Proceedings of the Eighth Global Vaccine Research Forum and Parallel Satellite Symposia

Institut Pasteur, Paris, France
29 June–2 July 2008

Immunization, Vaccines and Biologicals
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Immunization, Vaccines and Biologicals
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>Aeras</td>
<td>Aeras Global TB Vaccine Foundation</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>APC</td>
<td>Antigen-presenting cell</td>
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<tr>
<td>ARI</td>
<td>Acute respiratory infection</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette Guérin (vaccine)</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention (Atlanta, GA, USA)</td>
</tr>
<tr>
<td>CHAVI</td>
<td>Centre for HIV Vaccine Immunology</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-mediated immunity</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CTB</td>
<td>Cholera Toxin B subunit</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic T lymphocyte (CD8+)</td>
</tr>
<tr>
<td>CVP</td>
<td>Children’s Vaccine Program (USA)</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<tr>
<td>DHF</td>
<td>Dengue haemorrhagic fever</td>
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<tr>
<td>DHHS</td>
<td>Department of Health and Human Services (USA)</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOMI</td>
<td>Diseases of the most impoverished (Program)</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly-observed treatment short-course (TB)</td>
</tr>
<tr>
<td>DTP</td>
<td>Diptheria-Tetanus-Pertussis vaccine</td>
</tr>
<tr>
<td>EC</td>
<td>European Community</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric mean titer</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HA</td>
<td>Haemagglutinin</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenzae type B</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
</tr>
<tr>
<td>ID</td>
<td>Intra-dermal (route)</td>
</tr>
<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IM</td>
<td>Intra-muscular (route)</td>
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IP  Intellectual Property (rights)
IPV  Inactivated polio vaccine
IVI  International Vaccine Institute (Seoul)
IVR  Initiative for Vaccine Research (WHO)
JE  Japanese Encephalitis
MAb  Monoclonal antibody
Men A  Meningococcus serogroup A
Men B  Meningococcus serogroup B
MDR  Multiple drug-resistant (TB)
MHC  Major Histocompatibility Complex
Mt b  Mycobacterium tuberculosis
NA  Neuraminidase
NAb  Neutralizing antibody
NGO  Non-governmental organization
NIAID  National Institute of Allergy and Infectious Diseases (USA)
NIH  National Institutes of Health (USA)
OPV  Oral polio vaccine
PAHO  Pan-American Health Organization
PATH  Program for Appropriate Technology for Health (USA)
PEP  Post-exposure prophylaxis (rabies)
PPD  Purified protein derivative
PS  Polysaccharide (capsular)
QC  Quality control
R&D  Research and Development
RIG  Rabies Immunoglobulin G
RV  Rotavirus
SARS-CoV  SARS coronavirus
SBA  Serum bactericidal antibody
SCID  Severely compromised immunodeficient
STI  Sexually-transmitted infection
TB  Tuberculosis
TOC  Test-of-concept (trial)
TT  Tetanus toxoid
UNAIDS  United Nations Programme on AIDS
UNICEF  United Nations Children’s Fund
VLP  Virus-like particle
VRC  Vaccine Research Center (NIH, USA)
WHA  World Health Assembly
WHO  World Health Organization
YF  Yellow Fever
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1. Highlights of recent WHO activities on the research and development of new vaccines

Moderator: Alice Dastry
Speaker: Marie-Paule Kieny

1.1 Global progress in access to immunization

The years 2007-2008 have seen increased and global momentum on child survival initiatives. Indeed, as the clock is ticking and reminding the world that half time has passed in the race towards achieving the Millennium Development Goals (MDG), measurement of performance shows that a number of targets are at risk, and in particular those related to MDG4, which aims at reducing by half the number of deaths in children under 5 years of age. Therefore, and although significant progress has been made with under 5 mortality rates falling for the first time below 10 million per year, international immunization partners and donors are mobilized to ensure that prevention of death due to infectious diseases are maximized to contribute to MDG4. The recent past has demonstrated that this contribution is likely to be major, as exemplified by the achievements of measles control programs, which brought down measles deaths from 757,000 in 2000 to 242,000 per year in 2006.

Also very encouraging is the progress on immunization process indicators, with DTP3 (diphtheria-tetanus-pertussis third dose) coverage on track to reach the GIVS (Global Immunization Vision and Strategy) goal of 90% in 2010 in several WHO regions, although difficulties in the South-East Asian region still threaten attainment of the goal at the global level. Advancement is also startling with introduction of Haemophilus influenzae B (Hib) vaccine, which increased from 64 countries in 2000 to 150 countries in 2008 (vaccine introduced or soon to be with GAVI funding), including 61 countries with less than US$1000 GDP.

Moreover, advances have been made in the area of financial sustainability, thanks to the decrease in tetravalent (DTP-HepatitisB) vaccine price following entry on the market of new producers (from over 1.2$ in the early 200’s to 0.7$ in 2007). A similar effect is expected starting in 2009 for pentavalent (DTP-Hepatitis B-Hib) vaccine.

Finally, the new vaccines’ pipeline has further expanded, giving hope that many new products will be available for introduction into immunization programmes, which will be crucial for decreasing the burden of deaths due to communicable diseases. Some of the new advances in which WHO are particularly involved are discussed below.
1.2 New vaccines research, development and introduction

**Meningitis A.** Several MenA-containing conjugate vaccines have been developed in the recent years, or are close to coming to the market, which offers hope for eliminating epidemic Meningitis A as a public health problem in the African Meningitis Belt. These include conjugate tetravalent Men A/C/Y/W135 vaccines from Sanofi Pasteur, Novartis Vaccines and GSK, as well as conjugate bivalent Men A/C and monovalent Men A vaccines from Chengdu Institute of Biological Products in China. The Meningitis Vaccine Project, a WHO-PATH partnership, which intends to facilitate and promote the development of meningococcal A conjugate vaccines for Africa, is coming close to its objective, with a monovalent MenA vaccine manufactured by Serum Institute of India moving towards registration for use among 1 to 29 year-olds, with an extension intended in infants. The introduction of this vaccine is planned in Burkina Faso in 2009 through mass vaccination campaigns, with an introduction price of US$ 0.40 /dose. It is envisaged that this vaccine will be deployed throughout the Meningitis Belt over the period 2009-2015 thanks to funding by GAVI.

**WHO Measles Aerosol Project.** This project, financed mainly through a grant from the Bill and Melinda Gates Foundation, intends to license at least one method (vaccine and delivery device) for respiratory delivery of currently licensed measles vaccines. The new product needs to be safe, immunogenic, inexpensive and easier to administer than injection. It will use standard attenuated measles vaccine, with the same dose, the same vaccination schedule, and same use recommendations.

Following completion of Phase I age descalation in India, determination of optimal usability and logistics characteristics of the device, down-selection of potential vaccine/device combinations, the measles aerosol vaccine will enter pivotal clinical trials in India in 2009, with a plan to seek licensure in this country in 2011.

**Product Research and Development: the Global Adjuvant Development Initiative (GADI).** This initiative is being launched by IVR because broader availability of potent adjuvants could greatly accelerate development of vaccines, but a lack of knowledge and know-how in the public sector, as well as issues of comparability, safety and access, are hampering these developments. The proposed Initiative will comprise a research centre in Switzerland to evaluate, optimize and develop adjuvants using standardized readouts, generate new scientific knowledge and innovation. The GADI center will also create and share public sector expertise and provide vaccine formulation services for public sector. During 2007 and 2008, analysis of Intellectual Property Rights and Freedom to Operate in this area were conducted, interested groups of users of new adjuvants were identified (to constitute the AdjuNet network), and funding options were reviewed with major research funders.
1.3  Pneumococcal vaccine AMC: Target product profile

The Advance Marketing Commitment (AMC) concept is based on a financial commitment by donors to subsidize vaccine purchase at a set price, provided it meets a specified target product profile and is in demand by GAVI-eligible countries with the goal of motivating increased supplier participation and investment to accelerate the introduction of life-saving vaccines in the world’s poorest countries. A group of donors have selected in 2007 conjugate pneumococcus vaccines for a pilot AMC. In order to implement the AMC, WHO was entrusted to set up the vaccine’s Target Product Profile (TPP), as defined in the AMC framework document. The TPP sets the required minimal public health performance standards for AMC eligibility, such as effectiveness in target populations; safety, reactogenicity, contra-indications; dose-scheduling; compatibility with available delivery systems; and product presentation, stability and packaging.

Through a consultation process held throughout 2007, IVR proposed a draft formulation of a consensus TPP, which was then endorsed by the WHO Strategic Advisory Group of Experts (SAGE) and approved by WHO Director-General. Finally, the TPP was communicated to the AMC secretariat at GAVI. This TPP specifies, *inter alia*, that the pneumococcus serotypes included in the vaccine must cover at least 60% of the invasive disease isolates in the target region, and must include serotypes 1, 5 and 14, that dosage schedule should be compatible with the EPI schedule and consist of not more than 3 doses in the first year of life, that the product must be presented as mono-dose (vial or auto-disposable syringe) or on low multi-dose presentations with a Vaccine Vial Monitor (VVM), must be stable at 2-8°C with a shelf-life of at least 24 months, and be WHO pre-qualified.

1.4 Ethics of vaccine clinical trials

Two important guidance documents on the conduct of preventive clinical trials were prepared and published in several languages. A specific training workshop is being prepared to ensure proper dissemination.
1.5 WHO prioritization of vaccine-preventable diseases

The objective of the project was to prioritize or categorize vaccine-preventable diseases by public health priority in order to provide guidance to WHO Member States, partners, and industry on which diseases to prioritize activities. Diseases under consideration were 15 diseases for which vaccines are currently licensed and available (but not routinely recommended or widely used) and three diseases for which vaccines may be available (licensed) by 2012.

The methodology used was based on a “Rational consensus” decision-making method. Structured input was first sought from the global health community and experts on diseases and criteria used to make public health priorities. The figure below illustrates how the respondents ranked the various priority criteria.

Following this first phase, the 18 diseases were evaluated through the 10 above quantitative or qualitative criteria. Combining the two phases generated the following global level disease prioritization:

- **Very high priority**: malaria, pneumococcal disease
- **High priority**: cervical cancer (HPV), cholera, dengue, influenza, Japanese encephalitis, meningococcal disease (groups ACYW135), rabies, rotaviral enteritis, typhoid fever, yellow fever
- **Medium priority**: hepatitis A, hepatitis E, meningococcal disease (group B), mumps, rubella, varicella
A similar exercise will be conducted at regional levels to assess whether priorities are different from those determined at the global level.

In summary, there is in 2008 a rich pipeline of new or near market vaccines, which have potential for making a significant impact on MDG-4. The immunization community needs to finish the agenda with Hep B and Hib vaccine introduction, and to prepare for the introduction of pneumococcal, rotavirus and other vaccines. This will significantly increase the cost of immunization but there are now new opportunities for financing, like the AMC. Nevertheless, clear decision-making pathways to make informed and rational choices on vaccine introduction should be in place for use by countries.
2. Keynote address:
The long quest for an HIV vaccine

_Moderator: Tony Nelson  
_Speaker: Seth Berkley, IAVI, New-York, USA_

In the 25 years since HIV was identified by Luc Montagnier, Françoise Barré-Sinoussi and Jean-Claude Cherman’s group at the Pasteur Institute as the virus responsible for AIDS, the HIV vaccine field has known remarkable achievements as well as dramatic set-backs. The year 2007 was a particularly challenging one, as it saw the interruption of the Phase IIb TOC trial of the Ad5-vectored experimental HIV vaccine from Merck & Co, which proved ineffective and caused increased susceptibility to HIV infection in Ad5-preimmune volunteers. Although many had questioned the potential for this vaccine to provide significant protection, especially in view of the mediocre results obtained in nonhuman primate models, this was a sad blow to the field.

The announcement that the trials were interrupted have lead some to question whether an AIDS vaccine is realistically feasible and whether funding these efforts should be continued. One should not forget however that in pharmaceutical R&D, including vaccine R&D, failure is the rule and not the exception and is part of the pathway towards success. Although the Merck vaccine trial was a failure, we have learnt a lot from this trial, the outcome of which has moved the field into new directions, for example by leading to realize that the current assays used to measure cell immunity were misleading, and that results based on the use of HIV/SIV (SHIV) hybrid viruses in nonhuman primate models cannot be trusted.

The field of AIDS vaccines has only recently reached a critical threshold of resources and efforts. As of today, there only have been two AIDS vaccine candidates fully tested in Phase III clinical efficacy trials in the field, the gp120-based candidate vaccine developed by Vaxgen and the Ad5-HIV vaccine developed by Merck. A third candidate, the ALVAC-vectored vaccine developed by SanofiPasteur and combined with Vaxgen gp120 is still undergoing testing. We think that it is now even more imperative than before to work toward a new generation of vaccine candidates with capabilities to go beyond those currently tested. For example, we believe that a protective vaccine will need to block the virus at its site of entry, implying the need to elicit broadly HIV-neutralizing antibodies. We also believe that we will need to develop a new generation of T-cell vaccines that elicit more potent, durable, and mucosal site-specific cellular immune responses. This could necessitate the use of replicative vectors or other approaches.
Given the difficulty of the science and the challenge in front of us, we do not know how long it will take to develop an efficacious HIV/AIDS vaccine. We do know however that protection from HIV can be achieved by immunological processes, whether through humoral or cellular immune mechanisms. We therefore are quite optimistic that effective vaccine protection can be achieved. As a result, we believe that the next great milestone in HIV vaccine development will be the demonstration of vaccine-induced immune protection in humans. Whether such protection can be turned into a simple, cost-effective, durable and broad-based vaccine will then have to be determined. We know from history that perseverance and long-term commitment are absolutely necessary in that endeavor.
3. Session I: Pandemic influenza vaccine research and development

Moderator: Malik Peiris
Rapporteur: Laszlo Palkonyay

The continuous circulation and recent global spread of H5N1 avian influenza virus strains with pandemic potential and the associated human cases present a continuous threat to world health that needs to be addressed urgently. Influenza vaccine development and implementation are critical elements of pandemic influenza preparedness. Compared to highly effective vaccines such as polio, hepatitis B or measles, present influenza vaccines are relatively little effective. Therefore improvement of today’s vaccines or development of new vaccines with higher efficacy is an urgent task in the context of preparation for an eventual pandemic. The session provided a short summary of the ongoing global surveillance activity regarding influenza virus circulation and vaccine reference strain preparation, prototype pandemic vaccine clinical trial activity, and emerging novel concepts of seasonal and pandemic vaccine development.

3.1 Avian influenza surveillance (Keiji Fukuda)

The vast majority of human cases of avian influenza have been caused by H5N1 strains, but historical evidence shows that other virus strains such as H7N2, H7N3, H7N7 or H9N2 can also cause disease in humans. Since 2003, highly pathogenic H5N1 strains were isolated from wild birds or poultry in more than 60 countries. In 2007, the last complete calendar year, 29 countries reported H5N1 influenza outbreaks in poultry. This number fell to 18 countries during the first half of 2008, suggesting that veterinarian containment measures were beginning to show effectiveness. On the other hand, H5N1 strains were re-detected in poultry in many countries, possibly due to re-appearance and/or recurrence of the virus, although the exact mechanism allowing the virus to reappear remains elusive. H5N1 influenza virus has now been entrenched in poultry for five consecutive years in at least 5 countries: Bangladesh, China, Egypt, Indonesia, and Viet Nam.

At the date of the conference [end June 2008], 385 confirmed cases of human H5N1 influenza infection had been reported to the WHO including 243 deaths distributed in 15 countries on three continents. All age groups were affected from 3 months to 81 years of age, with the highest number of cases observed in the younger than 40 years-old group. The median age of the patients was 20 years. The main risk factor for human H5N1 disease was primary exposure to infected poultry, but human cases were not always linked by time or space with outbreaks in birds, as occasional human-to-human transmission cases were also documented. No circulation of H5N1 virus strains among humans was however detected.
Since 1997, the H5N1 virus underwent extensive genetic evolution, leading to the emergence of 10 different genetic clades in birds. Strains belonging to several of these clades jumped the avian-human species barrier. This extensive genetic drift mandates continuous surveillance and ongoing selection of H5N1 reference isolates for vaccine development through reverse genetic technology. At least 12 H5N1 reference strains already are available or are waiting for regulatory approval, representing multiple isolates belonging to clades 1, 2, 3, and 4. Additional H5N1 reference strains are also under development. The existence of this registry of international reference strains is the result of continuous collaborative efforts coordinated by the WHO. Reference strains for influenzaviruses with pandemic potential other than H5N1 are also available through WHO, namely H2N2, H5N3, H7N1, and H9N2.

The possibility that in the future H5 virus strains increase their transmissibility potential among people still exists. Therefore the WHO strongly emphasizes the importance of continuous pandemic preparedness.

3.2 Candidate H5N1 pandemic influenza vaccines (Linda Lambert)

Clinical trials of H5N1 prototype pandemic influenza vaccines were discussed under a historic perspective with emphasis on the remarkable progress achieved in the development of these vaccines during the last few years. After the first human cases of H5N1 influenza were detected in humans in Hong Kong in 1997, surrogate approaches were sought such as a H5N3 duck virus vaccine or a recombinant baculovirus-expressed H5 haemagglutinin subunit vaccine. After the reemergence of H5N1 virus in Asia in 2003, reverse genetics based reassortants were developed for producing experimental H5N1 pandemic prototype vaccines. Reverse genetics technology was also used to produce live attenuated prototype H5N1 influenza vaccines which now have entered clinical trials as well.

H5N1 vaccines manufactured through established seasonal vaccine technology, i.e. split or subunit non-adjuvanted products, resulted in an unacceptably low-level antibody response. Another challenge was the finding that with reverse genetics derived H5N1 vaccines, haemagglutination inhibition (HI) assays were not sensitive enough to accurately measure antibody responses. This led to modify the HI test through the use of horse blood cells, which increased the assay sensitivity, or to use alternative, more cumbersome methods such as the microneutralization test. To overcome the low immunogenicity of inactivated H5N1 vaccines, two basic approaches were used that proved to be very successful: adjuvantage of split/subunit vaccines with oil-in-water adjuvants; and the development of whole-virion vaccines with or without aluminium salts. Several manufacturers have reported clinical trials with pandemic prototype vaccines: Baxter (Austria): whole virus vaccine without adjuvant; GlaxoSmithKline Biologicals (Belgium, Germany and Canada), Novartis (Italy, Germany and the United Kingdom of Great Britain and Northern Ireland) and Sanofi Pasteur (France and USA): split vaccines with oil-in-water adjuvants; Microgen (Russia): A/Leningrad duck H5N2 live attenuated vaccine; IOMAI (USA): patch-delivered H5 haemagglutinin; Novavax (USA): VLPs; MedImmune (USA): live attenuated ca reassortant vaccine; as well as Biken, Denka-Seiken, Kitasato and Kaketsuken, a consortium of four manufacturers (Japan), Omninvent (Hungary), Sinovac (China): whole-virion vaccines with alum, and CSL (Australia), Solvay (The Netherlands): split/subunit vaccine with alum. All the vaccines tested so far showed acceptable adverse event profiles.
Antibody responses to these candidate vaccines depended on the type of the vaccine, the dose of antigen, and the presence or absence and the nature of the adjuvant. Thus, aluminum salts showed only mediocre or no adjuvant effects on traditional split or subunit vaccines. Whole-virion vaccines were capable to generate high antibody titers with a low antigen dose with or, in one case, without aluminum salts; the antibodies elicited by these vaccines showed cross-neutralizing activity against drifted H5N1 virus strains. Split or subunit vaccines adjuvanted with oil-in-water adjuvants were able to generate high antibody responses even with low antigen amounts, demonstrating a remarkable antigen dose-sparing effect. The antibodies they generated were cross-reactive, cross-neutralizing in vitro and cross-protective in animal models against drifted H5N1 variant strains. In humans, no advantage was demonstrated for alternative intradermal or sub-cutaneous immunization routes versus the usual intramuscular administration route, at least at the doses evaluated in the trials.

In order to explore the possibility of stretching the supplies of stockpiled H5N1 vaccines, the US Department of Health and Human Services plans to presently fund “mix and match” clinical studies with a stockpiled split vaccine without adjuvant that will extemporaneously be mixed with oil-in-water adjuvants. The stockpiled H5N1 split vaccine was produced by SanofiPasteur and will be adjuvanted with either MF59 from Novartis or AS from GSK, respectively.

In summary, there is at this time an unprecedented global vaccine development effort to meet the pending pandemic challenge. This effort also serves a number of critically important purposes such as 1) gaining experience in developing genetically modified H5N1 reference viruses and their testing reagents, 2) logistics of large scale manufacturing, 3) evaluating antigenically matched and imperfectly matched vaccines for their ability to prime and boost immune responses, 4) assessing immune enhancement strategies and vaccine delivery systems, and 5) stimulating research and development of novel vaccine approaches that may provide broader and longer lasting protection in the more distant future.

### 3.3 Novel influenza vaccine concepts (Albert Osterhaus)

Regarding vaccine-based responses to an influenza pandemic using currently approved vaccines, there are three important domains which require a coordinated approach: 1) the response time from the declaration of an eventual influenza pandemic to the release of the appropriate pandemic vaccine should be kept at a minimum; 2) vaccine production capacity need to be increased; and 3) human trials with H5N1 prototype vaccines should be continued and encouraged.

One important breakthrough of the last few years has been the impact of oil-in-water adjuvants on the antigenicity of split H5N1 influenzavirus vaccines. In general, except perhaps in the elderly, seasonal influenza vaccines do not require the presence of an adjuvant. In contrast, due to their inherent low antigenicity in immunologically naïve populations, pandemic H5N1 vaccines do require adjuvantation, whose beneficial effects can be seen in 1) antigen-sparing, 2) priming for an anamestic immune response, and 3) enhancement of the breadth of vaccine-elicited antibody protection as measured by cross-clade immunogenicity and cross-clade protection among the different clades of the H5N1 virus.
Hypersensitivity reactions in vaccinees following reexposure to the virus has been a theoretical concern for alum-adjuvanted whole-virion pandemic influenza vaccines. The concern came from the past experience with alum-adjuvanted, formalin-inactivated paramyxovirus vaccines in the sixties, when vaccinees exposed to the virus presented severe hypersensitivity reactions due to a TH2-skewed immune response to the vaccine. However, experiments in monkeys using a formalin-inactivated alum-adjuvanted split H5N1 vaccine showed that the vaccine was protective against homologous virus challenge without generating hypersensitivity reactions. These results are in line with decades long post-marketing surveillance data with alum-adjuvanted whole-virion seasonal influenza vaccine which confirm that a formalin-inactivated influenza vaccine in combination with an alum adjuvant is safe.

Of great importance is the demonstration that H5N1 viruses from other clades than the vaccine strain were neutralized by post-immunization sera collected from participants in the clinical trials of the oil-in-water adjuvanted split H5N1 pandemic prototype vaccines. These findings suggest that properly adjuvanted pandemic vaccines might be protective, at least to a certain degree, against different clades of the pandemic virus. Recently published animal data also support that conclusion, showing that cross-clade protection was achieved in ferrets against lethal challenge with H5N1 virus following immunization with an oil-in-water adjuvanted split virion vaccine.

The development of novel, future vaccines is a more complex task that requires identification of new target antigens and better knowledge of correlates of protection against influenza disease. Questions addressed in that field are numerous, such as: Is it possible to develop a «universal» influenza vaccine that would not need yearly immunization through the use of the influenza virion M2 protein or other structural proteins? Do antibodies against neuraminidase (NA) play a role in the protection provided by flu vaccines? Is the NA antigen less prone to drifting than the HA antigen, as there are only 9 known NA subtypes versus 16 HA subtypes? What role does cellular immunity play in protection against influenza? Is it possible to document vaccine-induced cross-protective immunity between different influenza virus subtypes? Can influenza vaccines provide sterilizing immunity or do they only provide clinical protection?

Among novel influenza vaccines under development are DNA vaccines, live attenuated influenza virus (LAIV) vaccines, live vectored vaccines, virus-like particles (VLPs), and peptide-based vaccines. Some of the vectored vaccines seem to be promising for longer term development. Similarly, live attenuated vaccines (LAIV), which already are in use against seasonal influenza, also appear to be promising pandemic vaccine candidates.
3.4 The importance of the fight against pneumococcal pneumonia
(Keith Klugman)

There are good scientific reasons to believe that pneumococcal vaccination would play an important role in the fight against a flu pandemic. The temporal association between peaks of seasonal influenza and peaks of mortality due to pneumococcal pneumonia is well documented. Pneumococcal pneumonia in humans follows RSV, influenza and probably other viral seasonal respiratory infections, leading to greatly increased morbidity and mortality every year. Studies in the mouse model have shown that the administration of a non-lethal dose of influenza virus followed seven days later by that of a nonlethal dose of *Streptococcus pneumoniae* results in 100% mortality in the animals. This did not happen when the two pathogens were administered in the reverse order, nor if one used mice that were double-negative for IFN-gamma, demonstrating the role of the cytokine response, especially IFN-gamma, that is elicited in the lung by the influenzavirus infection.

In a double-blind randomized pediatric trial, vaccination with the 7-valent pneumococcal conjugate vaccine (PCV) Prevnar™ prevented pneumonia associated with a wide range of viral respiratory pathogens. Children who received the PCV vaccine and developed laboratory-confirmed influenza were at 45% less risk of hospitalization due to influenza-associated pneumonia than unvaccinated controls. This suggests that the majority of influenza-associated pneumonias in children are due to pneumococcal super-infection. Pneumococcal conjugate vaccines (PCV) should therefore be used to prevent the occurrence of clinical pneumonia due to *S. pneumoniae* super-infection of influenza.

The analysis of the 1918 influenza pandemic also suggests the existence of a pathogenic synergism between influenza and pneumococcal infection. In contrast to prevailing ideas, more than 80% of the deaths due to the pandemic occurred seven days or more after the onset of symptoms, whereas, in more than 80% of cases, uncomplicated influenza resolves in less than 6 days. In autopsy studies of the victims of the 1918 pandemic, pneumococcus could be detected in the lung or heart blood of 60% to 90% of the victims. Records show that among 216 blood cultures taken from soldiers hospitalized with influenza pneumonia in 1918, *S. pneumoniae* was isolated in 46% of cases.

Scandinavian data on the 1968 influenza pandemic also show that *S. pneumoniae* was the most common bacterial pathogen identified from nasopharyngeal and respiratory specimens from flu patients. Identification of pneumococcus was associated with increased duration of fever, higher incidence of pneumonia, leukocytosis, CRP and ESR. These data suggest that pneumococcal conjugate vaccines might significantly reduce the morbidity and mortality associated with viral respiratory infections including pandemic influenza.
3.5 Optimization of pandemic vaccine distribution (Maarten Postma)

Limited supply of vaccines is a practical issue that public health officials have to face time after time during vaccine shortage crises. Also when epidemiologic considerations suggest a need to widen vaccine coverage or to introduce a certain vaccine into a new age cohort, the available vaccine supply is a significant, if not determining factor in the final decision taken by decision makers.

Current forecasts predict that in the case of a future influenza pandemic, there would be a significant gap between potentially available vaccine supply and international demand. It should be emphasized that based on experience from the three pandemics of the last century the actual mortality during the next pandemic is highly unpredictable, not to mention the difficulties to predict actual effectiveness of future pandemic vaccines. These two uncertainties make attempts at modeling optimization of pandemic vaccine implementation a difficult challenge. Nevertheless, prioritization of vaccine recipient groups will be different at the beginning and during the course of the pandemic. At the onset of a pandemic, vaccination is needed in priority for the most exposed groups, where incidence of the disease is the highest, whereas at later times, priority will go to groups with highest risks of complications.

3.6 Strengthening influenza vaccine production capacity in developing countries, a WHO project (Laszlo Palkonyay)

In order to strengthen pandemic-influenza preparedness and response, the Fifty-eighth World Health Assembly (WHA 58.5, Agenda item 13.9, 23 May 2005) asked the World Health Organization (WHO) Secretariat to seek solutions with international and national partners, including the private sector, to reduce the global shortage of influenza vaccines for both influenza epidemics and pandemics, including development and licensing of antigen-sparing vaccine formulations. Following this request, a consultation was held on 2-3 May 2006 in Geneva, Switzerland, which paved the way to the launching in November 2006 of the WHO Global Pandemic Influenza Action Plan (GAP) to increase vaccine supply. One of the three main identified approaches in the GAP document was to increase production capacity through building new vaccine production plants both in industrialized and developing countries.

In line with the GAP recommendations IVR created in February 2007, with significant support from the Department of Health and Human Services of the USA, the Government of Japan, and the Asian Development Bank, a seed fund to support influenza vaccine production capacity building in developing countries. Support to the selected manufacturers includes training, technical support, purchase of manufacturing equipment and/or direct financial help for the establishment of manufacturing infrastructure and processes. Three main approaches have been identified for the establishment of a new influenza vaccine facility: 1) construction of a filling/finishing facility that will depend on purchase of bulk product from established manufacturers; 2) complete technology transfer from a well established manufacturer; and 3) progressive acquisition of technology by the new producer with the help of expert consultants.
Six developing country manufacturers were awarded grants for an amount of approx. 2.0 million USD each to develop processes for the production of inactivated or live attenuated seasonal and/or H5N1 influenza vaccine or to establish filling facilities utilizing imported antigens. These are Bio Farma, Indonesia; Birmex, Mexico; Butantan, Brazil; Government Pharmaceutical Organization (GPO), Thailand; Institute of Vaccines and Medical Biologicals (IVAC), Viet Nam; and the Serum Institute of India (SII). Experimental H5N1 vaccine lots are now under production in Brazil and, pending regulatory approval, trivalent seasonal vaccine lots produced in Indonesia should be tested in clinical trials during the summer of 2008.

Technology transfer from industrialized country vaccine manufacturers has been limited so far to Butantan (Brazil), Bio Farma (Indonesia), and Birmex (Mexico). Another challenge the grantees are facing is the limited availability of qualified personnel at their sites. In order to respond to these challenges IVR established in December 2007, with the support of the Netherlands Vaccine Institute (NVI) and the Dutch Government, a platform (a “hub”) for future transfer of standard robust influenza vaccine production technology to developing countries. In order to obtain regulatory approval, NVI will be conducting clinical trials with the developed new vaccine produced under this agreement. Starting in 2009, the NVI hub will provide a technology platform for transferring a single robust production process with relevant documentation (SOPs, batch process records, validation procedures, analytical methods and release criteria); a technology package transferable without IPR hurdles to interested developing country vaccine manufacturers upon request (and possibly against fees), as well as complete transferable technology for egg based inactivated whole-virion influenza vaccine production.

These projects have met with broad interest from other developing country manufacturers as well, such as Argentina, Egypt or Islamic Republic of Iran to mention a few.
4. Session II.
Improving access to immunization

Moderator: Mary Kitambi
Rapporteur: Godwin Enwere

4.1 Access to immunization out of the Expanded Programme of Immunization (EPI) (Seth Owusu-Agyei)

The department of Health and Human Services (DHHS) has set up a site at Kintampo, in the middle of the Ghana belt which hosts a population of 150 000 persons. Another 450 000 population are followed up for maternal mortality. About 16 000 babies are born each year in the belt and are thoroughly followed up through a strict registration system.

The DHSS site has been used for various drug and vaccine trials including measles vaccine, malaria RTS,S vaccine and malaria drug trials, and as a sentinel site for assessment of EPI coverage and validation of data from routine reports. This covered the age of infants and children at the time of vaccination as well as factors that may impact vaccination coverage, such as education of the caretaker, negative perception issues (“unclean needles”, excessive waiting time…), operational issues (unavailability of vaccinators, insufficient vaccine supply…) and social issues (unfriendly health workers).

Immunization outside of the EPI is the best strategy for introduction of new vaccines and for implementation of additional vaccination efforts through national immunization days, home visits and mop-up campaigns. Introduction of new vaccines can better be done in such a setting, in addition to the EPI rather than within the frame of the EPI. This however requires adequate funding, sufficient staff, cold chain facilities and additional amenities such as transportation.

4.2 Community participation in health and the national vaccination campaigns in Nicaragua, 1980-2008 (Juan Jose Amador)

Nicaragua has a population of 6 million inhabitants, and a yearly average birth rate of 140 000 babies. A total of 65 vaccination campaigns have taken place over the past 28 years, 39 between 1980 and 1992, 20 between 1993 and 2002, and 6 since 2003. The success of the campaigns was mostly due to the fact that they encouraged community participation and the involvement of health “brigades”. Their number has progressively been decreasing due to the improvement in the National Health System and effectiveness of systematic vaccination delivery and also the costs of running the campaigns.
The advantages of the National Immunization campaigns is that they cover a high percentage of children, offer opportunities for education and training, allow for interaction with and within communities and provide a possibility of reaching children in remote areas with difficult access where there are no permanent health personnel. The campaigns use “brigades” composed of highly motivated volunteers from defense committees, community movements, community boards, citizen power councils and NGOs and involve about 1% of the general population at any time. Another goal for the National Immunization campaigns is that they cater to the distribution of vitamin A, antihelminthic drugs, oral rehydration salts and iron supplementary diets.

The main disadvantages of the campaigns are their cost as well as the fact that they mobilize health workers to the point that they become entirely devoted to the campaign and are not available to care for other needs.

The campaigns however have been a success as judged by the fact that 90% of children are vaccinated, and that polio was eradicated in 1981, diphtheria in 1994, measles in 1995, and rubella in 2005. There also has been a significant reduction in pertussis and tetanus incidence in the country.

4.3 Public Health versus individual protection (Paul Fine)

According to the “games theory”, an individual vaccination strategy would be to convince everyone else to be vaccinated, whereas a Public Health strategy would be to convince everyone to be vaccinated for common good. In the United Kingdom of Great Britain and Northern Ireland, a TV documentary on possible neurological complications following pertussis vaccination led parents to refuse vaccinating their children, resulting in a dramatic increase in the incidence of pertussis cases. This highlights the dilemma between individual perception of the benefit of vaccination and the government responsibility for encouraging vaccination or even making it compulsory.

It can be useful to define certain terms such as Vaccine efficacy, that refers to individual protection against the targeted disease in trial conditions; Vaccine effectiveness, which relates to individual protection in normal conditions of vaccination of the population; Direct effect of vaccination, which is the risk reduction provided by the vaccine in the population, and equates, in other words, vaccine effectiveness multiplied by percent vaccine coverage; Indirect effect of vaccination, which is the vaccine-induced reduction of disease transmission in the overall community; and Total effect of vaccination, which is the sum of its direct plus indirect effects.

The benefits of vaccination are multiple, disease eradication being the ultimate health benefit vaccination can provide. Thus, smallpox eradication prevented millions of deaths and saved the world more than 50 billion USD. However, in spite of about 12 billion USD already spent in a major effort to eradicate polio, it remains unclear if the disease will be eradicated and when. Other benefits of vaccination include reduction in mortality, at times even greater that can be attributed to the vaccine alone, as observed in the case of measles; improvement of implementation of the cold chain; improvement in management skills in the country; increase in national surveillance efficacy; and immunization serving as a platform for other health interventions such as the distribution of vitamins or IPT. Disadvantages of vaccination include the cost of the vaccine and associated costs as well as the possibility of adverse events related to vaccination.
Immunization policies vary with the national ethical, social and political context. Thus countries such as Canada, Sweden or the United Kingdom of Great Britain and Northern Ireland favor voluntary vaccination policies whereas countries such as France, Belgium or Italy favor mandatory vaccination policies. In some countries such as Austria, Australia, Poland and the USA, incentives are at the parental level, whereas in countries such as Ireland and the UK, incentive is mostly placed on health workers.

The aching question that remains is that of the implications of these policies for the sharing of responsibilities and for the issue of compensations.

4.4 Are user fees desirable? (Aparnaa Somanathan)

The benefit of vaccination is not specific to individuals or points in time as vaccines provide long-term immunity, prevent the spread of diseases in the general population and often can elicit herd protection. The impact of user fees on immunization can be analyzed by plotting the price of the vaccine versus immunization coverage and factoring social marginal benefits and costs. This shows that user fees increase the marginal costs to users, increase financial barriers, and lead to reduced immunization coverage. Available data show that the poor are more sensitive to user fees and that abolition of user fees generates increased utilization of health facilities by the poor. There also is no evidence to suggest that user fees will improve providers’ motivation. On the contrary, it can create perverse incentives and lead to under-the-table payments.

Typical net user fee contribution amounts to less than 5% of government recurrent health expenses, which is far from sufficient to meet the US$ 11 billion – 15 billion funding gap in immunization, not counting administrative costs. The alternative is to improve the efficiency of health spending and to increase prepaid sources of health care financing via taxes and insurances. User fees also cannot reduce volatility in public funding. The alternative is to invest in budget planning and resource management capacity at the level of the Ministry of Health and at that of health facilities.

In conclusion, there is a strong case for public financing of immunization, as user fees are likely to lead to under-utilization of vaccines. The impact of user fees on the revenue is in any case too limited to be of much help. This is why there currently is a strong tendency to move away from user fees for health services in general. Thus, DFID wants it abolished, WHO sees its abolition as part of the poverty reduction efforts, and the World Bank wants it abolished but under conditions.

It was highlighted in the discussion that it was difficult to assess the impact of user fees on immunization, as immunization is free in most countries. Individual choice probably impacts more deeply immunization programs, at least in places where immunization is on a voluntary basis. There nevertheless are available data on the negative impact of user fees on other aspects of health care. The issue of vaccine liability was also raised and it was admitted that it could have a negative effect on vaccination. It was thought that scientists should be more proactive in the spread of information and the dissemination of knowledge, especially in regard of the huge impact a single negative report in the press can have on acceptability of vaccination, as seen in the UK example.
5. Session III.
New tuberculosis vaccines

Moderator: Jelle Tholle
Rapporteur: Ulli Frith

5.1 Epidemiology of tuberculosis (TB) and potential impact of new vaccines (Christopher Dye)

Vaccination is expected to make a major contribution to the goal of eliminating tuberculosis from the world by 2050, but the mode of action and possible impact of new vaccines are still unclear. In 2006, there were 9.2 million TB cases and 1.7 million deaths due to TB in the world. The incidence of TB in Africa, which increased 200% during the 1990s, appears now to be stabilizing. The same tendency is observed in Europe, where TB incidence had increased by 30% in the 1990s. In the other WHO regions (SE Asia, Western Pacific, Eastern Mediterranean and Americas) incidence rate is also falling, albeit slowly. The millennium development goal that applies to TB is “to have halted and begun to reverse incidence”, with the reference year being the 1990 figures. The WHO strategy for treating TB, the so-called “DOTS”, has been implemented in over 30 million cases worldwide, resulting in treatment success close to the target of 85% and case detection over 60% (2005 target: 70%). Nonetheless, the incidence of multiple drug-resistant tuberculosis (MDR-TB) and in particular of extensive-resistant strains (XDR-TB) is alarmingly increasing worldwide. The impact of DOTS will therefore not be sufficient to reach the 2050 goal of eliminating TB as a public health problem, defined as less than 1 annual case of TB per million population.

With regard to vaccines, the only currently available TB vaccine, Bacillus Calmette-Guérin (BCG), is credited with an efficacy of 52% but the actual protection it provides varies considerably according to settings and to end-points. Better TB vaccines will be needed to reach the millennium development goal. Some of these vaccines will be given in the context of routine vaccination programs and others to more or less everyone through mass vaccination campaigns. Modeling suggests that pre-exposure vaccines, that are given to neonates and ideally prevent infection, will be most useful as an addition to drug treatment for TB patients when the detection rate of active TB cases is low. By contrast, post-exposure vaccines, which stop progression from latent to active TB, have a relatively small impact when used alone but act in synergy with the treatment of active disease. In this context, it is unlikely that elimination of TB will be possible by 2050 without a combination of treatment of active cases and prevention of infections using post-exposure vaccines, thus drying out the pool of potential future active cases. No new TB vaccine is likely to be used in a stand-alone fashion, but will be part of a comprehensive TB control approach, comprising detection, prevention and treatment strategies.
5.2 Antigen selection for TB vaccines (Jerald Sadoff)

The natural history of TB infection and disease offers several potential goals for vaccination, such as vaccines to prevent infection, vaccines to prevent acute or early disease in the infected, vaccines for the prevention of latency, and vaccines for preventing the reactivation of latent TB. Ideally, a vaccine antigen should be active in more than one type of TB infection. Despite the absence of defined surrogates of protection, and indications that both antibody-based and cellular immune mechanisms may protect against TB, cell-mediated immune responses remain the “canonic” type of protective responses against TB. This hypothesis is based on many observations, such as increased frequency of TB in the case of interferon (IFN)-gamma-receptor mutations, reactivation of latent TB under TNFalpha antagonist and antibody treatment, as well as increased TB reactivation in HIV positive individuals undergoing decline of CD4+ T cells. Antibody-mediated mechanisms may also play a role, as Mycobacterium tuberculosis (Mtb) is covered by a large carbohydrate-based capsule and may secrete proteins involved in dissemination beyond the lung. Selection of potential antigens uses criteria such as expression during distinct phases of the “life cycle” of Mtb, protective efficacy when used as a vaccine in animal models (mice, guinea pigs, and nonhuman primates), and immune recognition by humans that are actively infected or who present with non-progressive latent infection.

Aeras has undertaken in collaboration with the Israel Institute of Biological Research a bioinformatic analysis to select potential TB vaccine candidates. From 3989 open reading frames from the Mtb genome, 189 candidate antigens were first selected based on a combination of 11 criteria such as role in survival in macrophages, hypoxic (intracellular) survival, secretion, or dormancy, as well as immunogenicity and efficacy when used as a vaccine. By applying several rounds of increasing stringency, a total of 45 top-ranked vaccine candidates were finally identified, 32 of which were also identified in an antigen-screening program performed in the context of one of the “Grand Challenges” projects (GC6). Thirty of the 45 antigens are related to latency or reactivation processes. These latency/reactivation antigens are particularly interesting as potential components of future post-exposure vaccines, and are currently evaluated in animal models. Only clinical efficacy trials will allow establishing their value as vaccines in humans.

5.3 TB subunit vaccines (Peter Andersen)

Subunit vaccines against TB are being designed as add-ons or boosters to neonatal BCG which will most likely remain the cornerstone of TB vaccines for the mid- to long-term. Three types of BCG booster vaccines are currently being considered: those that are to be administered together with BCG, or at the same time; those that will be given as an “early” booster immunization, i.e. a few weeks or a few months after BCG vaccination; and those of the “late” booster type, which will be given later in childhood or in early adolescence. Several subunit vaccines have now been extensively evaluated in animal models and found to provide efficient protection - equivalent or superior to BCG - against Mtb challenge. The most advanced of these vaccines, such as the ESAT6-Ag85B or the TB10.4-Ag85B fusion proteins, are now in clinical trials where their safety and immunogenicity look very promising. Current focus is on evaluating the potency of different adjuvants, as well as the influence of routes of immunization and prime-boost regimens on optimal expression of immunity in the lung, boosting of BCG and maintenance of immunological memory.
Vaccines to be used as “late” BCG boosters would typically be administered post-exposure to latently infected individuals. Since current vaccination strategies fail to activate T cell clones against antigens that are expressed in the chronic or latent stage of the disease, an intensive search is ongoing to identify latency-related Mtb antigens. To that end, the “grand Challenges” team that is trying to develop a post-exposure TB vaccine has developed in vitro criteria to mimic the different stages of the natural history of TB. This research indicates that starvation-related antigens may be promising post-exposure vaccination candidates. Interestingly, several of these starvation-induced antigens are located on the Mtb genome region referred to as RD11, which BCG lost during its selection process. This might at least partly explain the inability of BCG to control TB latency. Combining early and late antigens into multi-stage subunit vaccines has provided encouraging initial results with regard to both preventive as well as post-exposure protective efficacy in animal latency models.

5.4 Development of viral-vectored tuberculosis vaccines (Adrian Hill)

Many new TB vaccine candidates are currently being developed, using a broad variety of vaccine delivery systems. Two of the most advanced vaccine candidates, which already are in clinical trials, are live recombinant vaccines based on the use of viral vectors: Aeras 402, which is based on an adenovirus 35 (Ad35) vector (sponsored by the Aeras Global TB vaccine Foundation); and MVA85A, a Modified Vaccinia Ankara (MVA) virus recombinant, which has been developed at Oxford University. MVA85A has been shown to provide better protection than BCG against Mtb challenge in nonhuman primates as well as against M bovis pulmonary challenge in calves.

Initial safety studies of MVA85A were performed in healthy, BCG-naïve adults in the United Kingdom of Great Britain and Northern Ireland. Subsequently, safety trials were done in BCG-primed and HIV-co-infected individuals, in both the United Kingdom of Great Britain and Northern Ireland and in several African countries. Trial objectives included dose-escalation, age de-escalation (adults-adolescents-children-infants) and evaluation of safety and immunogenicity of the vaccine in people who were latently infected with TB or coinfected with HIV and TB. No severe vaccine-related adverse events, no signs of immunopathology and only mild local and systemic reactions were reported. High and sustained Antigen 85A-specific immune responses were induced by a BCG prime -MVA85A boost vaccination regimen, with highly polyfunctional antigen-specific CD4+ T cells responses. Interestingly, peak and plateau immune responses were independent of the interval between priming and booster vaccinations (from 1 month to 18 years). A Phase II clinical trial is currently under way in South Africa. In HIV+ individuals, immunogenicity of MVA85A was found to be unchanged and importantly, no change in CD4+ T cell counts nor in HIV viral loads were observed. In summary, MVA85A was safe and immunogenic in all cohorts tested so far and induced high level of antigen 85A-specific T cells of a polyfunctional, non-terminally differentiated phenotype. The first phase IIb (preliminary efficacy) trial of the vaccine is planned to commence in the Western Cape province of South Africa in late 2008 or early 2009 on 16 weeks-old infants vaccinated with BCG at birth.
5.5  Old and new live vaccines against tuberculosis (Brigitte Gicquel)

Amongst the TB vaccines which have been evaluated for efficacy in humans to date, only BCG or live mycobacteria of the Mtb complex like \textit{M. microti} confer protection against TB. Extracts of mycobacteria of the Mtb complex or killed mycobacteria do not protect against TB. BCG provides efficient protection only against the severe forms of tuberculosis in children, but not, or at least no reliably against pulmonary TB in adolescents and adults. Therefore, new vaccines that could be used in addition to BCG or replace BCG are being investigated. New live vaccine candidates are being developed using different approaches, including genetically modified BCG strains that express major Mtb antigens or genes from other bacteria that may modify the immune response. Rational attenuation of Mtb has also been used to generate new live attenuated vaccine candidates, such as auxotrophic mutants or the PhoP/PhoR (regulatory) “knock-outs”, which provide high level protection in several animal models.

The utilization of live vaccines has always been an ethical issue due to the risk of vaccinating immunocompromised individuals whose exposure/immune status is unknown at the time when they are vaccinated. However, because TB continues to be a leading cause of death worldwide, live vaccines are major initiatives whose cost/benefit remains remarkable.

5.6  BCG vaccination induces different immune responses in European and African populations: implications for the design of new tuberculosis vaccines (Hazel M Dockrell)

There is clear evidence that protective efficacy provided by BCG varies with geographic locations. Many of the new TB vaccines which are being developed are designed to either improve the BCG vaccine or to boost the immunity induced by BCG. However, the factors that are responsible for the variable efficacy of BCG may also affect these new vaccines. It would therefore be very useful to understand why BCG vaccination provides such variable protection.

Response to BCG was measured in young adults and infants in Malawi and the UK, using a 6 day IFN-gamma release assay on diluted whole blood cultures stimulated by PPD. In Malawian adolescents and young adults, BCG vaccination did not enhance IFN-gamma responses 12 months post-vaccination compared to pre-vaccination. This is in contrast to the marked increase seen in UK vaccinees, most of whom were non-responders prior to vaccination. Although newborn infants should not have been exposed to environmental mycobacteria prior to vaccination, Malawian infants did not develop as strong IFN-gamma responses as the UK infants. A number of factors that might affect immunogenicity of BCG vaccination were investigated. The only factor that showed an association with the strength of the INF-gamma response to PPD after BCG vaccination was season of birth. These studies highlight the importance of obtaining a better understanding of how BCG vaccination induces and maintains immunity in different settings, in order to design improved vaccines to fight TB.
6. Session IV.
Update on vaccines against GAVI priority diseases

Moderator: Vitaly Zverev
Rapporteur: Marie-Pierre Preziosi

6.1 Overview

In terms of vaccine research and development, important questions discussed concerned the validation of correlates of protection, how accurately can thorough and standardized evaluation of immunogenicity predict vaccine effectiveness, the need for studying pathogen carriage to assess potential herd immunity and the overall validity of results. Key issues in terms of new vaccine introduction are the determination of optimal immunization schedules, policy and regulation, advocacy and communications, monitoring of vaccine safety, evaluation of vaccine effectiveness and programmatic and financial sustainability. These issues were discussed through a series of presentations that dealt with meningococcal vaccines, rotavirus vaccines, Hib vaccine, pneumococcus vaccine and the introduction of new vaccines in developing countries with financial support from the GAVI Alliance.

6.2 Nearing success: the development of an affordable Group A meningococcal conjugate vaccine for elimination of epidemic meningitis from Africa (Simonetta Viviani)

Through a public-private partnership that includes the WHO, PATH and the Bill and Melinda Gates Foundation, the Meningitis Vaccine Project has succeeded in developing an affordable new Group A meningococcal (MenA) conjugate vaccine which already has been tested in a Phase I trial in India, Phase II trials in Mali and The Gambia, and a Phase II/III trial in several sites in India and Africa. The vaccine induced 4-fold increases in MenA bactericidal antibody titers in 78% to 96% of vaccine recipients, with GMTs much higher than those elicited by non-conjugated PS vaccines. The new MenA conjugate vaccine should now soon reach licensure and will be introduced at the price of US$ 0.40 per dose in the countries of the African meningitis belt where it will be used to eliminate MenA meningitis epidemics from Sub Saharan Africa. Key issues to be addressed in the near future concern the design of adequate and high quality post-licensure studies in terms of monitoring vaccine safety and vaccine effectiveness, including validation of correlates of protection. This will require sustained surveillance efforts and the thorough development of standard protocols in countries where the vaccine will be introduced.
6.3  **Progress in the development of Group B meningococcal vaccines**  
* (Elizabeth Miller)

An acceleration in the development of Group B meningococcal (MenB) vaccines has been observed in the last few years and several candidate vaccines are now in clinical trials. Outer membrane protein PorA-based vaccines, presented as an outer membrane vesicle (OMV), were shown to induce strain-specific bactericidal antibodies and were successfully used in several countries to eliminate MenB epidemics caused by an homologous MenB strain with the same PorA sequence. Field experiences in Norway, Cuba and Brazil, and, more recently New Zealand, have allowed to determine that the best correlates of protection against MenB is the serum bactericidal antibody titer determined in assay using human complement (hSBA).

A number of new candidate vaccines are currently in development, including a nonavalent vaccine with 9 PorA antigens that cover 80% of the MenB strains. An ‘universal’ MenB vaccine was developed by the reverse vaccinology approach, i.e. the identification in the MenB genome of gene sequences that encode putative surface proteins: the candidate vaccine is made of several such genome-derived proteins that are highly conserved between meningococcal strains (h HBP1-1, Nad A, Gar A2132) combined with a PorA antigen and delivered in the form of OMVs. Other MenB vaccines in development include a purified recombinant Factor VIII-binding protein (rLP2086 vaccine) that induced close to 90% seroconversion against five serologically different subfamilies of MenB strains; as well as a novel recombinant OMV vaccine developed by the down-and-up regulation approach. If these protein vaccines happened to work against both MenB and other meningococcal groups, they could constitute an universal meningococcal vaccine. At this time however, efforts are hampered by the variability of the hSBA assay, which requires considerable standardization efforts before it can be used in a reliable fashion.

6.4  **Rotavirus vaccines in the developing world: update on clinical trials in Africa and Asia**  
* (Kathy Neuzeil)

The newly introduced rotavirus (RV) vaccines are expected to save more than 200 000 lives every year. Several questions however remain which hamper the acceleration of their introduction into developing countries. This has to do with the observation that live oral vaccines often perform fare less well in developing countries than in industrialized countries. Additional efficacy trials of RV vaccines in African and Asian countries are therefore needed to assess vaccine efficacy in a context of wide diversity of serotypes and to help define optimal doses and schedules.

Phase III vaccine efficacy trials are underway in representative populations in Africa (Mali, Ghana, Kenya, Malawi and South Africa) and in Asia (Bangladesh and Viet Nam) under public-private partnerships, testing RV vaccines in co-administration with Expanded Programme on Immunization (EPI) vaccines, including OPV. Interim analysis results in South Africa show close to 83% protection against severe RV disease and 66% protection against any severity disease at 7 months after vaccination in a setting where multiple serotypes of rotavirus circulate. Even if RV vaccines were to show lesser efficacy in the developing world as compared to the industrialized world, their use would still be highly beneficial to public health as most of the deaths due to RV disease occur in Africa and Asia. Post-licensure effectiveness studies will be additional important sources of information for public health benefit.
6.5 Rotavirus vaccine introduction in Latin America and the Caribbean: status and lessons learnt (Jon Andrus)

As early as 2006, five South American countries, Brazil, El Salvador, Nicaragua, Panama, and Venezuela introduced the RV vaccine in their official childhood vaccination program. Three more Latin American countries have now followed. This is a remarkable example of the accelerated introduction of a new vaccine into the national immunization programs of developing countries, which was made possible through regional partnership. It emphasizes the importance of communication and advocacy and of building policy and regulation, implementation capacities, and financial sustainability. The use of the PAHO revolving funds was a precious asset in ensuring sustainability of national programs. Economic studies, partnerships and surveillance networks, together with the development of standard procedures were key components in the introduction of the vaccine. The importance of surveillance still remains paramount to evaluate the overall vaccine effectiveness, its tolerance, the cost-effectiveness of different doses, and the eventuality of serotype replacement. The possibility of reducing the administration of the vaccine to a single dose is yet to be confirmed. Matters are made more difficult by the fact that the 2 newly available RV vaccines show different presentations, different administration schedules and different messages on age indication limits in different package inserts. Recommendations for harmonization of the age indication window for both products are under way.

6.6 The Hib initiative: update and lessons learnt (Rana Hajjeh)

Accelerating *Haemophilus influenzae* type b (Hib) vaccine introduction in developing countries follows a similar pattern to that of the RV vaccine introduction. The Hib Initiative has focused its action on three areas: communication, research and coordination of partners. This already led to a rapid increase in adoption of Hib vaccines in GAVI eligible countries, which was facilitated by recommendations and policy development, increase and diversification in vaccine supply, and establishment of co-financing mechanisms. Standardization of information, enhancement of surveillance and vaccine impact monitoring all contributed to these progresses. Remaining questions comprise the need for a booster dose and a careful economic evaluation in developing countries. The experience of the Hib vaccine introduction can be an useful model for the introduction of other new vaccines into developing countries. It clearly shows that delay in introducing new vaccines into these countries is not justifiable, as while there are many obstacles, none are insurmountable. The importance of awareness of the magnitude of the disease burden and of the vaccine efficacy among public health professionals and decision-makers, as well as the power of a focused communication strategy in the context of overall child survival cannot be overemphasized.
6.7 What serotypes cause pneumococcal diseases among children around the world (Kate O’Brien)

A comprehensive assessment of disease-causing Streptococcus pneumoniae serotypes in children less than 5 years of age is underway at a regional and global scale. Preliminary results show that in all regions a limited set of less than eleven serotypes account for 50% to 80% of disease, with seven serotypes accounting for 66 to 76% of disease globally. Africa and Asia share the same top eight serotypes. Serotype 14 is the most common serotype in all regions, while serotype 1 is the most common serotype in Africa and Asia among children over two years of age. Actually, serotype 14 is the most prevalent among 0 to 23-month olds while serotype 1 dominates among 24 to 59-month olds. The currently available 7-valent pneumococcal conjugate vaccine is estimated to cover 50% to 75% of disease-causing serotypes in children under 5 years of age, corresponding to the prevention of 480 000 deaths every year. The 10- and 13-valent vaccine formulations will cover more than 75% of serotypes causing disease in children, with less regional variability than the 7-valent vaccine, and could theoretically save 700 000 and 750 000 lives every year, respectively.

Questions remain, however, concerning a possible bias introduced by the over-representation of hospital strains and the limited data from important countries such as China, India, Indonesia and Nigeria. The USA experience with S pneumoniae serotype replacement has shown that complete colonization replacement occurs after vaccination but is accompanied by only a small increase in the rate of replacement disease, except in the case of otitis where replacement disease was often observed. Aside from the existing PS vaccine formulations, substantial efforts are being made to develop pneumococcal protein vaccines, or combinations of protein and capsular vaccines, that could overcome the question of serotype variability.

6.8 Expanding GAVI’s portfolio (Julie Kallenberg)

Accelerating the introduction of new vaccines remains a key objective for GAVI, which is currently studying how to support the introduction of new vaccines that are expected to be licensed and available in the 2007-2010 Strategic Plan period. GAVI’s support for immunization in developing countries initially focused, in the period 2000-2005, on introducing underused vaccines such as Hepatitis B, Haemophilus Influenzae type b (Hib) and Yellow Fever vaccines. The vaccine landscape became increasingly complex during GAVI’s second phase of operation (2006-2011), with new prioritization needs emerging. In 2006, pneumococcal and rotavirus vaccines were added to the list of newly introduced vaccines. In 2007, the focus was on measles vaccine campaigns and the constitution of polio vaccine stockpiles.

A new comprehensive strategy is now being developed for the upcoming five years (2009-2013) to ensure the best use of available resources, maximize impact and best inform all stakeholders. The strategy includes prioritization of vaccines, implementation plans and associated activities. WHO has provided a global priority list of eighteen diseases and vaccines as a starting point for consideration, which includes malaria, pneumococcus, MenA, influenza, HPV, cholera, rabies, JE, RV, typhoid fever and dengue fever. Pneumococcal and RV vaccines already are in GAVI’s list of priorities.
MenB and influenza vaccines fall out of the scope of the GAVI project. The remaining vaccines were prioritized according to a variety of criteria such as improvement of children health, strengthening underused vaccines, country preferences and impact on disease burden (both morbidity and mortality). From that analysis, seven vaccines that will protect children health as well as women health, have been placed in the short list. These are: HPV, cholera, JEV, MenA, rabies, rubella and typhoid fever vaccines. Implementation of these vaccines should prevent about 2 million deaths every year. The prioritization of dengue and malaria vaccines was postponed until 2013, in view of the non-availability of the vaccines at this time, but their usefulness and the need to speed up their development was strongly underlined.
7. Session V: Therapeutic vaccines

Moderator: Helen Rees
Rapporteur: Saladin Osmanov

The development of therapeutic vaccines to fight chronic viral infections and non-communicable diseases is considered as an important strategy for the treatment of diseases which have a major public health impact worldwide, such as chronic viral infections, cancer, Alzheimer disease, nicotine addiction and atherosclerosis. This session provided a forum for effective cross-cutting exchange of information and dialogue between experts working in the fields of traditional vaccinology and clinical researchers in non-communicable diseases, who usually communicate rarely one with the other due to established professional and specialization barriers.

7.1 Chronic viral Infections: overview of the theory of tolerance and clinical results (Pierre Van de Papelière)

Various intracellular pathogens can establish long-lasting and even life-long chronic infections that may lead to clinical disease. Among them are viruses, such as those of hepatitis B (HBV) and hepatitis C (HCV), Human papillomaviruses (HPV), Herpes simplex virus (HSV) and Human immunodeficiency virus (HIV); bacteria, such as Mycobacterium tuberculosis; and parasites, such as Leishmania or Trypanosoma spp. Immunological mechanisms are involved both in the establishment and the maintenance of the tolerance towards these pathogens. In some cases, the immune reaction of the host towards the pathogen serves as the main pathogenic cause for the establishment of persistence and chronic infection. The establishment of a chronic infection and disease can best be explained by a delicate balance between the pathogen trying to persist in the host and triggering the development of disease, and the immune system attempting to eliminate it from the host, while protecting the latter from too important damages.

The involvement of the immune system in the pathogenesis and control of chronic infections justify the development of immunotherapeutic strategies, in particular therapeutic vaccination, which could be defined as a pathogen-specific, active immunotherapy. Despite a strong scientific rationale and promising results in animal models, most clinical trials of therapeutic vaccines conducted to date have failed and none of the therapeutic vaccine candidates have yet demonstrated any clear indication of clinical efficacy in humans. As an example, HBV is a systemic pathogen with specific tropism for hepatocytes. The virus is not pathogenic by itself and the development of hepatic lesions is mostly immune-mediated. HPV infection is different in its own way. After primary infection the virus remains located in the epithelial cells of the mucosa or the skin, and is barely exposed to the systemic immune response.
Both HBV and HPV infections are able to attenuate the effectiveness of the immune mechanisms that are meant to control or eradicate them. However, not all HBV and HPV infections evolve towards chronicity. In fact, the majority of HBV and HPV infections are self-limited and resolve, with more or less severe clinical manifestations, due to a successful control of the pathogen by the immune system.

The basis for the development of therapeutic vaccines relies on the expectation that vaccination should be capable of enhancing existing effective immune responses that are too weak or too little specific to overcome viral immune escape mechanisms and/or to revert immune tolerance mechanisms towards adequate active immune control. However, the factors that trigger the shift from tolerance to active immune control are difficult to determine. Moreover, even if we knew the type, quality and quantity of effective immune responses, their induction in chronically infected and immune tolerant individuals would still be a major challenge.

These considerations apply to the development of therapeutic vaccines for chronic infectious diseases in general. Prophylactic vaccines aim at educating a naïve immune system and provide a protection that depends on immunological memory, which requires initial activation of CD4+ T cells. Ultimately, classical preventive vaccines induce pathogen-specific antibodies, although the role of cell-mediated immune responses should not be underestimated, especially for pathogens such as TB, HIV or malaria. In contrast, therapeutic vaccines target an immune system which has already encountered the antigen. The goal of therapeutic vaccination is therefore not to induce memory and to generate an adaptive immune response, but rather to stimulate immediate effector mechanisms and T cells that are able to persist and proliferate in such an environment. In addition, the antigen is presented in the context of major immunological impairments, as chronic infection and persistence of antigen actively distort both the innate and the adaptive immune systems in a number of ways. Therapeutic vaccination must therefore confront multiple immunological challenges, such as breaking tolerance, circumventing immune ignorance and inducing specific stimulation, despite the presence of circulating antigen in amounts that by far exceed what could be administered by any vaccine. The combination of active antigen-specific vaccination with antiviral or antibiotic treatment and/or with active non-specific immunotherapy could be a way to face these challenges.

### 7.2 Vaccines against cancer (Benoît Van den Eynde)

Therapeutic vaccination of cancer patients is a promising approach for cancer therapy. It is based on molecular definition of tumor antigens recognized by cytolytic T lymphocytes (CTL), which correspond to peptides resulting from intracellular degradation of tumor-specific proteins. These peptides are presented to CTL recognition by MHC class I molecules on the surface of tumor cells. Cancer vaccines aim at enhancing immune responses against these peptides in order to induce immune rejection of the tumor cells. A number of vaccination strategies have been tested in clinical trials, including peptides, recombinant viruses, recombinant proteins with various adjuvants, and antigen-loaded dendritic cells. These trials mainly involved vaccines against melanoma, for which a large number of tumor antigens have been defined, including those encoded by the MAGE family of cancer germ line genes.
Regression of metastatic melanomas was observed in 10-20% of the patients, in the absence of any toxicity. A detailed analysis of the anti-tumor CTL response in treated melanoma patients indicated a massive infiltration of the tumors by anti-tumor CTL. This infiltration was actually already observed before vaccination: it appears to result from a spontaneous CTL response, which is made inefficient at the tumor site. Thus, an important factor limiting the efficacy of cancer immunotherapy is the development of mechanisms that allow tumor cells to resist immune rejection. The challenge is to identify these mechanisms and to design therapeutic approaches to overcome them.

In addition, a powerful tumor resistance mechanism is based on the expression by tumor cells of indoleamine 2,3-dioxygenase (IDO), an intracellular enzyme that catalyses rapid tryptophan degradation, resulting in a local tryptophan depletion that severely affects T lymphocyte proliferation and thereby is profoundly immunosuppressive. Many human tumors express IDO in a constitutive manner. Using of a mouse model system, it was shown that the constitutive expression of IDO endows tumor cells with the ability to resist immune rejection by preventing T cell attack in vivo. Importantly, this effect could partly be reversed by systemic treatment with 1-methyl-L-tryptophan, an inhibitor of IDO. These results suggest that the efficacy of therapeutic vaccination of cancer patients could be improved by concomitant administration of an IDO inhibitor. Clearly, better characterization of the mechanisms of tumor immune resistance is needed (e.g., secretion of Galectin-3 by tumor cells and its use as a target antigen). Also, application of immune therapies should be performed at earlier stages of the disease for improving their effectiveness.

7.3 Vaccines against neurodegenerative disorders: Alzheimer disease (AD) (Achim Schneeberger)

Current scientific and clinical data suggest that the accumulation of the neurotoxic amyloid β peptide Aβ is central to the pathogenesis of AD. This concept served as a basis for the development of a first anti-Aβ Alzheimer vaccine (AN1792). A new generation of Alzheimer vaccines has recently been developed that uses short mimotopes of the Aβ peptide as their antigenic component. AFFITOPES (= mimotopes identified by AFFiRiS GmbH) mimic native epitopes (in this case, human Aβ) and provide the basis for the multi-component safety concept of AFFITOPE vaccines. First, as they are non-self, AFFITOPES do not need to break tolerance barriers typically established against self proteins. This allowed the use of aluminium hydroxide (alum) as an immunological adjuvant. Secondly, AFFITOPES employed in this candidate Alzheimer vaccine are only 6-7 amino acids in length, which prevents activation of Aβ-specific autoreactive T cells. Thirdly, and above all, the AFFITOPE technology allows to control the specificity of the vaccine-induced antibody responses, focusing them exclusively on the Aβ peptide and preventing cross-reactivity with its precursor molecule, the amyloid precursor protein APP.
In a programme based on two AFFITOPEs from the N-terminus of Aβ, this approach was taken all the way from concept to clinical application. A Phase I trial was launched to assess the safety and tolerance of the two AFFiRiS Alzheimer vaccine candidates (termed AFFITOPE AD01 and AD02, respectively) in human volunteers. Patients (n=24/trial) exhibiting mild to moderate AD received 4 immunizations with a single dose of each vaccine at 4-week intervals. Patients were closely monitored for adverse effects for up to 2 months after the last immunization. Initial clinical data support the safety concept inherent to AFFITOPE vaccines. In addition, information on the immunological potency and clinical effectiveness of the two vaccines was gathered. Ongoing clinical trials will provide immunological and clinical data to validate the mimotope vaccine concept, tested for the first time in human beings.

7.4 Life-style vaccines: nicotine addiction (Martin Bachman)

Smoking is one of the major preventable causes of chronic diseases and death along with unhealthy diet, excessive food uptake and lack of physical activity. Despite the development of a number of drugs to help interrupting smoking, the long-term efficacy of these replacement strategies has been rather limited. The development of an effective vaccine that could block nicotine in the blood stream and prevent it from entering the central nervous system, thus decreasing its addictive effects, has been entertained. Animal studies using rodents and monkeys have demonstrated that passive administration or active induction of antibodies against addictive drugs such as cocaine, heroin or nicotine result in a significant reduction of addictive self-behavior of animals. Nicotine itself is too small a molecule to be immunogenic on its own and therefore needs to be coupled to carriers to render it immunogenic and capable of inducing nicotine-specific antibodies. A candidate vaccine based on the use of virus-like particles (VLPs) chemically linked with a nicotine derived immunogen, called CYT002-NicQb, has been produced by Cytos Biotechnology AG. VLPs offer a number of advantages, they are very stable and can be economically produced with high yields in bacteria. To optimize the induction of B-cell responses the antigen was presented as an ordered and repetitive motif array.

The candidate vaccine was shown to be highly immunogenic in mice, inducing high levels of anti-nicotine antibodies able to inhibit 70% of the nicotine brain uptake after administration of a labelled nicotine challenge. The vaccine candidate was then tested in a randomized placebo-controlled dose escalation phase I trial (from 50 to 100 μg), involving 40 volunteers. The trial showed that the vaccine was safe and well tolerated and that it induced high levels of anti-nicotine antibodies in the peripheral blood. The antibody concentration and affinity were in the range required for an effective therapy. A further randomized, double-blind, placebo-controlled multi-centre study, involving 341 volunteers, documented that the vaccine was safe and capable of inducing high titres of antibodies against nicotine, which did efficiently facilitate the smokers’ will to quit. Vaccinees who received this candidate vaccine could actually be divided into 3 categories: low, medium and high responders, where the “high-responders” group was characterized by higher rates of abstinence from smoking (57% at 6 months and 42% at 12 months after immunization). The vaccine is currently undergoing further clinical development to finalize dose and regimen and to optimize its formulation.
7.5 Vaccines against chronic diseases: atherosclerosis (Jan Nilsson)

Atherosclerosis is a chronic disease that affects medium and large-sized arteries. It is initiated by the accumulation of low-density lipoprotein (LDL)-derived lipids that aggregate and undergo oxidative modification. Different oxidation products cause inflammation and fibrosis that are at the origin of the formation of atherosclerotic plaques. Both innate and adaptive immune responses play important roles in this process. Components of innate immunity such as scavenger receptors and natural IgM antibodies represent a first line of defence against the toxic effects of oxidized LDL while a concurrent activation of innate Toll-like receptors promotes the inflammatory response. The presence of large amount of oxidized LDL auto-antibodies in plasma along with a frequent expression of oxidized LDL-specific T cells in atherosclerotic plaques suggest that atherosclerosis may in part be an autoimmune disease against modified endogenous lipoproteins. This idea is also supported by animal experiments in which apo E-/- and LDL receptor -/- mice were cross-bred with mice deficient for various components of the adaptive immune system. Somewhat surprisingly, however, immunization of the animals with oxidized LDL generated a protection against atherosclerosis. This suggests that the adaptive immune response may be shifted towards protection and that it may be possible to develop an immunomodulatory therapy against atherosclerosis.

The structures in oxidized LDL that induce a protective immune response have been identified as small peptide fragments of the LDL-binding protein Apo B-100. Immunization with these peptide fragments was found to reduce the formation of atherosclerotic plaques in up to 70% of hypercholesterolemic mice. Candidate vaccines based on this concept are being developed for human use and are expected to undergo the first trials in humans within a couple of years. Protection against atherosclerosis was also achieved in the mouse model by mouse transfer of recombinant Apo B-100 specific IgGs, suggesting that humoral responses play an important role in protection. Recent findings suggest that the mechanisms involved include increased clearance of oxidized LDL from the circulation, facilitation of reversed cholesterol transport by stimulating macrophage expression of ABCA-1 and down-regulation of macrophage chemokine release. Evidence for a potential protective role of anti-ApoB-100 antibodies also comes from epidemiological studies demonstrating that low levels of auto-antibodies against Apo B-100 fragments are associated with an decreased risk for development of acute cardiovascular events. The effects of these antibodies in humans are currently under study.
8. Satellite Workshop on vaccine cost-effectiveness

Chair: Maarten Postma,
Rapporteur: Raymond Hutubessy

8.1 Overview

The WHO Expanded Programme on Immunization (EPI) is rightly considered to be one of the most efficient health programs using scarce resources. Today, many new vaccines become available, and many more are still to come, which in the short- to medium-term will not cost the few cents per dose that the traditional vaccines cost, but will be ‘multi-dollar’ vaccines. In view of limited health care budgets, decision-makers will need information on their relative cost-effectiveness (CE). The methods and tools of economic evaluation are rooted in the fundamental issue which characterizes decision-making, i.e. making a choice between at least two alternatives in the context of scarce resources. Economic evaluation compares the costs and outcomes of alternative programs, one of which may be ‘doing nothing’. The choice is often framed in the question: “which intervention should have priority?”.

Two complementary WHO Guides on CE analysis have recently been published and were presented at the workshop: the ‘WHO Guide on Standardization of Economic Evaluations of Immunization Programs’, which provides special attention to vaccine effectiveness and mathematical modeling options of vaccine programs; and the ‘WHO Generalized Cost-Effectiveness Analysis Guide’, which allows decision-makers to compare immunization programs from a broader health sector perspective. The impact of methodological choice of economic evaluation on policy decision in the field of immunization is evident when appraising the value of immunization programs, which itself influences the timing of the decision to introduce new or underused vaccines, particularly in low and middle income countries (LMICs). Among the major issues which influence the decision of whether or not to introduce a new vaccine in a country are the perspective of the analysis (e.g. societal versus provider perspectives), the level of discount rate, whether the rate is similar for both costs and effects, the inclusion of indirect costs, and the issue of how to value productivity losses.

The use of CE evaluations in the field of decision-making analysis of vaccines is best illustrated by GAVI’s use of the comprehensive multi-year plan (cMYP) costing tool to help decide to invest into rotavirus and pneumococcal vaccines. Similarly, CE analysis was most important for the introduction of new and underused vaccines in Latin-America through the Pan-American Health Organization’s (PAHO) ProVac Study. This work is intended to provide countries in Latin America with practical, field-based tools for estimating cost-effectiveness that do not require the academic rigor for models utilized in research settings, but that remain sufficiently robust to provide useful information for vaccine introduction decisions.
8.2 Standardization of economic evaluations of immunization programs
(Damian Walker)

A number of reviews have indicated that there is scope for improving the transparency, completeness and comparability of economic evaluations of vaccination programs and to improve their quality. Adherence to general guidelines would increase the quality, interpretability and transferability of future analyses. However, there is reason to believe that there might also be a need for more specific advice for vaccination programs. For example, there are inconsistencies in the methods used to estimate the future benefits of vaccination programs, and their relative efficiency can be sensitive to some of the more controversial aspects of general guidelines, such as the inclusion of indirect costs and the discounting of health outcomes. To face these issues, the WHO recently developed a CE Analysis Guide that meets the needs of decision-makers for relevant, reliable and consistent economic information for immunization programs. The aim of the Guide is to provide clear and concise, practical and high quality guidance for those who conduct economic evaluations.

8.3 Modeling options for economic evaluation (Phillipe Beutels)

Many countries have set up guidelines for performing economic analyses in health care. Whilst these guidelines generally apply, there are a number of important aspects that need to be carefully considered when evaluating a vaccination programme. These aspects include perspective, time preference, time span, Quality Adjusted Life Year (QALY) estimates in young children, and parameter uncertainty. For any economic evaluation, a model should be chosen that minimally meets the analytical requirements in function of the pathogen, the endemic situation and the nature of the intervention. In view of the many specific advantages and disadvantages of various modeling attributes for specific infections and interventions, it is not however possible to make a generic “one size fits all” recommendation on which model to choose. For instance, one can discern static versus dynamic, deterministic versus stochastic, open versus closed, aggregate versus individual, and discrete versus continuous time models. A most influential choice for the estimation of the CE of vaccination is the choice between static and dynamic models. Most economic evaluations of vaccines have been based on static, single cohort models. Although this has often been a justifiable choice, the use of a more sophisticated (e.g. dynamic) model can often be necessary, taking into account the nature of the pathogen, the target group, the epidemic baseline and the level of immunity in the population.
8.4 Evaluating the guidelines: the impact of methodological choice on the CE of vaccination programs (John Edmunds)

Modeling and economic analysis is increasingly used in health-care decision-making. The process of constructing models for economic analyses involves many choices: choices about parameter values and how to represent uncertainty in these; choices about the structure of the model; and choices about the methodological framework that should be adopted (e.g. CE or cost-benefit analysis). To reduce the possibility of bias resulting from choices that favor a particular intervention, as well as to help comparability between studies, many countries have adopted guidelines for economic analyses. As there are particular issues pertinent to vaccination Guide programs, such as indirect effects, the WHO recently issued a specific immunization-related guidelines that apply to a number of countries and will help determine the impact that different methodological choices can have on recommendations. This can best be illustrated by the cases of the varicella vaccine and the rotavirus vaccine.

8.5 Towards optimizing the impact of CE analyses on policy decisions: Assessment of the GAVI investment cases for rotavirus and pneumococcal vaccines (Deborah Atherly)

CE analysis can play an important role in vaccine policy-making at the global, regional and country levels. CE results are often presented as part of the overall evidence base including clinical, epidemiologic and financing data. In November 2006, the GAVI Alliance Board approved financing for rotavirus and pneumococcal vaccines after submission of Investment Cases for each vaccine. CE data were presented as part of the submission, and contributed to the final decision.

Three major factors were important in determining the role that CE played in the GAVI decision. The first was the perceived quality of the analyses. Adherence to well-accepted guidelines for conducting CE evaluations was important to GAVI and its advisors. In addition, the quality of data sources and assumptions were also carefully scrutinized. The second was the comparability of the analyses to each other. GAVI requested that the two analyses - one for pneumococcal and one for rotavirus vaccines - be harmonized where possible, and that a summary of the similarities and differences between the two be provided to assist the decision-making process. The third factor was the effective translation of CE results to GAVI. Although standard results such as cost per DALY averted and cost per death averted were reported, other outcome measures that communicated the value and impact of the vaccines were also used—including number of deaths and number of hospitalizations averted per 1,000 children vaccinated, and total economic and health impact over time. Although decision-making processes can vary significantly from one setting to another, attention to these factors can help optimize the contribution of CE analyses in policy-making.
8.6 **cMYP tool and cost-effectiveness** (*Patrick Lydon*)

The need to evaluate costs when planning new immunization programs dates back from the start of EPI in the late 1970’s. Yet, with the new and more expensive vaccines becoming available, coupled with the pressures to reach the Millennium Development Goals, the context for planning in immunization has changed in recent years. To address this changing context and in line with the Global Immunization Vision and Strategy (GIVS), WHO and UNICEF, together with GAVI Alliance partners, developed in late 2005 guidelines for comprehensive ‘Multi-Year Planning’ (cMYP). Through the GIVS initiative and framework, the cMYP process marks current efforts to streamline immunization planning processes at national level into a single strategic and comprehensive plan including costs-assessment. The cMYP was seen as the first step at implementing GIVS at national level.

By the end of 2007, over 60 countries had developed 5-year cMYPs with detailed costing, financing and gap analyses using a standardized tool. The data from these plans were extracted into an on-line database. In early 2008, a review of the costing and financing data from the cMYP was prepared that highlighted important trends. These data can be of use for CE analysis and for benchmarking purposes or modelling work related to CE of vaccine introduction and immunization systems.

8.7 **Dissemination of CE tools: On-Line international Vaccine Economics and Statistics (OLIVES) project**  
 (*Colin Sanderson and Andrew Clark*)

New vaccines tend to be strongly advocated by their ‘champions’, but policy makers need analyses for comparison and priority-setting based on data that are consistent, up-to-date and reliable. Decision-support models should be transparent, flexible and valid. Current obstacles to sound and timely analysis include barriers to information access, multiplicity of information sources, inconsistent formats and definitions, and unknown or variable data quality.

To create and maintain a website that supports vaccination policy analysis and decision-making, by drawing together data, models, guidelines and references to research and policy analysis from authoritative sources, the London School of Hygiene and Tropical Medicine is developing a website, ‘OLIVES’, that will provide an information base for policy analyses of children’s vaccines, initially covering BCG, DTP1, 2 & 3 and measles vaccines, then Hib, rotavirus and pneumococceus vaccines. It will cover low and middle income countries, including the 72 GAVI eligible countries and will include data on demography, disease burden, economic indicators, vaccine schedules, vaccine coverage, vaccine efficacy, vaccine costs/prices and, for vaccine-preventable diseases, care and treatment costs. The site will present these data in a coherent and accessible structure on a timely basis and will have them checked for quality and validity using consistent, documented methods and facilitating ‘triangulation’ when there are overlapping sources of data. It will secure permissions/procedures for users to download material and will be closely linked to other e-initiatives in the field.
9. Satellite workshop on aging and immunity

*Moderator: Alex Kalache*

*Rapporteur: Martin Friede*

### 9.1 Overview

The aging of the world population is a real time-bomb on which we are sitting. Although the population is aging rapidly, we have not yet undertaken any serious evaluation of how to protect the elderly from infectious diseases. Vaccines could provide a very significant benefit in that population, but, as the immune system becomes impaired with aging, it probably will be necessary in the future to develop specific vaccines with improved efficacy, together with appropriate policy to promote their use.

The elderly population is exploding in developing countries, yet all of the studies of immune competence in the elderly have been done in industrialized countries. It is not known whether the elderly in developing countries will display a similar response as numerous factors may come into play, such as life-long exposure to microbial pathogens and infectious diseases, regional diets, pollution, etc. It is therefore urgent that studies be undertaken to establish the burden of infectious diseases in the older population of developing countries, at what age immune senescence begins in these populations and to determine which vaccines would benefit them and which vaccination schedules would be the most appropriate. A general rule seemed to emerge at the meeting that pediatric vaccines are not potent enough to be of use in the elderly, whereas vaccines that are immunogenic in the elderly are too reactive to be used in children. It therefore may be necessary to develop different vaccines for the elderly and for children.

The suggestion was made that WHO establish an expert committee on the immune response and vaccination of elderly adults to study these points.
9.2 Population aging: A challenge for the 21st century
(Alexandre Kalache)

Population aging was one of humanity’s greatest triumphs in the 20th century - and is now one of society’s greatest challenges for the 21st century. Increased child survival and improved global health lead to longer life expectancy in all regions of the world, which, combined with decreasing fertility rates, is resulting in a rapid aging of the world’s population. Over the next 50 years the total population of the world is predicted to increase by 50% to reach 9 billion persons, at which time the population over 60 years of age will represent 2 billion persons, i.e. 25% of the population. This increase will mostly occur within developing countries. Thus, while the older (over 60 years old) population in industrialized countries is projected to grow from 0.2 billion to 0.3 billion persons, in developing countries it will explode from the current 0.4 billion to 1.7 billion persons, a growth of more than 350%. A significant increase will already occur within the next 20 years in many developing countries such as Thailand or China, where the proportion of the population that is over 60 years of age is expected to grow from the current 7%-8%, to 20%.

Although life expectancy is increasing on a global scale, numerous inequalities are met in the process, such as:

1) **Geographic inequalities**: Life expectancy in Japan is over 85 years of age, while in Sierra Leone it is barely 35 years. In every country, including both these extremes, a certain amount of time is spent in poor health towards the end of life. This period accentuates the inequalities: thus, the 7 years of predicted poor-health in the Japanese population represents only 7% of their life, whereas in Sierra Leone the average terminal 5-6 years spent in ill-health represents 16% of their life.

2) **Socio-economic inequalities**: within the same city, including cities in highly industrialized countries, life expectancy across different socio-economic areas varies widely, with higher socio-economic areas having longer life expectancy (for example in London life expectancies differ by up to 11 years between different parts of the city). Risk factors that favor an early death in industrialized cities mostly are associated with behavior, obesity, smoking and lack of physical exercise, which translates into increased risks of cancer, stroke or neurological diseases.

3) **Gender inequalities**: almost everywhere women have a longer life expectancy than men. This difference varies from <5 to >10 years, being very low in countries such as India, Bangladesh or Pakistan, where women have limited access to health care, and very large in countries such as Russia, due to early male mortality. A 60 years-old woman living in an industrialized country has an average 30 years life expectancy, whereas a 60 years-old man only has a 20 years life expectancy. The biological reasons are not well understood but include the female hormonal protection from atherosclerosis during their period of reproductive capability. This difference results in the older population becoming very predominantly female, which is accentuated by the societal behavior of men marrying younger women. As a consequence, women are likely to outlive their husbands by many years, which, depending on the society, can create a new period of dependence.
Global aging will put increased economic and social demands on all countries. However, it is in the developing countries that this will be the most serious: industrialized countries became rich before they became old and acquired a significant elderly population with associated health care burden; developing countries are becoming old before they become rich and the health care of the elderly in these countries will put a heavy burden on their health systems. As more and more people survive beyond the age of 60 it is more necessary than ever to develop health policies that will target this fast increasing population sub-group. In this respect the WHO developed a policy framework under the title “Active Aging” which was defined as “the process of optimizing opportunities for health, participation and security in order to enhance quality of life as individuals age”. Among different opportunities close consideration must be given to new technologies and pharmacological products that can prolong healthy life expectancy for people aged 60 and over. A particular emphasis should be given to vaccines that can offer some of the most cost-effective interventions for preventing diseases which have serious, often fatal consequences.

9.3 Age-related changes in immunity: Implications for vaccination in the elderly (Beatrix Grubeck-Loebenstein)

The function of the immune system progressively changes with age, which leads to increasing occurrence and severity of infectious diseases and decreased responsiveness to vaccines. There are a number of reasons underlying this phenomenon:

1) Reduced responsiveness of the innate immune system: Due to subclinical ubiquitous inflammatory processes that develop in the elderly (“inflammaging”) the threshold for the induction of a “danger” signal to be induced by vaccines with adjuvant increases. Migration of dendritic cells to the lymph node is impaired due to age-related mechanical changes and functional defects of antigen-presenting cells may hamper the uptake and presentation of antigens.

2) Thymus involution and decreased T cell generation: The thymus gradually inverts with age, a process that occurs from adolescence to the mid-40’s, at which point it is almost inactive and no maturation of new T cells occurs. As the thymus gradually loses its ability to replenish the population of naïve T cells, the population of T cells in the body changes from being predominantly naïve T-cells in the young to a mixture of naïve, memory and effector T cells in healthy adults, and then to only memory and effector T cells in the elderly. In the elderly population, naïve T cell are very rare, they show a restricted diversity and shortened telomeres. The elderly are therefore unlikely to mount a full immunological response following exposure to new antigens.

Studies show that among the elderly, however, some individuals show significant number of CD8+ CD25+ memory T cells which are not regulatory T cells and are good producers of IL-2 and IL-4. These T-cells have good proliferative potential as indicated by long telomeres and can partially compensate for the lack of fully functioning naïve T cells. This elderly population subgroup is able to respond to vaccines, while, in contrast, the rest of the elderly population, which shows a high ratio of effector to memory T cells and low CD25 expression, does not respond well. The accumulation of effector T cells may be related to age-dependent inflammation and is inhibitory to antibody production.
3) **Prolonged exposure to chronic infection and ‘saturation’ of the immune system:** In the elderly population with a high ratio of effector to memory T cells, a high percentage of the effector cells are directed to cytomegalovirus antigens (CMV). This suggests that chronic infection with endogenous viruses may promote the accumulation of effector cells and the associated non-responsiveness to neo-antigens.

4) **Reduced B cell generation:** Aging also has a direct effect on B cell production and hence antibody production. Decrease in bone marrow functionality leads to decreased levels of naïve B cell production, and increased memory B cell population. This is evident when looking at the intensity and duration of the response to vaccines. For example, young people immunized with tetanus toxoid produce a strong response which is maintained for over 20 years, whereas in older people the response is not only weak but also decays rapidly. Frequent booster immunizations are therefore needed in the elderly population.

In conclusion, booster immunization works much better than primary immunization in elderly persons. Primary immunization should therefore be performed as early as possible in life and be complemented by regular booster shots in later life.

9.4 **Cellular analysis of impaired immunity and immunosenescence**  
*(Graham Pawelec)*

Aging is associated with increased susceptibility to infectious diseases, and to reduced response to vaccination, all of which derive from decline in the immune responsiveness (immunosenescence). All compartments of the immune system are affected, but for several reasons, including thymic involution, T cells are particularly susceptible. The distribution of T cell subsets in peripheral blood changes in an age-associated manner, with decreased representation of naïve T cells and increased proportions of memory T cells. A similar pattern of decreasing numbers of naïve cells, increasing number of memory cells, and progressively restricted repertoire is also seen with B cells. Components of the innate immune system such as antigen-presenting dendritic cells, phagocytes and natural killer cells also are affected by age, but in a less dramatic fashion.

In order to understand how environmental conditions and interventions affect immunosenescence, a definition of biomarkers has been attempted on a cohort of elderly donors based on a set of clinical parameters (“clinical SENIOR” protocol), or clinical plus laboratory parameters (“full SENIOR” protocol), selecting only donors in perfect health so as to distinguish between alterations caused by aging and those caused by disease. Similarly, the OCTO longitudinal study in Sweden identified a panel of immune markers representing an “immune risk profile” (IRP), which appears to be grossly independent of genetic background or state of health at baseline, and which can predict mortality during the following 2-, 4- or 6-year follow-up. IRP is characterised by a CD4:CD8 ratio of < 1, poor T cell proliferative responses, increased CD8^+ CD27^-CD28^- cell counts, low B cell counts, CMV seropositivity and increased number of EBV- and CMV-reactive CD8^+ T cells. The number of different T cell clonal expansions specific for CMV antigens first increases as people age, but actually decreases again towards the end of life. Preliminary data suggest that the IRP may begin to become relevant to health and mortality at about the age of 65 years, but is not yet predictive in 55 year-old persons.
These studies also suggest that age-associated immune alterations are accelerated by the requirement for constant immunosurveillance against persistent pathogens, including herpesviruses and particularly Cytomegalovirus (CMV), with which the majority of the population in industrialized countries becomes infected during the course of their life.

Thus, oligoclonal T cell expansions followed by clonal attrition, together with increased accumulation of individual CMV-specific dysfunctional cells, is associated with incipient mortality in old people. Anergic T cells actually begin to accumulate in middle age, especially in CMV-seropositive people, and the process continues throughout life. Longitudinal *ex vivo* studies in the elderly, as well as the utilisation of cell cultures as *in vitro* models of T cell clonal expansion and contraction under chronic antigenic stress, are essential for understanding T cell immunosenescence and for testing interventions that might improve responses to vaccination in the elderly, such as functional foods, use of anti-inflammatory drugs and anti-viral agents, cytokine supplementation and, even, adoptive cell therapy.

### 9.5 Evaluating T cell responses to influenza vaccination in older adults

*Janet McElhaney*

Influenza is a serious illness and probably the single most important cause of excess disability and mortality during the winter months. Serious complications of influenza illness have been identified among the six leading causes of catastrophic disability and loss of independence in older adults, together with strokes, pneumonia, cancer, hip fractures and congestive heart failure (CHF). Successful prophylaxis of influenza is therefore crucial to extending the healthy and active phase of late-adult life. However, the efficacy of current split influenza vaccines in older adults is only 30%-40% as compared to 70%-90% in younger adults, and despite wide use of the current vaccines, influenza- and pneumonia-related morbidity and deaths have increased significantly over the last two decades.

A major challenge to vaccine development is that the current regulatory approval process use anti-HA antibody titers as the sole measure of vaccine efficacy. A study was undertaken to evaluate whether the anti-HA titers correlate with protection in the elderly population, or whether other mechanisms are better predictors of influenza protection in this group. Cohorts of young and old volunteers received split influenza vaccines over a 4-year period and both their anti-HA antibody titer and cell-mediated immune response were monitored as well as their infection by influenza. CMI was measured by incubating PBMCs from the volunteers with live influenza virus and monitoring the production of IFN-γ, IL-10 and granzyme, a marker of functional CTL activity.

The results of this study showed that the anti-HA antibody response was significantly lower in older people than in younger people but that it did not correlate with protection. The cytokine response (IFN-γ/IL-10 ratio) to the virus did correlate with protection: volunteers with a low IFN-γ/IL-10 ratio tended to become infected whereas those with a high ratio tended to not get infected, independent of their anti-HA titers. The granzyme response to the virus also correlated with protection against infection.
Older people therefore do maintain an effective immune memory response to vaccination, which also includes a Th1 response, and which is protective against homosubtypic influenza infection. These data suggest that the decline in influenza vaccine efficacy with aging may be due to a limitation of the current split-virus (killed) vaccine formulations, rather than to an inability of the aging immune system to mount a robust cellular immune response. It might therefore be advantageous to develop alternative vaccines which would contain the internal influenza virus proteins (NP, M), together with adjuvants able to enhance the Th-1 response to the vaccine.

9.6 Seasonal influenza vaccination by intradermal microinjection

(Marie-José Quentin-Millet)

While inactivated trivalent influenza vaccines have provided protection to hundreds of millions of individuals, the immune response in the elderly is lower than in young adults. Yet the risk of serious complications or death following influenza infection is highest among elderly adults and those with chronic illnesses such as asthma, diabetes and cardiovascular diseases: 90% of influenza-associated deaths occur in this group, and there are 174 to 205 per 100,000 hospitalizations for pneumonia and influenza in the group as compared to 13-33 for persons under 65 years of age.

To improve the efficacy of influenza vaccines in the elderly population, Sanofi Pasteur investigated the intradermal (ID) delivery of the standard split influenza vaccine. Since intradermal delivery with standard needle and syringe is difficult to achieve reliably, a microinjection system was developed in collaboration with Becton Dickinson which consists of a pre-filled syringe with a 1.5 mm-long micro-needle designed for perpendicular insertion into the skin and includes a needle shielding system to minimize the risk of needle stick injury and prevent illicit use. This design permits consistent and reliable administration of the vaccine into the dermis, targeting an area of high density of antigen presenting cells.

A phase II dose-ranging study was conducted on 1107 medically-stable elderly aged 60 to 85 years. The safety and immunogenicity of the vaccine was evaluated comparing 21μg and 15μg HA administered ID versus 15μg administered IM. Anti-HA GMTs against all strains were significantly higher with the ID-administered vaccine than with the standard IM-administered vaccine. In a subsequent phase III study, 3701 medically-stable 60-94 years-old volunteers were enrolled in a multicentered, randomized trial which compared ID microinjection of the 15μg hemagglutinin/strain vaccine with an IM control. Seroprotection rates against all strains were significantly higher with the ID-administered vaccine, demonstrating superiority of this route of administration over the IM route. In both studies the ID-administered vaccines were well tolerated, elicits only minor transient reactions at the point of injection. Systemic reactions were mild and comparable in the ID and IM groups. Intradermal influenza vaccination therefore leads to an increased immune response to the vaccine in the elderly. Licensure of the ID vaccine is pending.
9.7 Herpes zoster vaccine (Elaine Esber)

The causative agent of chicken-pox is the varicella-zoster virus (VZV). Infection with VZV is common in childhood and generally resolves without complications. However, after clinical symptoms have disappeared, the virus remains in a dormant state in the dorsal route neural ganglia of the host where it can reside for 20-30 years before eventually being reactivated, traveling along the sensory nerves and causing herpes zoster (also known as shingles), a painful rash accompanied by blisters along the line of the nerve on one side of the body only. Although the rash usually resolves within a few weeks, about 25% of sufferers experience complications. The most common complication is a stabbing, lacerating pain that can last for months or years, a condition called postherpetic neuralgia (PHN), which is difficult to manage and significantly interferes with activities of daily life. Other serious effects including palsies, facial paralysis, heavy visual impairment and more rarely encephalitis or pneumonia can also occur.

The incidence and severity of herpes zoster increase exponentially with age. Over 90% of the population has been infected with VZV, and there is no way to predict who will go on to develop zoster. More than 67% of zoster cases occur in people over 50 years of age, and by 85 years of age, approximately 50% of individuals usually have had zoster. The duration and intensity of complications such as PHN increase in older patients. The risk factors for zoster are prior infection with VZV, advancing age and waning immunity, particularly cell-mediated immunity. The treatment options for acute zoster are limited: antiviral therapy works if initiated within 72 hours of onset of symptoms. For PHN, analgesics show only marginal efficacy and consultation with pain specialists is usually required.

Merck has developed a vaccine aimed at boosting the cell-mediated immunity to VZV and prevent herpes zoster. The vaccine is based on the live attenuated VZV OKA strain, used at a dose 14 times greater than in the pediatric chicken-pox vaccine. A placebo-controlled clinical study was launched on 38,500 volunteers to evaluate the efficacy of the vaccine to prevent zoster. About one half of the volunteers were 60-69 years of age and the other half more than 69 years old. Immunogenicity, safety and occurrence of zoster, duration and intensity of pain as well as occurrence of PHN were first monitored for 1 year then followed up for a further 4 years. The vaccine was generally well tolerated. It showed an overall efficacy of 51% against herpes zoster and 66% against PHN, with efficacy being slightly lower in the elder subgroup. The 4 year follow-up showed a significant decrease of zoster and PHN incidence in the vaccine group.

Although the vaccine has been shown to significantly decrease the risk of zoster and its complications, it is not being widely prescribed, possibly due to its high price (US$150 per dose) and the fact that it is not covered by many health insurance groups. A cost-effectiveness analysis however suggests that the vaccine at $16000-$25000 per QALY is as cost-effective as other preventive measures such as cholesterol management or hypertension medication.
10. Session VII.
Vaccination of special groups

Moderator: Claude Leclerc
Rapporteur: Teresa Aguado

10.1 Introduction of HPV vaccines in adolescent populations: update of the PATH project (Scott Lamontagne)

HPV vaccines offer an unprecedented opportunity to reduce the global burden of cervical cancer through primary prevention. However, there are very specific challenges in the developing countries’ context, including socio-cultural challenges (the vaccine is new), logistical/technical challenges (in relation to supply and delivery) and political challenges (local-level decisions could represent important barriers to their introduction).

The HPV project leaded by PATH attempted to gather the needed information and evidence to guide decision-making at country level. The model applied combined qualitative formative research grounded in a theoretical conceptual framework, with quantitative operations of results obtained through HPV implementation demonstration projects. Four countries were selected to conduct this research: Peru, Uganda, Viet Nam and India. Key findings from formative research in all four countries have now been used to plan and implement the demonstration projects. Formative research addressed questions such as “who” are the right populations for vaccine delivery? “what” are the messages needed? and “which” is the appropriate advocacy strategy?

The methodology was mixed, as were the study populations to which it was applied: parents/other adults, civil society leaders, health care/education systems, decision-makers. A data analysis was prepared and submitted to relevant ethics committees for approval. Most of the people had very little knowledge of cervical cancer and HPV and there was quite a lot of confusion between the causes of cervical cancer, its symptoms and sexual behavior, but in general the vaccine was quite well accepted, with parents, particularly mothers, playing an important role in final decision.

There was some concern regarding possible side effects but the different populations opted for vaccine delivery with EPI being perceived as the best entry point, provided vaccine introduction was coordinated with official departments such as Epidemiology (Peru), Reproductive Health and School Health (Uganda), Women and Child Development and Youth Affairs (India) or Women’s Union (Viet Nam).

Building on this information, PATH designed four demonstration projects, using different vaccine delivery strategies in the four target countries, albeit with the same goals: to achieve high vaccine coverage, to ensure feasibility and to quantify costs. The preliminary results which were presented showed high vaccine coverage (92%) in Uganda but lower figures (57%-61%) in Peru. The Uganda and Viet Nam projects are school-based and target 10-11 years-old girls.
Preliminary lessons learnt are that vaccine acceptance was high. Informed consents may have a significant impact and directed, comprehensive community sensitization can much facilitate acceptance. With regard to logistics, school-based delivery can work, cold chain capacity can be made available, but use of resources needs planning and coordination between departments of health and education. A vaccine campaign requires 4-6 months to prepare the logistics, sensitize the population and mobilize all players.

10.2 Malaria vaccines and pregnancy

(Graham Brown)

In the absence of overall protection, pregnant women are particularly vulnerable to malaria, especially as illness can occur in previously immune girls who become susceptible again during pregnancy. About 50 million women are at risk worldwide, especially at the time of their first pregnancy: this was well documented in the study of a cohort of young mothers in Kenya, where prevalence of malaria, which was 85% at first pregnancy, successively fell to 60% and 35% at time of second and third pregnancy, respectively. Women therefore progressively develop immunity for subsequent pregnancies. A pregnancy-specific malaria vaccine would be highly desirable to prevent maternal deaths, fetal and infant deaths, severe maternal malaria, low birth weights, mothers’ anemia, and placental malaria.

The term “Pregnancy Associated Malaria” (“PAM”) has various interpretations, and is sometimes abusively interpreted as placental malaria, which is characterized by Plasmodium infection of the placenta in the absence of peripheral parasitaemia: the parasites are sequestered in the placenta, which binds infected red blood cells (RBCs), leading to inflammation, fibrin deposits and necrosis. Parasite adhesion occurs through binding to chondroitin sulfate A (CSA). Pregnant women develop antibodies that recognize CSA and inhibit adhesion, explaining the decreased incidence of PAM in subsequent pregnancies. Almost all Plasmodium placental isolates show increased expression of the var2csa gene, the product of which could thus be a target for vaccine development. There still are, however, many pending issues with documenting the full antigenic polymorphism and variability of the antigen, as well as understanding the control of var2csa expression during gestation. Human sera recognize diverse and conserved regions within var2csa, and anti-sera against expressed domains cross-react with some but not all isolates.

10.3 Vaccination against nosocomial infections

(David Kaslow)

The major infectious agents encountered in the hospital environment are Staphylococcus aureus, Pseudomonas, Acinetobacter and Enterococcus spp. S aureus is responsible for 0.5 million nosocomial infections every year in the USA, especially in intensive care units, and shows increasing antibiotic resistance: 50% of US hospital strains are now methicillin-resistant (MRSA). S aureus also is a major agent of community-acquired infections in the elderly. A good approach to fight staphylococcal infections would be a holistic strategy that includes a prophylactic vaccine, monoclonal antibodies and antibiotics.
Several *S. aureus* candidate vaccines are under development. The most advanced candidate, a conjugate vaccine based on capsular PS from 5 different serotypes, failed to show efficacy in a Phase III trial in human volunteers with end stage renal disease and had to be stopped. The next most advanced candidate, which is under development at Merck, is based on the iron surface determinant B (IsdB), a protein which is expressed on the bacterial cell surface during the growth period of the bacteria. IsdB is a member of the C-terminal sorting signal (LPXTG) protein family that is linked to cell wall peptidoglycans on the cell surface of Gram-positive pathogens. Induced by low iron concentrations, as found in human tissues, it is one of the pathogenicity factors enhancing virulence and survival of the bacteria by promoting resistance to H2O2-mediated killing by neutrophils.

Experimental IsdB vaccines provided good protection against challenge in several animal models, including i.v. challenge in a mouse sepsis model and a rat indwelling catheter model. The vaccine generated a functional antibody response as measured by an opsonization test using HL60 cells in culture. A couple of Phase I clinical trials of the vaccine have been completed and a Phase II trial is currently beginning in adult patients scheduled for cardiothoracic surgery. A second Phase II trial is planned to begin in 2009 in patients with end-stage renal disease or chronic haemodialysis.
Today, an estimated half-billion episodes of *Plasmodium falciparum* malaria occur yearly, which are associated with about one million deaths worldwide. The development of a malaria vaccine has been a major challenge, due to the antigenic variation between the various stages of development of the parasite (whether pre-erythrocytic (hepatic) sporozoite stage, erythrocytic merozoite stage or gametocyte stage), the difficulty to define the right target antigen in view of the huge complexity of the *Plasmodium* genome, which codes for about 5300 different proteins, added to the number of haplotypes of each antigen, and to their intrinsic sequence variability. The development of a vaccine also is hampered by the limitation of animal models. Animals develop an acute, lethal form of malaria, whereas malaria in humans is primarily a chronic disease with an overall case fatality rate of only about 1%-3%. Monkeys also quickly develop an immune protection against reinfection, whereas protective immune responses to *Plasmodium* develop only slowly in humans, as seen in people living in malaria-endemic countries who seldom reach an immune status before the age of 15 - 20 years.

The most advanced candidate malaria vaccine at this time is the RTS,S™ vaccine, which was developed by GSK based on a fusion protein between the surface glycoprotein of HBV (HBsAg) and the C-terminal part of the *P. falciparum* circumsporozoite protein (CSP), which is mixed with a water-in-oil adjuvant (AS01 or AS02). The RTS,S vaccine was tested in more than 2000 young children in Mozambique, where it was shown to provide, over a 4-year follow-up, 30% protective efficacy against all cases of malaria and 38% protection efficacy against severe malaria cases requiring hospitalization. In children less than 6 months of age, the vaccine showed a 60% efficacy in the prevention of a 1st episode of the disease. A Phase III clinical study of the vaccine is planned to begin by the end of 2008/beginning of 2009, which will involve 16 000 6-12 weeks old and 5-17 months old infants among 10 different sites in six African countries (Burkina Faso, Gabon, Ghana, Kenya, Mozambique and the United Republic of Tanzania).

Another CSP-based candidate vaccine under development is a live recombinant vaccine which uses an adenovirus (Ad35) as a vector. The prime-boost combination of the Ad35-CSP vaccine with the RTS,S vaccine was found to be very immunogenic and to induce robust protection against challenge in rhesus macaques. The Ad35-CSP vaccine has however not entered clinical studies yet.
Other candidate malaria vaccines have been developed that target surface antigens of the merozoite form (i.e. the blood stage) of the parasite, which also are expressed on the surface of infected RBCs. These vaccines however fared much less well that the CSP-based vaccines. Thus, a MSP-1-based vaccine adjuvanted with AS02, which had shown promising protective efficacy against experimental challenge in nonhuman primates, failed to induce protection in 1-4 years old children in Kenya and did not decrease parasitemia in the infected children. Similarly, a LSA-1-based candidate vaccine and a live recombinant MVA vector expressing the *P. falciparum* TRAP protein, have only yielded mediocre immunogenicity results.

The study of naturally immunized adults who live in malaria-endemic regions in Africa may hopefully change that bleak prospect. These individuals were demonstrated to have developed cyclophilic IgG1 and IgG3 antibodies to the parasite that block adherence and entry of the *Plasmodium* into RBCs *in vitro*, and, when mixed with human monocytes/macrophages, completely inhibit the growth of the parasite *in vitro*. This observation led to the development of a test, the antibody-dependent cellular inhibition (ADCI) test. When injected to malaria-sick children in Asia, ADCI antibodies were able to reduce the parasite load to low levels of parasitemia. These antibodies were found to be specific for a small number of merozoite antigens, among which the MSP-3 protein. A MSP-3-based candidate vaccine was developed and is currently being tested in a Phase IIb clinical trial in children in Mali.

It may be that, in the end, an effective malaria vaccine will require a combination of a pre-erythrocytic stage vaccine such as RTS,S, that prevents infection, with an erythrocytic stage vaccine such as MSP-3, that will decrease parasitemia and block parasite replication.
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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

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

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

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

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

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

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