects and constructions (building facilities, commissioning production plants, etc).

Case-study: technology transfer of hepatitis B vaccine production to Panacea Pharmaceuticals, Inc.

In 1998 Centro de Ingeniería Genética y Biotecnologia (CIGB) and Panacea began developing a relationship, and in 1999 a contract was signed as a 50–50 joint venture between CIGB and Panacea.

The steps for technology transfer included a preliminary phase in which raw materials and an existing building were evaluated. Next, a Cuban project team was sent to develop the project and determine priorities. The team selected construction companies and equipment suppliers and began the installation and start-up phase in which personnel were trained and six mock processes were run to verify and correct operational parameters. When installation was complete, the Cuban team conducted a warranty test to ensure that the process and controls tests met WHO standards.

Following this successful technology transfer (Panacea is now producing prequalified hepatitis B vaccine), Cuban institutes are working with other countries on technology transfer, including a Hib vaccine project in South Africa.

3.4 Example of successful north-to-south technology transfer: Hib from GlaxoSmithKline to Bio-Manguinhos *(Akira Homma)*

There are only four public-sector vaccine manufacturers in Brazil and no private laboratories involved in production. Since the early 1980s, the Brazilian Government has invested in modernizing laboratories, and currently Brazil has the capability to produce all the basic vaccines used in the country's immunization programme. When Hib vaccine was introduced, technology transfer was required for manufacturing Hib vaccine in Brazil.

Technology transfer must be a win–win situation. In the case of GSK and Bio-Manghuinhos, the supplier (GSK) received exclusive market access during the technology transfer period. The PAHO Revolving Fund was used as a price reference to avoid excessive pricing.

The companies identified several preconditions for success.

- The recipient country must have a structured national immunization programme with long-term vaccine forecasting to predict needs and market (Brazil has 12 different vaccines in its national immunization programme).
- The recipient country must have an organized national regulatory authority, fulfilling the six functional operations as defined by WHO.
- The market size must be sufficiently large for economic sustainability (Brazil has 3.3 million neonates every year).
- Negotiators with experience in vaccine production and R&D are required on both sides.
- The recipient country must have GMP laboratories, government commitment, trained staff, expertise in the technology, knowledge of national legislation and international treaties, and be open to working with a private company.
- The technology supplier must have commitment from senior management, and assurance that the same technology and quality will be provided.
- The supplier must provide "hands-on" training and technological information.
- The supplier must be willing to work with the recipient as equal partners.

The technology transfer took place in several steps.

1) Training was offered at the technology supplier site, including training in quality control and quality assurance, final production and assistance in upgrading facilities.
2) Operations began with imported bulk (feasibility lots, consistency lots, assistance for licensure) and provision of expert assistance at the recipient site.
3) All production cycles were initiated at local facilities (manufacture of bulk, formulation, and finish). Assistance from the technology supplier was provided with validation, field trials and licensure.

Discussion

During the discussion, the points outlined below were made.

- While technology transfer from big pharma to developing-country pharma is desirable, it seems that ultimately the Cuban model is more needed, i.e. R&D must be done in developing countries so that the exchange of technology goes both ways, otherwise the burden of expensive R&D rests on OECD manufacturers. Increasing R&D investment is needed among developing country vaccine manufacturers.
- If developing country vaccine manufacturers (DCVM) do not develop their own R&D, then any technology received will soon be obsolete. In Brazil, a special budget is being allocated to specific priority vaccine research.
- The field of vaccines is a relatively small business: the total for worldwide vaccine sales is less than that for a single top pharmaceutical product. Some participants noted that while it is a good thing to have more manufacturers, this creates competition and could create new barriers.
- When IP becomes a blocking element new methods must be found, but for new vaccines the problem may be technical feasibility rather than IP.
- The issue was raised regarding DCVM access to OECD markets. The vaccine market is US$ 6 billion, while the UN agency market is only US$ 200 million. DCVM do not have access to the OECD market – they experience resistance. The market these manufacturers have entered is for basic diseases where profitability is minimal (an area vacated by big pharma). However, DCVM are also seeking access to OECD markets to generate more significant revenue, which would support R&D for new vaccines.
- The cost of performing research in developing countries will be roughly equal to that in OECD countries. Therefore, unless DCVM have access to the (profitable) OECD markets, how will they recover their R&D costs? Part of the challenge, therefore, is seen as the access of DCVM to industrialized markets.
- Who funds the technology transfer and is the recipient allowed to export? For CIGB, the funds were from both parties (CIGB and Panacea), and Cuba allows Panacea to export to some territories on a case-by-case basis. In Brazil, the Brazilian Government guaranteed to GSK that it would purchase the vaccine for five years from GSK. The price of purchase was however fixed at the PAHO price, thus providing GSK with a market, while protecting Brazil from unreasonable price fluctuations.
- After 2005, process patents could potentially suffocate DCVM. For example, there is a patent on the use of aluminium phosphate for combination vaccines. This patent is currently being opposed and the outcome of the opposition may provide some insight on the future impact of global enforcement of IPRs.

4. Emerging viral respiratory infections

4.1 Human infections with avian influenza viruses and pandemic potential *(Tim Uyeki)*

Influenza A viruses cause both annual epidemics and periodic pandemics in humans and infection in a variety of animal species. The natural reservoirs for infection are aquatic birds.

Infection and disease are seasonal in temperate climates but occur year round in tropical climates. Influenza A is associated with considerable morbidity and mortality, with the highest rates of infection in children under 2 years and in adults over 65 years of age. In fact, 90% of deaths occur among people over 65 years of age. Data on influenza mortality in children is limited, but in the USA, 92 deaths were reported during the last season.

Annual influenza epidemics are caused by antigenic "drift" in which point mutations in the haemagglutinin (HA) gene cause minor antigenic changes to haemagglutinin. Pandemics, on the other hand, are caused by antigenic "shift", which is the emergence of novel virus subtypes through genetic reassortment or direct animal/poultry-to-human transmission. Because there is little or no immunity to a novel virus, the virus is efficiently transmitted among humans. Such pandemics lead to considerable morbidity and mortality. The Spanish influenza pandemic in 1918 to 1919 was estimated to have caused 20 to 50 million deaths. Using mathematical models, it is estimated that a future pandemic may result in 314 000 to 734 000 hospitalizations and 89 000 to 207 000 deaths in the USA alone. Mortality in developing countries would likely be much higher.

Avian influenza viruses infect the respiratory and gastrointestinal tracts of birds. They are shed in faeces, and can survive at low temperatures and in water. The viruses may have low pathogenic potential and cause no disease in the wild aquatic birds but may cause outbreaks in domestic poultry. Strains with higher pathogenic potential, usually subtypes H5 and H7, can cause high mortality in domestic poultry.

A number of pandemic scares have occurred in recent years. These include several outbreaks that originated in Hong Kong:

- 1997 (H5N1: 18 confirmed cases and 6 deaths)
- 1999 (H9N2: 2 confirmed paediatric cases and 6 additional cases in China)
- 2003 (H9N2: 1 paediatric case, survived)
- 2003 (H5N1: 2 confirmed cases and 1 death; no pandemic; distinct strain from 1997).

Additional outbreaks were reported in other countries:

- Netherlands in 2003 (H7N7: 89 confirmed cases and 1 death)
- British Columbia in 2003 (H7N3: 2 cases)
- Virginia in 2002 (H7N2: 1 case)
- New York in 2003 (H7N2: 1 case).

A recent outbreak occurred in Asia in the winter of 2003/04 with human cases reported in Thailand and Viet Nam (34 confirmed cases and 23 deaths). The outbreak affected poultry in eight countries and over 100 million poultry were culled. The outbreak was characterized by the severity of infection in both humans and birds. Most of the human infections were acquired through close contact with poultry, and there is no evidence for efficient human-to-human transmission. The influenza A virus strains in this outbreak were distinct from the H5N1 strains from the outbreaks in 1997 and 2003 and were resistant to amantadine and rimantadine but sensitive to oseltamivir.

The avian influenza A virus strains responsible for the recent outbreaks have thus far not shown efficient human-to-human transmission and, therefore, have no pandemic potential. However, the occurrence of these outbreaks is a reminder of the danger of a pandemic should such a strain emerge. Currently, there are no effective vaccines available against subtypes H5, H7 or H9. In the absence of such vaccines, pandemic control might prove to be difficult.

4.2 H5N1 2004 avian influenza outbreak in Asia and the international response *(Klaus Stohr)*

Past experience shows that influenza pandemics are associated with very high morbidity and mortality. International coordination and preparedness is essential for controlling such pandemics and limiting morbidity and mortality.

WHO plays an important role in disease surveillance and response and in providing leadership and guidance for research and outbreak response. A number of partners are involved in outbreak response, including public health officials, the Food and Agriculture Organization of the United Nations (FAO), manufacturers (vaccines and drugs), national regulatory agencies, and ministries of health. Partners are highly interdependent when establishing an effective surveillance and response to potential pandemics.

Since 1997, there has been an acceleration in the number of cases of influenza with pandemic potential. The most recent outbreak of H5N1 avian influenza A disease demonstrated the rapidity with which disease may spread.

WHO has undertaken a number of activities to help countries to: (1) reduce risk by eliminating the animal reservoir and protecting high-risk individuals; (2) strengthen disease surveillance in animals and humans; and (3) improve pandemic preparedness through vaccine development, improved access to antiretrovirals, and national and international pandemic response plans. For example, WHO has published guidelines and recommendations to help countries achieve the above objectives. WHO has also developed the prototype strain for H5N1 vaccine production in collaboration with St Jude's Hospital, the UK National Institute for Biological Standards and Control and the US Centers for Disease Control and Prevention. Vaccine clinical production and testing will be taken up by industry.

Experience from the 1957 Asian influenza pandemic shows that progression from a localized outbreak to a global pandemic can be as short as six months. Given the increase in air traffic in the past several decades, the disease may spread even faster in the next pandemic. Timely availability of vaccine to control pandemics – even in Europe where manufacturing capacity is highest – is unlikely unless a number of obstacles are overcome, including:

- surveillance and characterization of potential pandemic strains;
- the lag between strain characterization and the beginning of significant vaccine production;
- the lack of knowledge about the optimal dosage and vaccine formulation;
- limited production capacity; and
- unresolved regulatory and legislative issues.

In summary, influenza A pandemics do pose a serious global health problem and are likely to result in large numbers of deaths if not controlled. Vaccines offer one approach to control these pandemics, provided they can be made available globally in a timely fashion. However, vaccines present a number of constraints and challenges that can only be addressed through a coordinated approach requiring considerable resources, partnership-building, strong leadership and coordination among stakeholders.

Discussion

The discussion that followed included the observations outlined below.

- Though evidence for receptor switching is a theoretical possibility, there is no evidence for true recombination in negative-strain RNA viruses.
- Better inter-pandemic control will lead to increased vaccine production capacity and use, and ultimately better pandemic control. This approach could possibly lead to vaccine production in developing countries. The use of reverse genetics would contribute to biosafety in the vaccine production process.
- Increased detection of avian influenza since 1997 may in part be due to increased surveillance and a search specifically for avian influenza.

- The level of prevalence of influenza in developing countries, especially those in Africa, is unknown because of the lack of epidemiological data and lack of adequate surveillance (currently only two sub-Saharan African countries, Senegal and South Africa, have national surveillance centres). However, outbreaks are known to occur in Africa (e.g. Central African Republic, the Congo and Madagascar).
- A repository of avian viruses that can be used for reverse genetics and vaccine production would facilitate timely availability of vaccine. Currently WHO does not collect surveillance data for avian viruses or other animal influenza viruses but discussions are ongoing with FAO to link human surveillance with animal surveillance to prepare for pandemics. Currently national influenza surveillance centres are not funded by WHO; additional funds would be required to support this activity.
- The role of pneumococcal vaccine in reducing hospitalization and mortality in influenza pandemics needs to be explored.
- There is evidence to show that poultry segregation helped control the avian influenza outbreak in Hong Kong, but this may be difficult to replicate elsewhere with unregulated bird markets and breeding.
- Even if vaccine production occurs in a timely fashion, will we be able to distribute it in all countries in the short time required for pandemic control? Are we prepared to handle the logistics of distributing vaccines? This is absolutely necessary, but is not yet on the WHO activity list due to the absence of a vaccine supply. Can we use the EPI process and channels in developing countries where appropriate?

4.3 Round-table discussion on development of vaccines against pandemic influenza

4.3.1 Reverse genetics and influenza virus vaccines (Peter Palese)

Reverse genetics uses recombinant complimentary DNA (cDNA) to rescue infectious viruses. Rescued viruses are created by transfecting Vero cells with transcription plasmids and protein expression plasmids. A backbone of six gene segments of a high-yield influenza A virus strain combined with the gene segments for haemagglutinin and neuraminidase (NA) of the prevalent virus strain is used to create virus strains for vaccine use.

The resulting recombinant virus strains grow better (to higher titres) than the prevalent pathogenic strain. Since the backbone is well defined and the new components consist of only two new segments, the process can be done quickly. In addition, through the reassortment process one can ensure that the vaccine strains are non-pathogenic and that strains overcome the biosafety problems during manufacture.

Reverse genetics has been used to rescue a chimeric influenza A virus with influenza B HA and NA. True recombination (between A and B strains) does not occur in nature but can be produced in the laboratory using reverse genetics. This technology can be used for many other negative strand RNA viruses (e.g. RSV, parainfluenza and human metapneumo virus).

4.3.2 Live attenuated intranasal influenza vaccine: an instructive tale (Harry Greenberg)

Developing and licensing new vaccines take time and money. The development of the cold-adapted influenza virus vaccine spanned a period of 36 years and cost hundreds of millions of dollars. The vaccine was made by reassortment and contained six gene segments of a master donor virus strain that confer attenuation with the HA and NA gene segments of the relevant wild-type virus.

The vaccine is a trivalent blend of 10^7 each of influenza A/H1N1, A/H3N2 and B viruses. It is delivered by large particle aerosol, cost US$ 45 per dose, and was recommended for use in healthy individuals 5 to 49 years of age. The vaccine had a slow uptake that was marked by periods of vaccine shortage.

The cold-adapted influenza vaccine (CAIV) was shown to be efficacious but caused an increased risk of asthma (relative risk = 4.06, 95% CL 1.3, 17.9) in children 18 to 35 months of age. Though there appeared to be a trend towards asthma protection in children 12 to 17 months, there was an increased risk of wheezing or shortness of breath following vaccination in this age group. However, there was no temporal relationship between vaccination and asthma within 42 days of vaccine administration.

The vaccine virus is genetically stable. Though shedding occurred, only one case of transmission was reported.

Currently, attenuated H5N1 strains are being developed as pandemic vaccine seed strains. Three cold-adapted H5N1 strains have been rescued and evaluation of cold adaptation, temperature sensitivity and animal pathogenicity is ongoing.

4.3.3 Development of live, cold-adapted attenuated influenza vaccine (Stanislav Markushin)

Tissue-culture derived, cold-adapted attenuated influenza viruses have several advantages over the conventional chick-embryo-derived vaccines. Vaccines from cell banks are easier to characterize for adventitious agents than are vaccines from primary cells. They are easier to standardize than chick-embryo vaccines, free of avian retroviruses, and can be made in serum-free media, which precludes allergic reactions. Moreover, chick-embryo passage can cause loss of one or more Ag domains of HA.

The vaccine is prepared using Madin-Darby canine kidney (MDCK) cell lines fulfilling WHO cell standards (free of mycoplasma, endogenic and foreign viruses, including retrovirus and with no oncogenic potential). The vaccine virus strains grow well in MDCK cells using a fermenter with serum-free medium, and are genetically stable. Further development of the vaccine is in progress.

4.3.4 A universal (M2 protein based) influenza A vaccine (Walter Fiers)

Of the two protective antigens used in conventional influenza A vaccines, HA drifts and shifts whereas NA is labile and is hardly present in many vaccines. The M2-protein is the third transmembrane protein and is present in abundance on the surface of infected cells. It is also stable and remains constant. Its sequence is almost 100% conserved since the first human influenza A virus was first isolated in 1933.

The extracellular domain of M2 (M2e) is fused to hepatitis B virus core antigen (HBc) to form constructs that may be used as a vaccine (M2e_HBc). The vaccine induces long-lasting protection in mice, and that protection can be passively transferred using immune serum (antibody mediated). However 100% protection is not induced by the antigen alone and requires the addition of an adjuvant, either alum or non-toxic enterotoxin mutant LTR192G. Vaccine immunogenicity can be improved by using multiple copies of M2e in the construct.

The M2e-HBc core increases the response to M2e and also induces response to HBc.

The antibody produced by this vaccine has been shown to bind to peptides from a variety of influenza A virus strains belonging to different subtypes, indicating that it may provide broad protection against influenza A viruses.

4.3.5 Industry perspective on pandemic influenza A vaccine development (Bram Palache)

Pandemic influenza is a real threat, yet we are still unprepared for it. Vaccination for all age groups is a key tool in controlling pandemic influenza. However, there is currently no production capacity to meet this need. The current manufacturing capacity is only sufficient to cover 5% of the world's population, and it is unlikely that the currently available vaccine supply will be sufficient to curtail the first wave of infection. Therefore, it is very desirable to increase supply to meet the demands of both initial and subsequent waves of infection. Such an effort needs collaboration and partnership and cannot be undertaken by any single company alone.

Solutions to increase the supply of pandemic vaccine include using low-antigen schedules, using adjuvants to increase immunogenicity, and increasing the use of vaccine in the interpandemic period to boost production capacity.

The vaccine industry faces several constraints, including:

- the need to anticipate pandemics and invest in vaccine production;
- technological challenges;
- regulatory constraints;
- production timelines;
- interference with interpandemic vaccine production;
- risk that vaccine produced will not be used; and
- liability.

These obstacles can only be overcome by economic incentives, technical support and risk sharing by public sector entities.

Europe is the only region that has published guidance for developing a pandemic vaccine, and the vaccine industry has responded. The European strategy involves an initial phase of developing a mock pandemic vaccine of the H5N1 subtype and carrying out evaluation of the prototype, including dose-ranging studies, vaccination schedules, and use of adjuvants during the inter-pandemic period. A complete dossier of the mock vaccine is then submitted for registration. During a pandemic, the pandemic vaccine can be rapidly developed and registered, requiring only quality data for the pandemic virus strain but with a commitment by the manufacturer to collect clinical data during use in a pandemic.

To be successful, this effort will need strong public-sector support. Administrative issues such as intellectual property, national genetically-modified organism (GMO) regulations, global registration requirements, and vaccine injury compensation should be resolved by international collaboration and coordination.

4.3.6 Round-table discussion

Points made during discussion include those outlined below.

- The best way to increase production is to increase inter-pandemic coverage. The main players in immunization need to give clear guidance on target populations, schedules, and how vaccine will be used.
- Logistically, single-dose schedules are desirable for pandemic control.
- Immunogenicity trials of the prototype H5N1 vaccines are critical.
- Public perception about influenza has to change to enhance the pandemic preparedness. Currently influenza is generally regarded as a mild disease, and the demand for vaccine during the inter-pandemic period is low. Changing the name influenza or "flu" to MARS (mass acute respiratory syndrome) was suggested to raise awareness of pandemic influenza.
- It was suggested that raising awareness of the dangers of an influenza pandemic cannot be on the agenda of WHO or industry alone. This has also to be on the agenda of national governments, the G8 and other such groupings.

4.4 SARS discussion on public health needs in the case of re-emergence *(Christophe Fraser)*

Analytical epidemiology is a technique that uses epidemiological analysis to determine key disease parameters, disease transmission routes, heterogeneity and risk factors for disease spread, and effectiveness of disease control/risk reduction techniques. These data are then applied in mathematical models to predict outbreaks and develop measures to control them. Standard epidemiological tools are often inadequate for this purpose, as infectious disease epidemiology is a dynamic and non-linear process. Analytical epidemiology was used to model the Hong Kong SARS outbreak. There was a close fit between the epidemic curves generated by the model and those using actual data.

The rate of spread of an epidemic is determined by the number of secondary cases caused by a primary case (basic reproduction number or R_0), the number of cases caused by each new case over a period of time (effective reproduction number or R_t) and the time between getting infected and infecting someone else (generation time or T_g). The reproduction number can be used to determine the change in dynamics of an epidemic when control measures are introduced. Thus, when R is brought below 1, the outbreak is controlled, as was demonstrated by the Hong Kong epidemic.

There were several factors that contributed to the control of SARS. The percentage transmission that needs to be blocked to achieve epidemic control is determined by R_0. Thus for SARS with R_0 of 2–5, 50–80% of transmission needed to be blocked to control the epidemic. In contrast, for influenza with an R_0 of 5–25, 80–97.5% of transmission needs to be blocked for epidemic control.

In addition, in the case of SARS, transmission generally occurred after the onset of symptoms in the primary case. Since most cases attended hospitals and therefore could be isolated, infection was easier to control. Thus, SARS could be controlled by isolating 90% of cases. Since influenza is often transmitted before the onset of symptoms, isolating and tracing prior contacts may potentially control influenza epidemics. However, RNA viruses can evolve fast and the new epidemic strains of SARS could have different epidemic potential and therefore may require re-analysis. Finally, modelling suggests that the isolation practices, which were successful in blocking the SARS outbreak, would be insufficient to control an influenza epidemic.

Many methods and insights from outbreak epidemiology can contribute to the development of control policies. However, this requires effective information systems for communicable disease control as a permanent infrastructure, closer collaboration between academic institutions and service providers on new developments in communicable disease control, and enhanced monitoring of veterinary infections and "minor" zoonoses, particularly in resource-poor settings.

4.5 Round-table discussion on development of SARS vaccines

4.5.1 Could SARS vaccines induce immunopotentiation? (Albert Osterhaus)

Corona viruses (CoV) cause respiratory or enteric diseases in both animals and humans, and are classified into four groups. The SARS CoV belongs to group four and causes respiratory disease in humans.

Several candidate vaccines have been developed to protect against feline infectious peritonitis caused by a feline CoV. Results of immunization were inconsistent, but the vaccines often caused sensitization and enhanced disease upon challenge with wild virus. This sensitization could be transferred through passive immunization with sera, suggesting that it was antibody mediated, but could also be mediated by antibody to the structural protein of CoV. This phenomenon has not been seen with any other CoV.

Immunopotentiation has also been shown in humans vaccinated with formalin-inactivated whole virus vaccines against measles and RSV, both of which include alum as adjuvant. A number of hypotheses have been postulated to explain this phenomenon. Studies have documented that the vaccines induced antibodies with low F-protein neutralizing potential, immune complexes with low avidity, and complement-fixing potential and skewing of cellular immune response to Th2.

Studies have also demonstrated that formalin inactivation leads to the addition of reactive carbonyls to the antigen, which elicit a Th2 bias in the immune response.

Immunopotentiation can be caused by different mechanisms, is not virus specific, and needs different animal models to be demonstrated. One needs to exercise caution in testing formalin-inactivated vaccines, especially among those who might be exposed to wild virus, as there is potential for adding reactive carbonyls that might skew the immune response toward Th2 and possibly enhance disease.

The efficacy and safety of formalin-inactivated SARS vaccines may be investigated using animal models. While ferret and mouse models do not show enhancement of disease following immunization, monkey models appear most promising for studying the potential for immunopotentiation with SARS vaccines. Studies in monkey models are ongoing.

4.5.2 Inactivated SARS vaccine: status of development in China (Yin Hongzang)

Following the recent SARS outbreak, China has made the development of a safe and efficacious vaccine a high priority, and has provided government support for fast-tracking vaccine development. The Chinese FDA has established the requirements for vaccine development with specific guidelines for the development of SARS vaccine.

A phase I clinical trial has been approved and four volunteers have been vaccinated and followed for 14 days. No serious adverse events were reported during this phase. The plan is to include 14 volunteers in the next phase of the study.

Questions remain about the design of phase II and III vaccine trials, the optimal methods to measure safety and efficacy, and the development of alternative approaches such as other inactivated vaccine candidates and ribosomal DNA (rDNA) vaccines.

4.5.3 Development of inactivated SARS CoV vaccines (Marie-Paule Kieny)

Three vaccine manufacturers, using very similar processes (i.e. virus grown in Vero cells and inactivated using beta-propiolactone or formalin) are developing candidate vaccines against SARS.

Manufacturers have shown that the virus can be grown to high titres in tissue culture. The S and N protein can be demonstrated easily in the purified product, and the vaccines induce neutralizing antibodies in primate models. Good correlation has been demonstrated between ELISA and neutralizing antibody titres. In animal challenge models, the vaccines have been shown to induce protection. It is expected that clinical batches will be ready for evaluation by the end of 2004.

4.5.4 Attenuation of SARS CoV for vaccine development (Mark Denison)

Development of SARS vaccines presents several challenges including:

- a history of failure with other CoV vaccines;
- limited understanding of virulence and immunity determinants;
- evolution of the virus;
- risks of growing virus to high titres;
- laboratory-related outbreaks; and
- biosecurity issues.

Attenuated CoV can provide a platform for research and a platform for developing inactivated vaccines. These viruses can also be developed into live attenuated vaccine.

The goals for a research programme for genetic attenuation of the virus are to: (a) target highly conserved sequences or proteins; (b) retain wild-type growth in tissue culture; (c) attenuate (eliminate) virulence and disease; (d) protect against wild-type virus challenge; and (e) prevent reversion or recombination.

Mutations in the cleavage sites and replicase proteins result in mutant strains of virus that will grow to titres similar to wild virus and also induce protection against challenge with wild-type virus. However, a number of issues and challenges remain with the development of attenuated virus strains for research or vaccine development.

4.5.5 Round-table discussion

Points made during the discussion included the points outlined below.

- Concerns were raised about dealing with biosafety for a virus that grows to high titres and the need to maintain a BSL3+ environment. This would be an issue should there be an epidemic requiring high volumes of vaccine.
- What is the market incentive given the great uncertainties? If vaccine manufacturers cannot respond to a world threat, then who can? But in financial terms this doesn't make sense. Registration based on animal protection would certainly be a help.
- SARS should be seen as an opportunity to develop private–public partnership models that would be useful in the future (e.g. pandemic influenza vaccines).

5. New delivery systems for measles and rubella vaccines

5.1 Epidemiology of measles and rubella *(Peter Strebel)*

Measles is an important cause of morbidity and mortality. WHO estimates that there were 610 000 measles deaths in 2002 with a large proportion of the deaths occurring in Africa. WHO and the United Nations Children's Fund (UNICEF) have set a goal to reduce measles deaths by 50% by 2005 (compared to 1999 estimates).

WHO estimates that there were 110 000 congenital rubella syndrome (CRS) cases in 1996. As of 2004, 124 (57%) countries have introduced rubella vaccine in their routine schedule. There is no global rubella eradication goal; however, the Region of the Americas has set a goal to eliminate rubella by 2010.

There are some differences in the epidemiology of measles and rubella:

- measles is more infectious than rubella;
- there is a shorter inter-epidemic interval for measles;
- there is a younger age for measles infection than there is for rubella;
- there is a higher herd immunity threshold needed for measles control than for rubella (measles 92–95% and rubella 83–90%).

There are also some differences in the vaccine schedules, vaccine effectiveness at different ages, and control strategies.

Successful experiences with measles and rubella control and elimination have been documented in different parts of the world. Finland has had a two-dose measles–mumps–rubella (MMR) strategy in place since 1982 with very high coverage and has eliminated measles and rubella. In Albania a catch-up campaign in 2000 and introduction of MR in the routine schedule has greatly reduced measles and rubella transmission.

The implementation of a measles elimination strategy in the Region of the Americas (i.e. "catch-up, keep-up and follow-up") has resulted in excellent progress against measles, and virus genotype D6 has been eliminated from the entire Region. Current challenges for the Americas are measles importations from other regions. For example in 2003 and 2004, H1 genotype imported from Asia has been circulating in Mexico. With the major reductions in measles virus circulation in the Americas, measles surveillance systems have provided important information about the epidemiology and burden of disease of rubella in the Region. With this valuable information, countries have developed appropriate strategies for preventing rubella and CRS. In recent years, many countries of the Region have conducted campaigns among adult males and females with rubella-containing vaccines.

Using a strategy similar to that used in the Americas, major reductions in measles cases and deaths have been observed in southern Africa as well. This strategy is now being implemented in many other African countries with support from the Africa Measles Partnership.

5.2 The need for new tools for measles and rubella control

(Ciro de Quadros and Ana Maria Henao-Restrepo)

Immunization stands as one of the greatest public health achievements of the 20th century. Millions of deaths have been averted, smallpox was eradicated in 1979, polio is on verge of eradication, measles mortality has been dramatically reduced, and about two thirds of countries have eliminated neonatal tetanus.

Current measles vaccine is safe, effective, heat-stable before reconstitution, inexpensive, and has demonstrated efficacy. However, the vaccine must be discarded six hours after reconstitution and, as with other vaccines, there are challenges to overcome regarding safe injections and safe disposal of used syringes and sharps. These problems are more critical during mass campaigns when millions of doses of vaccines are administered in a very short period of time. Alternative delivery systems could help overcome these problems, particularly if they are:

- safe and effective
- cheap
- needle-free
- suitable for currently-available vaccines
- good for both campaigns and routine
- portable and
- pre-sterilized.

There are a number of tools available that facilitate safe and/or efficient vaccine delivery including: auto-disable syringes and safety boxes, Uniject™ for tetanus toxoid and hepatitis B vaccines, combination vaccines, and vaccine vial monitors. In addition, improved waste management and improved monitoring has helped reduce some of the safety issues.

New products that are currently in the pipeline include measles aerosol vaccine and jet injectors.

- Measles aerosol vaccine:
  - successful experiences in trials in Mexico and South Africa;
  - as immunogenic and safe as subcutaneous;
  - ongoing efforts to license by 2007;
  - planned trials in 2004 including phase I trial in India and phase II trial in Mexico.

- Jet injectors:
  - new generation of jet injectors in 2003;
  - safety issues (unable to prove absolute safety and a real, but small risk);
  - WHO is pursuing alternate devices (such as disposal cartridges).

The anticipated impact of improved delivery systems is easier administration and higher population acceptance, thus resulting in higher immunization coverage. The challenges are a) to gather the necessary resources, and b) to create the political will to ensure these new tools are accessible to all.

Discussion

During the discussion that followed, several observations were made.

- There has been great progress towards achieving the 2005 global measles mortality reduction goal.
- Measles is still a high burden in some parts of the world, especially Africa and South and East Asia.
- Excellent strategies exist for controlling measles.
- Great progress has been made in controlling measles in many developing countries. However, measles remains endemic in some developed countries, such as Japan.
- New delivery systems may help to accelerate current measles mortality reduction efforts.
- Although global measles eradication is probably technically feasible, the global goal should be excellent control and mortality reduction, not eradication.
- With improved measles control, rubella emerges as a public health priority.

5.3 Measles aerosol immunization *(Jose Luis Valdespino)*

Aerosol administration for measles vaccines in mass campaigns was first proposed by Dr Albert Sabin. Factors favouring the aerosol route include its:

- non-invasiveness;
- documented immunogenicity in seronegative and seropositive children;
- potential to stimulate local respiratory tract immunity and prevent reinfection;
- better acceptance by the population as it does not require parenteral injection;
- reduction in the risks of cross-infection entailed by parenteral application;
- lower cost; and
- easy administration by non-medical personnel.

The aerosol method using a jet nebulizer and a compressor was designed by Dr Fernandez de Castro. Droplet size is important in aerosol viral vaccination: 1–5 µm particles reach alveolar immune cells. Devices producing particles 2–5 µm include some small volume nebulizers (SVN), some large volume nebulizers (LVN), and ultrasonic nebulizers (USN). Aerosol administration of measles vaccine has been used in mass campaigns in Mexico and administered both as primary and booster dose to nearly four million children, with fewer side-effects reported than those usually observed after subcutaneous vaccination.

Recent studies on school-aged children have confirmed superior immunogenicity at four months after administering aerosol measles vaccination with Edmonston Zagreb vaccine solely, and in combination with rubella vaccine as a booster dose, compared with subcutaneous vaccination with this same vaccine and Schwarz measles vaccine. An evaluation of local immune responses of aerosol measles vaccination in school-aged children demonstrated higher immunogenicity of the aerosol route. Immunological studies in infants aged 12-months have shown that measles-specific T and B cell responses were lower after aerosol than with subcutaneous immunization, indicating a need to use a higher aerosol dose to achieve optimal immunogenicity. Results of studies show that the vaccine is safe, immunogenic and efficacions.

- **Safe:** no serious adverse effects, similar to subcutaneous route.
- **Immunogenic:** (a) induced a response greater than 80% among infants less than 9 months of age; (b) induced a 86–100% response in studies among children at or over 9 months and among school-aged children; (c) provided mucosal and cellular immunity among school-aged children; and (d) had a good response with rubella vaccine.
- **Efficacious:** lower measles attack rate in children immunized using the aerosol route. In the outbreak in Mexico (1988–90), children who had been immunized with aerosol had an attack rate of 0.8% (efficacy of 97%), while those that were immunized subcutaneously had an attack rate of 14% (efficacy of 46%). Among the unimmunized group, the attack rate was 26%.

The Measles Aerosol Product Development Group is advising WHO in the development and licensing of at least one method (vaccine and delivery device) for respiratory delivery of currently licensed measles vaccines. Bench studies have shown that 8–30% of particles from the Mexican jet nebulizer are between 1µ and 3µ and 28–52% between 1µ and 5µ. Studies in juvenile macaques (monkeys) have shown that immunogenicity of the jet-nebulized vaccine is equivalent to that of injected vaccine, but that immunogenicity of ultrasonically-generated nebulized aerosols or dry powder aerosols is limited. No evidence was found for a safety problem associated with aerosol measles vaccination.

Remaining challenges with measles and rubella aerosol vaccination include the following:

- the dose needs to be precisely determined;
- the potential risk of vaccine contamination to family and health personnel surrounding the vaccination site needs to be assessed;
- some vaccine strains show a loss of potency when aerosolized;

- characterization and design of the equipment (nebulizer, compressor) need further work;
- animal studies and clinical trials are needed to assess safety in asthmatic and HIV-infected patients.

The Measles Aerosol Project has developed a workplan for 2002 through 2009 which will include several steps to licensure. A Phase 1a study will take place in India (2004) to determine the safety of live Edmonston Zagreb attenuated measles vaccine given aerosolized to healthy adult males and children (1 to 19 years of age). A Phase II randomized clinical trial to evaluate a number of devices for aerosol measles vaccination will take place in Mexico to compare safety and immunogenicity of two or four devices. It will involve a primary dose given to 12-month-old children and a booster dose to school-age children. Additionally there will be three satellite protocols.

1) Evaluation of aerosol-administered measles viral transmission to health workers participating in vaccination sessions and family contacts.
2) Analysis of potential microbiological contamination of the devices; for example, the risk of vaccine contamination by compressed air input or contamination of mask and spacer by the patient (using the multiple-use nebulizer).
3) Analysis of costs of operation and vaccine administration.

5.4 Round-table discussion on potential safety issues with aerosol delivery of vaccines

5.4.1 Safety of nasal measles immunization (Jacob John)

The continued interest in nasal vaccine delivery lies in its potential to overcome some disadvantages of parenteral inoculation. Immunization of young infants may be desirable in communities where measles occurs early in infancy. Aerosol immunization may be desirable since mucosally inoculated virus may be less likely to be neutralized before primary infection takes place, as illustrated by polio vaccine virus in neonates. In addition, aerosol immunization avoids syringes and needles and this would be advantageous – both for the family (fear of syringes and needles) and for the environment (disposal of plastic and used sharps).

Safety issues to include the points outlined below.

- **The vaccine virus may reach the central nervous system (CNS).** Olfactory nerve endings are exposed to the nasal cavity at the roof of the nose and neurotropic viruses pose a potential hazard. A liposomal (virosomal) inactivated influenza vaccine with *E. coli* enterotoxin adjuvant was given as spray and resulted in an unexpected facial palsy of unknown pathogenesis.
- **Aerosolized measles vaccine could trigger or exacerbate asthma attacks.** Some data suggested that cold-adapted influenza virus may have caused exacerbation of wheeze in asthmatic children under 5 years of age and caused the "oculo-respiratory syndrome" (ORS) in adults. The consequences of respiratory infection in the very young, in the immunocompromised and in chronic disease including asthma, need to be carefully assessed. Vaccines contain excipients, each of which needs to be evaluated for safety of mucosal application.

- **Long-term safety issues.** Safety questions are not only short term but also long term (such as triggering asthma).
- **Environmental risks**. There is a risk of immunizing bystanders and transmitting virus from the vaccines.

In conclusion, the actual need for aerosol immunization deserves further scrutiny.

5.4.2 Potential safety issues with aerosol delivery of vaccines (Beth Laube)

There are several good reasons for vaccinating by aerosol. First, this route of administration eliminates the use of the needle, thus preventing the possibility of spreading blood-borne diseases such as AIDS and eliminating the pain associated with injection therapy. Vaccination by aerosol also follows the natural route of infection of many common diseases. Thus, it induces protection by exposing the airway mucosa to the vaccine, which works well in young children because the persistence of maternal antibodies does not interfere with mucosal immunization.

Thousands of people have been successfully vaccinated with aerosols of live-attenuated strains against measles in Mexico and anthrax, plague, smallpox and tularaemia in the former Soviet Union. However, there are potential risks with this route of vaccination:

- risk of exposing the brain to the vaccinating agent;
- risk to immunocompromised persons;
- risk of exposure to respiratory pathogens from contaminated delivery systems; and
- risk to people with asthma.

The risks associated with this mode of vaccination are low and can be further reduced by improvements in the delivery technology, adequate screening of the patient population, protection of caregivers, and monitoring for possible side-effects after vaccination.

5.4.3 Discussion

During the discussion that followed, several observations were made.

- It may be difficult to determine the time required to administer a dose of vaccine through nebulization. Valved holding chambers (spacers) may not be effective to ensure the delivery of a standard dose. It remains unclear exactly what dose a child receives, and it is important that this is established.
- There is a risk that the delivery device could become contaminated and transmit respiratory pathogens to children who are vaccinated subsequently. However, modern devices include specifications designed to avoid this risk.
- Some studies suggest that aerosol immunization may be effective in overcoming maternal antibodies. Nevertheless, it is important to review the methods used in those studies and ascertain the need to conduct additional ones. Similarly, participants indicated that it is important to review the extent and quality of the data available on primary response to aerosol versus subcutaneous injection.

- A thorough review of the evidence on the safety of aerosol administration is important, particularly regarding special groups such as children with asthma.
- Additional assessment on the merits of delivering powder formulations should be made in light of the identified potential safety issues.
- Public acceptance of new delivery methods needs to be assessed.
- It is important to determine the target tissue for aerosol delivery: there is perhaps no need for vaccine deposition in the alveoli, thus reducing the device requirements and avoiding some of the safety concerns.
- There is a need to gather more information regarding feasibility of aerosol immunization with mumps vaccines.
- Emerging evidence suggest that the Bell palsy observed after immunization with a certain nasal influenza vaccine does not seem to be linked to the adjuvant reaching the CNS. However, it was stressed that careful evaluation of the safety concerns related to the CNS is highly recommended.

5.5 Round-table discussion on status of development of new jet injectors and potential safety problems

5.5.1 Progress with multi-use jet injectors (Darin Zehrung)

Under funding from the Bill & Melinda Gates Foundation, PATH has partnered with Felton International, Inc. in the design development and testing of a new generation jet injector, which utilizes a disposable, auto-disable protector cap. The protector cap is engineered to prevent cross contamination from one patient to the next.

This jet injector has been designed to deliver a fixed dose of 0.5 cc for mass vaccination and eliminates the use of sharps. A study in Senegal demonstrated a high workload capacity (six injections per minute). The device has obtained 510k clearance by the United States Food and Drug Administration (USFDA), indicating that it is as safe as the previously licensed Ped-O-Jet® device. Its main safety characteristic is the disposable protective cap. An in vitro contamination report indicates that it has lower rate of contamination than the Ped-O-Jet. The new design is also interlocking to further prevent risk of contamination. However, the current design requires sterilization at district level or availability of several fluid paths. The Human Subcutaneous Injector (HSI-500) is intended for use in mass immunization campaigns.

Several approaches have been proposed to evaluate the safety of multi-use jet injectors. Initially it was suggested to assess the presence of hepatitis B virus (HBV) instead of albumin, but a recent WHO consultation concluded that none of the methods proposed was robust enough to determine safety. The company has decided to attempt to obtain permission from the local national regulatory authority for a trial to further assess safety. The injector design is near completion (including an "interlock" feature); human clinical safety testing involving high-titre hepatitis-B-infected volunteers is planned for 2004 and 2005. This trial will not present any risk of contamination for the participants.

5.5.2 New high-speed jet injectors for mass vaccination: pros and cons of disposable-cartridge jet injectors versus multi-use nozzle jet injectors

(Bruce Weniger)

There is a long history of using jet injectors for mass campaigns, including during the smallpox eradication effort, yellow fever outbreak control campaigns, and at the start of measles elimination efforts in the Americas. The Ped-O-Jet and many similar devices are filled by suctioning vaccine into their dose chambers. They are capable of 600 to 1000 injections per hour. Because the same nozzle and fluid pathway are used for consecutive patients, existing high-speed devices are classified here as ***multi-use-nozzle jet injectors*** (MUNJIs). Recently the potential of jet injectors has been highlighted in light of bioterrorism threats and on recommendation from WHO and other public health agencies worldwide.

Initial safety concerns around jet injectors were linked to an hepatitis B epidemic in a weight loss clinic in 1980. A Med-E-Jet® MUNJI was implicated in an outbreak of several dozen cases of hepatitis B in California. Subsequent bench studies of it and the more common Ped-O-Jet indicated that their nozzles could become contaminated with hepatitis B virus and pose a risk for transmission between consecutive vaccinees.

Felton Medical International, Inc. (Lenexa, Kansas, USA), with assistance from PATH (Seattle, USA), is applying long-term experience and designs from the Russian MUNJI industry to use a new disposable, auto-disabling safety cap on a new BI-100™ model. A major obstacle for this approach is that there remains no validated in vivo or in vitro methodology of sufficient sensitivity, specificity, repeatability and overall rigour for regulatory review of the safety in order to permit or recommend their use.

D'Antonio Consultants International (New York), with financing from US CDC, is developing a disposable cartridge jet injector system suitable for both high-speed and routine vaccination settings. Its advantages include an auto-disabling disposable cartridge that can be prefilled by the manufacturer, as well as by end-users in the field from multi-dose vials at separate filling stations. Estimated cost for sterile and wrapped magazines is approximately US$ 0.06 per cartridge. Obstacles include convincing manufacturers to prefill vaccines into such cartridges, and ensuring that end-user filling of sterile, empty magazines would be clean and safe.

5.5.3 Discussion

During the discussion that followed, several observations were made.

- An assessment of the potential advantages of using these devices is required. Some participants suggested that jet injectors could be very useful for mass campaigns. Furthermore, the speed of administration is expected to be greater with jet injectors than with needles and syringes. In addition, immunization with these devices may be relatively painless, although pain may also be a function of what is injected – for example greater pain could be expected if the formulation contains adjuvants. Finally, participants recommended an evaluation of whether this potential for increasing reactogenicity would be an obstacle for licensure.
- For pre-filled technology, it is important to estimate the cost of consumables and its impact on the cost per dose. Furthermore, some participants expressed concern because the adoption of the pre-filled technology may need universal

buy-in and this may pose an additional challenge.

- Economic analysis is required, including assessment of what will be the investment costs and the opportunity costs.

Maintenance and reliability of devices, especially with early models, has been an issue. New devices have to be assessed regarding this and provide information on how any issues will be handled.

6. Progress towards vaccines

against HIV/AIDS, malaria and tuberculosis: Overview and highlights

6.1 Update on RTS,S malaria vaccine trials in Mozambique *(John Aponte)*

Three clinical trials with an RTS,S candidate malaria vaccine were conducted in Northern Maputo, Mozambique. Malaria is endemic in this area and has incidence rates that range from 0.13 in children aged 1 to 2 years to 0.08 episodes per person years for children aged 4 to 5 years. *Plasmodium falciparum* accounts for 90% of all malaria infections, and *Anopheles funestus* serves as a major malaria vector.

The first trial was a phase I, safety, reactogenicity and immunogenicity trial of a candidate malaria vaccine RTS,S/AS02A (GSK) in children aged 1 to 4 years. The trial design was controlled, randomized, and double-blind with three intra-muscular injections of RTS,S/AS02A (25 µg) or Engerix-B vaccine as a control at 0, 1, and 2 months. Twenty-seven subjects received all three doses in each group.

The trial demonstrated that a 25 µg dose of the RTS,S/AS02A candidate vaccine is safe with an acceptable level of reactogenicity when administered to children 1 to 4 years of age. Adverse events were infrequent and transient, resolving without sequelae. This candidate vaccine is characterized by good immunogenicity, inducing high titres of antibodies against circumsporozoite protein (CSP) and hepatitis B surface antigen (HBsAg).

The second trial is an ongoing, double-blind randomized controlled phase IIb study to evaluate the safety, immunogenicity and efficacy of GSK's RTS,S/AS02A candidate vaccine (25 µg) with the same vaccination schedule in toddlers and children aged 1 to 4 years in a malaria-endemic region of Mozambique. The primary objective of the trial is to determine efficacy against clinical episodes of *P. falciparum* malaria. The secondary objectives are to evaluate:

- efficacy in reducing severity of *P. falciparum* malaria and anaemia;
- efficacy against infection by *P. falciparum*;
- safety and reactogenicity; and
- immunogenicity as determined by humoral responses to CS and HBs.

The study design includes two cohorts: one cohort (1605 subjects) to determine efficacy against clinical malaria, and the second cohort (417 subjects) to determine efficacy against infection. The current status of the trial is well advanced with 2022 children enrolled, 92% of whom have already received all three doses. So far no safety issues have been identified. The results of this trial were expected in September 2004.

The third trial, also ongoing, is a phase I/II randomized double-blind bridging study to evaluate the safety and immunogenicity of GSK's RTS,S/AS02D formulated into

0.5 and 0.25 ml doses and administered intramuscularly at 0, 1 and 2 months in children aged 2½ to 5 years living in a malaria-endemic region (Manhica district) of Mozambique. The study involves two treatment groups of 100 subjects per vaccine and a control group. The trial is also well advanced: 200 children have been screened and enrolled, all 200 children have already received the first dose, and doses two and three are being given. The expected duration of the trial is 14 months per subject, and the results are expected in June 2005.

6.2 Prime-boost vaccination against malaria *(Adrian Hill)*

Several strategies have been developed to induce T-cell immunity for use in malaria vaccines. The importance of T-cell immunity to protect against malaria is suggested by a number of observations, including: (i) T-cell dependence of protection induced by irradiated sporozites; (ii) T-cell dependence of protection with some subunit vaccines in mice; (iii) T-cell associations with protection in the field; (iv) human leukocyte antigen (HLA) associations with severe cases of malaria.

One approach is based on heterologous prime-boost immunization, using a combination of DNA vaccines and Modified Vaccine Ankara (MVA) vectored vaccines. MVA represents an attractive vector, since it is based on a highly-attenuated strain of vaccine virus b, which has deletions in host range and cytokine genes. It can also replicate in chick-embryo fibroblasts, but not in most mammalian cells, and has an excellent safety record. Immunization sequence could be critical for protection, and primary vaccination with a DNA vaccine followed by an MVA boost may be the best strategy. Other candidate vaccines to be used in combination with MVA were also discussed, including fowlpox (FP9) and adenovirus (Ad5) vectors. These candidate vaccines encoded T-cell and B-cell epitopes that are derived from pre-erythrocytic antigens (ME) and fused to entire thrombospondin-related adhesion protein (TRAP).

These three candidate vaccines, based on MVA, fowlpox and adenovirus, have been individually tested for safety, immunogenicity, and protective efficacy trials in human volunteers, in the Gambia, Kenya and the United Kingdom (Oxford). All were shown to be safe and highly immunogenic, inducing CD4+ and CD8+ immune responses. However, despite high levels of T-cell immunogenicity, inadequate protection was observed with a TRAP-based vaccine. The DNA–MVA combination also resulted in a 78% reduction in parasite burden in the liver, which did not translate into significant field efficacy (<10%) against infection in adults. Recently, the first trial began with a prime-boost approach using a combination of FP9 and MVA ME-TRAP candidate vaccines. Preliminary re-challenge results with this combined vaccination approach showed effective reduction of parasite burden in the liver (up to 86%).

In summary, a number of future challenges were discussed, including the need to develop improved vectors, the use of alternative antigens, and testing different prime-boost combinations in adults and in children.

6.3 Tuberculosis vaccines *(Jerry Sadoff)*

The TB pandemic continues its spread at a rate of eight million annual infections, resulting in approximately two million deaths, every year. It is estimated that the total number of infected people in the world could be as high as two billion. TB together with malaria and HIV represent the major causes of deaths worldwide. Of special concern is a growing number of TB infections caused by multiple drug-resistant strains. It is therefore highly important to promote the development of effective TB vaccines that could be used as part of a more effective strategy to control this pandemic. With the existing sub-optimal vaccines, the vaccination strategies should target different population groups, including non-infected infants, adolescents and adults with latent infection, and, in cases of acute infections or highly infectious individuals, vaccination could be combined with treatment for better and more effective disease control.

The body of scientific data suggests that an effective second-generation TB vaccine could be developed. Data from human immunology indicate that humans with defects in interleukin-12 (IL-12) and interferon-gamma pathways are highly susceptible to TB infection. Animal models demonstrate that TB could be prevented with various vaccine approaches. And finally, by incorporating knowledge and experience gained in the past 20 years, a better choice of protective antigens can be used to develop different candidate vaccines.

The prime-boost strategy for protection against acute infection and disease in infants is being explored. Multiple vaccine candidates are being developed, including BCG, recombinant BCG (rBCG30, rBCGlysO, rBCGlysO/85a/X, RD1 replacement), and live attenuated recombinant TB variants (with double or single PhoP mutations). For the boosting component, several other candidate vaccines are being developed, including recombinant fusion proteins (Mtb72f, 85b/ESAT6, 85a/X, 85b/X) and vectored vaccine candidates (MVA, adenovirus, *Shigella*).

Vaccines targeted at preventing the latent state or reactivation are also under development. These are primarily based on recombinant proteins expressed during the latent state, and delivered in different vector systems (e.g. adeno, MVA and *Shigella*).

Preliminary results from different phase I clinical trials demonstrated safety and immunogenicty of these candidate vaccines. This, together with pre-clinical and animal model data allows for the best candidate vaccines to be tested in further human clinical trials.

In the discussion it was stated that: (a) a moderately effective TB vaccine combined with treatment could result in better control of the TB pandemic; (b) based on 20 years of research experience, the prime-boost vaccine strategy has a great potential, and could be licensed within the next 7 to 10 years; (c) the development of a new candidate vaccine to prevent reactivation may be possible within a timeframe of 10 to 12 years.

6.4 Status of the HIV/AIDS epidemic in Africa *(Daniel Tarantola, on behalf of K.V. Masupu who was unable to attend)*

HIV infection rates are still on the rise in most of sub-Saharan Africa. In 2003 alone, an estimated 3 million people became infected with HIV, adding to the 25 million already infected in the region.

There is no single epidemic in Africa and there are large and widening differences across the continent in levels, trends, and severity of HIV infection. Trends in HIV prevalence in the same antenatal clinics in recent years suggest that the growth of the epidemic levelled off in the late 1990s; however, HIV prevalence has not shown an overall decline in Africa. HIV prevalence in seven southern African countries is more than 17%, and some countries such as Botswana and Swaziland, show an HIV prevalence above 35%.

African women are the most vulnerable population for HIV infection, in particular women from 15 to 24 years old. There is little evidence of an overall decline in this trend. Rural HIV prevalence is considerably lower that the urban, although the magnitude of the difference varies between different countries in Africa.

Most of the African national HIV/AIDS prevention programmes focus on HIV surveillance in representative groups of the general population, but it is equally important to monitor HIV prevalence in special populations with higher risk for HIV infection, such as commercial sex workers. Behaviour-trend monitoring through national household surveys should allow us to better target and improve the existing intervention and education programmes. Further studies on risk factors and determinants of HIV transmission, such as male circumcision, sexual mixing patterns, migration and epidemiology of other sexually transmitted infections are required.

From experience we know that prevention works, and that prevention, care and treatment should go together. What is required is an intensification of all our efforts. Certainly the development of a safe, effective and affordable HIV vaccine will constitute an important complementary tool for existing prevention strategies.

6.5 The Global HIV Vaccine Enterprise *(José Esparza)*

It has been estimated that at least 29 million new HIV infections could be prevented by the year 2010 with greater access to proven HIV prevention tools and information. However, only one in five people worldwide has access to prevention interventions, such as condom use, behavioural change programmes, or treatment of sexually transmitted disease.

The development of an HIV vaccine represents the best long-term hope for the future control of this pandemic, especially in developing countries. However, the medical research largely ignores diseases that kill most people. In the USA, out of US$ 70 billion spent annually on medical research, only 10% is devoted to diseases that cause up to 90% of global illnesses and death. Product development is primarily focused on rich countries and, out of 1400 drugs approved by the USFDA in the last 25 years, only 20 were specifically relevant for diseases that affect people in developing countries.

Efforts to develop an HIV vaccine should be greatly increased. The creation of a new Global HIV Vaccine Enterprise, which has recently been endorsed by G8 countries, represents a new opportunity to address multiple challenges for the

development of an HIV vaccine. The rationale behind the Global Enterprise is the urgency of the pandemic, very high costs related to product development, risks associated with scientific failures, and the need to develop new strategies for collaborative partnerships. In addition, new scientific opportunities are emerging that need to be harnessed.

The Global Enterprise concept is based on three basic principles:

- a new way of thinking about the problems by formulating shared strategic plans;
- a new way of acting to solve problems by using common tools and optimized resources; and
- a new way of behaving as a global community by sharing information, deferring to evidence rather than advocacy, and establishing a correct balance between collaboration and competition.

The Enterprise represents an alliance of independent agencies, including leading research agencies such as France Agence National de Recherche sur le SIDA (ANRS), the UK Medical Research Council (MRC), and the US NIH, and various HIV vaccine research groups – e.g. International AIDS Vaccine Institute (IAVI) – universities, pharmaceutical and biotech industry, developing countries, and international organizations and communities such as the AIDS Vaccine Advocacy Coalition (AVAC), the European Commission (EC), the European and Developing Countries Clinical Trials Partnership (EDCTP), UNAIDS and WHO.

Over the past six months, the Global Enterprise has developed an initial scientific plan covering the following areas:

- vaccine discovery
- product development
- manufacturing
- laboratory standardization
- clinical trial capacity
- regulatory issues and intellectual property.

The scientific plan was reviewed and endorsed by the Steering Committee of the Global Enterprise in May 2004.

At present the Global Enterprise is further developing its structures, mechanisms and operations. Four major functional groups will be established:

1) the coordinating committee to ensure guidance and coordination of the overall effort

2) expert action groups to further develop a more specific scientific plan

3) funders' group to comprise traditional and new funders; and

4) annual stakeholders to provide a mechanism for feedback and dialogue

In conclusion it was emphasized that the Global HIV Vaccine Enterprise is not a new organization, but rather an alliance of independent partners. The Enterprise is a programme of the global HIV vaccine community where the Melinda and Bill Gates Foundation is currently serving as a convener and secretariat.

6.6 European and Developing Countries Clinical Trial Partnership: first partnership projects *(Piero Olliaro)*

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

In the area of vaccines, the EC is addressing two major challenges by: (a) supporting research projects to develop new and promising vaccine approaches and candidate vaccines, and ensuring their accelerated progress through pre-clinical development and human testing in early phase I trials; and (b) developing a programme to support phase II and III clinical trials in Africa. The latter challenge is being addressed by the newly created European and Developing Countries Clinical Trials Partnership (EDCTP) (comprising EU Member States plus Norway, developing countries, other donors and industry in a joint effort to combat poverty-related diseases).

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

The overall aims of the EDCTP are to:

- increase the effectiveness of Europe's investment in clinical trials for

interventions against poverty-related diseases;

- attract more resources for the development of these interventions;
- accelerate the development of candidate products and their processing through the development pipeline; and
- improve the capacity and capability of developing countries to test the efficacy of these interventions.

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

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

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

The EDCTP is financially supported by EU countries, the 6th Framework Programme for Research, and the private sector (foundations and industry). The organization has an overall budget of €600 million for five years. EDCTP activities will be supervised by an EDCTP Partnership Board represented by the EC, European States, developing countries, scientists, and private industry.

In 10 years the success of the EDCTP will be assessed by:

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

In 2004, EDCTP has already issued calls for proposals/tenders in the following areas: drugs (July 2004), clinical trial registry (July 2004), senior fellowships (July 2004), vaccine and microbicides (November 2004) and ethics (under discussion).

7. Discussion and summary

of the 2004 Global Vaccine Research Forum

(Meeting Co-Chairs and Secretariat)

The 2004 Global Vaccine Research Forum in Montreux, Switzerland, covered the most relevant aspects of vaccine development, the application of new vaccines, and technology transfer to developing countries. The following is a summary of what was discussed.

The forum began with an update on pneumococcal conjugate vaccine, which contains a mixture of protein-conjugated polysaccharides of the serotypes causing most paediatric invasive pneumococcal infections, and has had a major public health impact in the United States. Invasive pneumococcal disease rates have fallen dramatically in vaccinated children, but also a herd effect has been seen in the elderly, with a 30–50% reduction in disease. The American vaccine contains seven serotypes, but a nine-serotype vaccine has also been shown to be efficacious in South Africa. Interestingly, reduction of pneumonia after vaccination is only 20%, suggesting that much of that disease, when caused by pneumococcus, is not bacteraemic. Nevertheless, the herd effect, which is probably related to reduction of pharyngeal carriage of pneumococci, suggests that paediatric vaccination may reduce mortality in the elderly.

The possibility that serotypes not in the vaccine will replace those prevented by vaccination is being carefully watched. There is some evidence for it with respect to otitis media and pharyngeal carriage, but so far the increased incidence of those serotypes has been small.

Rotavirus continues to be a major cause of diarrhoeal morbidity, accounting for over 400 000 deaths in developing countries. The withdrawal of previously licensed vaccine in the United States due to temporally-associated intussusception represented a major setback in ameliorating this disease. Fortunately, two new vaccines – one containing five reassortants of bovine rotavirus and human serotypes one through four, and the other consisting of a single attenuated human type-one strain – are in late stages of phase III trials. The latter vaccine has already been licensed in Mexico, and both should be available soon in other countries. Although neither vaccine appears to be a risk factor for intussusception, post-marketing surveillance is of paramount importance. The fact that at least one vaccine is already licensed in a transitional country such as Mexico may prompt other developing countries in the Region to accept the vaccines on the basis of risk–benefit ratios, even in the presence of known or unknown risks.

In the past, only major, developed-country manufacturers produced new vaccines largely because manufacturers in developing countries had not had the technical capability, facilities and regulatory supervision to compete. That situation is changing

as technological expertise is spreading and capital becomes available. The GAVI initiative to introduce combination vaccines in developing countries has had two important effects. On the one hand, developing countries are assuming a greater role in the procurement of their own vaccines; and, on the other hand, as developing country manufacturers adopt WHO-approved good manufacturing practices and scale up production, they are rapidly becoming major players in vaccine manufacturing. Seven developing country manufacturers now sell vaccine to UNICEF, and 20 others are attempting to reach WHO-approved standards. Nevertheless, there is still a problem with regulation in many countries.

Vaccine manufacturers in developing countries have formed an organization with the aim of exchanging information, providing training, and facilitating technology transfer from major manufacturers. Examples of successful transfer include North–South partnerships such as one between Brazil and Europe, as well as South–South collaborations such as one being carried out by Cuba and India. Cuba has invested considerable effort to create a well-developed virtual vaccine company with technologically-advanced ability to do research and development.

It is noteworthy that more developing countries are sharing responsibility for financing vaccine programmes along with partners and donors. Countries are also showing considerably more interest in procuring combination vaccines, which generally result in higher coverage rates and reduced wastage; however, global availability of combination vaccines and their relatively high cost still represents a challenge in many developing countries.

WHO is evaluating alternative vaccine-delivery systems. While the parenteral route has been the most commonly used system of delivery, it is recognized that there are potential advantages to the oral route, the intranasal route, the transcutaneous route, and the aerosol route. Following pioneering work by Albert Sabin with aerosol delivery of measles vaccine during the 1989 to 1990 pandemic, Mexican investigators have accrued significant experience with aerosol delivery of both measles and rubella vaccines alone and in combination. High seroconversion rates have been demonstrated after using aerosol measles in mass campaigns and the measles–rubella vaccine in field trials. WHO is now studying this means of vaccination, in particular by evaluating modern aerosol devices that would combine better delivery and greater safety from contamination. Induction of asthmatic reactions will have to be carefully evaluated. Although jet injectors have been previously discredited for safety concerns, new devices that incorporate shields and disposable cartridges are being evaluated.

Influenza remains a worldwide problem. Annual epidemics occur in virtually all countries, and the possibility of a pandemic looms persistently. The greatest threat at the moment appears to be the adaptation of avian influenza strains to replicate in human tissues. Although the avian viruses have, up to now, not acquired the ability to attach to human glycoprotein cell receptors, only a few mutations would be necessary for that to happen. Attempts are being made to develop experimental vaccines against H5, H7 and H9 strains, but success has been variable. In any case, in the event of a new pandemic, tremendous increases in vaccine production will be necessary, and there are insufficient manufacturers for the task. Moreover, the volumes of vaccine necessary will almost certainly entail switching from production in embryonated chicken eggs to production in tissue culture.

The Global Vaccine Research Forum provided attendees with updates on the state-of-the-art in vaccine development against malaria, TB and HIV/AIDS. Regarding malaria vaccines, three clinical trials with an RTS,S candidates malaria vaccine are being conducted in Mozambique. In addition to these three trials, several strategies have been developed to induce T-cell immunity for use in malaria vaccines.

The TB pandemic continues its spread at a rate of eight million annual infections, resulting in approximately two million deaths every year. The body of scientific data suggests that an effective second-generation TB vaccine is possible. Two strategies, one based on prime-boost technology for protection against acute infection and disease in infants and another targeted at preventing the latent state of reactivation, are under development. Based on 20 years of research experience, the prime-boost strategy has great potential and could be licensed within the next 7 to 10 years. Developing a new candidate vaccine to prevent reactivation may be possible within a timeframe of 10 to 12 years.

In 2003, in sub-Saharan Africa, an estimated 3 million people became infected with HIV, adding to the 25 million already infected in the Region. African women are the most vulnerable population for HIV infection, in particular women from 15 to 24 years of age. The development of an HIV vaccine represents the best long-term hope for the future control of this pandemic, especially in developing countries. The creation of a new Global HIV Vaccine Enterprise, which has recently been endorsed by G8 countries, represents a new opportunity to address multiple challenges for developing an HIV vaccine. The Enterprise encourages shared strategic plans and a new way of acting to solve problems by using common tools and optimized resources.

In response to the pandemics of HIV/AIDS, TB and malaria, the EC is committed to supporting research projects to develop new, promising vaccine approaches and candidate vaccines, and ensuring their accelerated progress through pre-clinical development and human testing in early phase I trials. The EC is also developing a programme to support phases II and III clinical trials in Africa through the EDCTP.

The Global Vaccine Research Forum reached the goals it aimed to achieve by successfully analysing the current status of vaccine R&D against AIDS, malaria and TB; identifying opportunities for vaccine R&D within WHO/IVR; reviewing new vaccine technologies; reviewing opportunities and bottlenecks in vaccine R&D and introduction; and helping shape the global R&D priorities.

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