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

Geneva, Switzerland
26 - 29 June 2011
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<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
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<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
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<tr>
<td>AAVP</td>
<td>African AIDS Vaccine Programme</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<td>ANDi</td>
<td>African network for drugs and biologicals innovations</td>
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<tr>
<td>APC</td>
<td>Antigen-presenting cell</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute respiratory infection</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette Guérin (vaccine)</td>
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<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention (Atlanta, GA, USA)</td>
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<td>CHAVI</td>
<td>Centre for HIV Vaccine Immunology</td>
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<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
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<tr>
<td>CMI</td>
<td>Cell-mediated immunity</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CRF</td>
<td>Circulating recombinant forms</td>
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<tr>
<td>CFR</td>
<td>Case fatality rate</td>
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<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>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
</tr>
<tr>
<td>DCVM</td>
<td>Developing Countries Vaccine Manufacturers</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>
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<tr>
<td>DOMI</td>
<td>Diseases of the most impoverished (Program)</td>
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<tr>
<td>DTP</td>
<td>Diphtheria-Tetanus-Pertussis vaccine</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<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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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>GIVS</td>
<td>Global Immunization Vision and Strategy (WHO)</td>
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<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
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<td>GMT</td>
<td>Geometric mean titer</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HA</td>
<td>Haemagglutinin</td>
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<tr>
<td>Hib</td>
<td>Haemophilus influenzae type B</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<td>HPV</td>
<td>Human Papillomavirus</td>
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<tr>
<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
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<tr>
<td>ID</td>
<td>Intra-dermal (route)</td>
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<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
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<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IM</td>
<td>Intra-muscular (route)</td>
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<tr>
<td>IP</td>
<td>Intellectual Property (rights)</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive pneumococcal disease</td>
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<tr>
<td>IPV</td>
<td>Inactivated polio vaccine</td>
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<tr>
<td>IVI</td>
<td>International Vaccine Institute (Korea)</td>
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<td>IVR</td>
<td>Initiative for Vaccine Research (WHO)</td>
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<tr>
<td>JE</td>
<td>Japanese Encephalitis</td>
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<tr>
<td>MAb</td>
<td>Monoclonal antibody</td>
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<tr>
<td>Men A</td>
<td>Meningococcus serogroup A</td>
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<tr>
<td>Men B</td>
<td>Meningococcus serogroup B</td>
</tr>
<tr>
<td>MDR</td>
<td>Multiple drug-resistant (TB)</td>
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<tr>
<td>MHC</td>
<td>Major Histocompatibility Complex</td>
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<tr>
<td>M tb</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>NA</td>
<td>Neuraminidase</td>
</tr>
<tr>
<td>NAb</td>
<td>Neutralizing antibody</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-governmental organization</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases (USA)</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health (USA)</td>
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<tr>
<td>NVI</td>
<td>Netherlands Vaccine Institute</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
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<tr>
<td>PAHO</td>
<td>Pan-American Health Organization</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology for Health (USA)</td>
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<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PEP</td>
<td>Post-exposure prophylaxis (rabies)</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified protein derivative</td>
</tr>
<tr>
<td>PPV</td>
<td>Pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>PS</td>
<td>Polysaccharide (capsular)</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
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<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RIG</td>
<td>Rabies Immunoglobulin G</td>
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<tr>
<td>RV</td>
<td>Rotavirus</td>
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<tr>
<td>SAGE</td>
<td>Advisory Group of Experts on Immunizations (WHO)</td>
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<tr>
<td>SBA</td>
<td>Serum bactericidal antibody</td>
</tr>
<tr>
<td>SCID</td>
<td>Severely compromised immunodeficient</td>
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<tr>
<td>SIIL</td>
<td>Serum Institute of India, Ltd</td>
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<tr>
<td>STI</td>
<td>Sexually-transmitted infection</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll like receptor</td>
</tr>
<tr>
<td>TOC</td>
<td>Test-of-concept (trial)</td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>United Nations Programme on AIDS</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VLP</td>
<td>Virus-like particle</td>
</tr>
<tr>
<td>VRC</td>
<td>Vaccine Research Center (NIH, USA)</td>
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<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>YF</td>
<td>Yellow Fever</td>
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Acknowledgements

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Financial support
The Bill & Melinda Gates Foundation, Biofarma; Crucell; Cytos Biotechnology; Fiotec; GSK; Merck; Panacea; Pfizer; Sanofi Pasteur; Serum Institute of India; The Wellcome Trust
Immunization has significantly contributed to the lowest global ‘Under 5 mortality’ ever reported. Vaccination can still contribute to further reducing childhood mortality by rolling out some of the newer vaccines already implemented in some parts of the world, increasing coverage and introducing novel vaccines, with the malaria vaccine holding the greatest potential. Besides the challenge of reaching the marginalized populations, vaccination cost remains a major impediment to vaccine use, which needs to be addressed by price reductions, operational efficiency gains as well as a better understanding of the economic impact of immunization and disease prevention.

The Initiative for Vaccine Research (IVR), a unit of the Department on Immunization, Vaccines and Biologicals (IVB), is WHO’s unified vaccine and vaccination research entity and is part of the immunization department of WHO. It also hosts the WHO-UNAIDS joint HIV vaccine initiative.

IVR has a key role in facilitating and accelerating global vaccine development efforts for priority diseases, in particular HIV, TB, malaria and dengue. IVR’s approach consists of developing the scientific consensus on key approaches and methods to evaluate candidate vaccines. This approach allows for comparative evaluation of candidates along commonly agreed immunological and clinical criteria, information that is also used to develop the necessary regulatory standards for vaccine prequalification. Major progress has been achieved in relation to malaria and dengue vaccines, in particular. In addition, IVR, in close partnership with UNAIDS, is establishing and training on best practice guidelines for participation in HIV prevention trials.

IVR, as partner of the meningitis vaccine project MVP, has been deeply involved in the development, licensure and initial roll-out of the conjugated meningococcal A vaccine ‘MenAfriVac’. After prequalification in June 2011 the vaccine went through a first stage of roll-out in three countries of the African meningitis belt, targeting the populations aged 1-29 years to maximize individual and herd protection. Roll-out, coverage, and reported safety data were excellent, and initial impact data suggest that the disease is virtually eliminated from the regions covered by immunization campaigns. The paediatric indication of the vaccine is under development.

The global adjuvant development initiative, hosted at University of Lausanne, is collaborating with IVR by providing novel adjuvant technology and formulation know-how to developing country vaccine manufacturers for several products.

Another major area of work of IVR is the generation of evidence to help formulation of immunization recommendations. This entails both the collation and systematic analysis of existing evidence, as well as the conduct of special studies to generate...
critical missing information. In the area of seasonal influenza, IVR currently hosts a subgroup of the Strategic Advisory Group of Experts on Immunizations (SAGE) that is revisiting the existing evidence for seasonal influenza immunization, reviewing the bulk of information achieved over the past years related to the burden of disease in various target groups, vaccine performance, cost-effectiveness and operational issues. IVR also serves as focal point for the Global Action Plan to increase Pandemic Influenza Vaccine Supply.

As a lead project to inform immunization policy, IVR is coordinating a project on the optimization of immunization schedules. IVR is coordinating and advising on the process, tools and datasets that should ultimately allow countries to review and adjust their paediatric immunization schedules according to the local epidemiological situation, with due consideration of operational and cost-effectiveness criteria. For example, extensive data sets and mathematical models have been developed for the pneumococcal vaccine, which will be reviewed by WHO-SAGE in due course.

IVR also supports studies on the use of oral cholera vaccine, in addition to studies addressing socio-economic and cost-effectiveness of such a vaccine in defined settings. Mathematical model will assist in evidence informed decisions on cholera vaccine stock piles in the context of humanitarian emergencies.

Finally, the department IVB is involved in “Optimize” a research initiative in partnership between WHO and PATH, aiming at developing management and technology solutions for vaccine supply and logistics in developing countries. In particular, the project is studying the feasibility of a controlled temperature chain that would allow the storage and handling of vaccines outside the cold chain under controlled and monitored conditions, hereby relaxing the demand on cold chain and logistics in vaccine delivery at the peripheral level.
Opening lecture:
“Measuring the economic impact of immunization”

Moderator: Alan Hinman/Peter Ndumbe
Speaker: David E. Bloom

Introduction

Recent research suggests that prevalent economic evaluations of vaccination have failed to account for a variety of benefits that can result from immunization. Insofar as policymakers rely on the results of economic evaluations to inform vaccination policy, these underestimates could result in misinformed decisions regarding vaccine introduction. A broader framework is therefore required to: a) sufficiently capture the full benefits of vaccination; and b) encourage well-informed vaccination policies.

While measuring the full value of vaccination presents several challenges, this lecture seeks to describe tools and steps to guide comprehensive economic evaluations of childhood vaccinations.

Links between health and wealth

Recent research demonstrates that healthy populations are fundamental cornerstones of growing economies. For example, data show that a 10-year increase in life expectancy – a key measure of population health – translates into roughly 1 additional point of annual growth of income per capita.

There are several manifestations of this ‘health-to-wealth’ link. Specifically, data show that healthy workers have lower rates of absenteeism and are more physically and mentally robust than workers who are ill or fatigued. Relative to sick kids, healthy students are better able to attend school more often and to capture more from each lesson. They also avoid long-term physical and cognitive impairments that can result from childhood disease, such as stunting from rotavirus or blindness from meningitis, respectively. In addition, healthier individuals expect to live relatively longer, so they have a natural incentive to save more for longer period of retirement. This boost in savings translates into greater accumulation of capital.

Applying the health-to-wealth link to vaccination

This health-to-wealth link suggests that any intervention that improves health – such as vaccination – also has the potential to affect income. Despite new thinking on health and wealth, current economic analyses of vaccination have not accounted for its income-generating properties or other broad benefits. Rather, traditional evaluations have included only a subset of potential benefits, including health gains, health care cost savings, and averted care-related productivity losses. Applying the health-to-wealth logic, however, reveals a broader set of vaccination-mediated benefits, including: outcome-related productivity gains, behavior related productivity gains, and community externalities.
Outcome-related productivity gains refer to increased productivity because vaccination can improve cognition, physical strength, and school activity. Extrapolating further, these gains in schooling can result in greater earning capacity as an adult. Behavior-related gains refer to benefits accruing because vaccination improves child health and survival and thereby changes household behavior. For example, fertility rates may decline if a family can achieve its target family size through fewer births. Fewer children means that parents can invest more resources into each child, which can further improve health and educational outcomes. Last, community externalities refer to benefits accruing because vaccination improves outcomes in unvaccinated community members. These ‘herd effects’ can lead to additional improvements in health and educational outcomes.

Translating these conceptual findings into empirical terms requires a specific economic tool: benefit-cost analysis (BCA). In a BCA, outcomes are expressed in monetary terms, whereas CEA expresses effects in terms of natural units (e.g. number of deaths averted) or a composite metric (disability-adjusted life years (DALY)) (Figure 3). BCA can therefore account for both health and non-health effects because both are ultimately expressed in the same units – money – and can therefore be combined. By contrast, it is difficult for cost-effectiveness analysis to handle more than one outcome at a time.

BCA presents other advantages, too. For example, it can be used to compare health and non-health interventions because, again, each is expressed in monetary units. This is particularly appealing to ministers of finance, who ultimately must decide how much funding to allocate to the health budget versus the education budget. Having a common unit for purposes of comparison can help to facilitate the priority-setting process.

Evidence emerging from the application of this framework

Bloom presented three studies that apply the broader perspective to three specific cases: a GAVI program; the Philippines Cebu study; and pentavalent Hib vaccination.

The first study focuses on a preliminary GAVI vaccination program that aimed to extend the use of a new and underused childhood vaccines to 75 low-income countries during 2005-2020, at a cost of $US13 billion. Using the broad perspective, researchers accounted not just for reduced disease, death, and medical expenses, but also for the fact that healthier children who avoid disease and related sequelae can grow to be more productive learners and earners. The study conservatively estimated the rate of return on investment in the GAVI immunization program to be 12% by 2005, rising to 18% by 2020. These crude calculations played a role in the decision to establish immunization as a pilot project for the International Finance Facility, which currently invests roughly one billion dollars into childhood vaccination programs.

The second study examined data on efforts to immunize children in the Philippines against DTP, TB, polio, and measles. The data come from the Cebu Longitudinal Health and Nutrition Survey, which cover 1,975 children born between May 1983 and April 1984. The analysis focuses on children’s cognitive development as measured by test scores on language, math, and IQ tests. Cognitive ability can affect wages earned as an adult, thereby allowing a comparison of costly vaccines early in life to higher wages later in life. Using international evidence to translate those test score benefits into earnings gains as adults, and comparing those earnings gains to the $20 cost of the vaccination package, the study finds a 21% rate of return on the vaccine spending.
In both cases, the estimated returns on investment in immunization programs compare favorably with standard hurdle rates used by organizations like the World Bank in making loan decisions. They also compare favorably to the estimated rates of return on primary education, which is the most exalted instrument of economic growth and development.

The third study involves not a package of vaccines, but rather a single immunization: the *Haemophilus influenzae* type b (Hib) vaccination. Bloom et al. conducted a systematic review of the literature to identify which benefit types had been accounted for by existing benefit-costs analyses of Hib. Of the 11 articles identified by the review Bloom et al. found that none of the articles accounted for the full benefits of Hib vaccination. Furthermore, only one of the benefit-cost analyses accounted for the fact that the Hib vaccination can be delivered in multivalent form, which can reduce marginal systems costs such as cold-chain storage and waste disposal.

In all three cases Bloom notes that researchers have failed to account for the full set of vaccination mediated benefits and/or have overestimated costs. When properly accounted for, these features can have significant and decisive implications for vaccine introduction decisions.

**Next steps**

The vaccine sphere is rapidly evolving, with new products coming to market that protect against some of today’s leading health threats. These new products often rely on more sophisticated technologies, which can result in higher vaccine prices. These higher price points can be disconcerting for policymakers, especially in the context of scarce healthcare dollars. To help set priorities, many policymakers rely on economic evaluations, and it is critical that these evaluations account for the broader set of vaccinations to ensure that their value if properly assessed.
In January 2010, Bill & Melinda Gates called for the next ten years to be the “Decade of Vaccines”. The announcement included a commitment from their foundation of US$ 10 billion over the next 10 years to realize a vision embraced by the global community to save millions of lives by increasing investments and accelerating efforts- from discovery to delivery. Meeting this challenge is what inspired leading global health individuals and organizations to join together to form the Decade of Vaccines (DoV) Collaboration, a time-limited effort whose purpose is to enhance coordination across the global community by creating a global vaccine action plan that outlines the steps necessary to achieve the DoV vision:

“We envision a world where children, families, and communities enjoy life protected from the threat of disease. The purpose of the Decade of Vaccines is to extend the full benefits of immunization to all people, regardless of where they live”

This is a unique moment in time that needs to be seized fully, turning the moment into a movement:

- New vaccines are ready for country immunization programs: meningitis A, HPV, pneumococcal rotavirus
- Promising candidate vaccines are in the pipeline: malaria, HIV, tuberculosis
- National governments are prioritizing vaccines in health strategies- governments have dedicated more resources to immunizing their citizens

The aim of the DoV Collaboration is to enhance coordination across the global community by creating a global vaccine action plan. This plan represents the first big step of the DoV initiative. It is a time-limited global effort that was launched at the World Health Assembly (WHA) in May 2011 and will be presented at WHA in 2012.

The leadership council consists of Dr Margaret Chan, Director-General of WHO, Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, Ms Joy Phumaphi, Executive Secretary of the African Leaders Malaria Alliance, Mr Anthony Lake, Executive Director of UNICEF, and Dr Tachi Yamada, President of Global Health at the Bill & Melinda Gates Foundation (BMGF).

The two co-chairs of the steering committee are Prof Pedro Alonso (Director, Institute for Global Health of Barcelona) and Dr Christopher Elias (President and CEO, PATH).
Regional consultations will take place in the next year in Africa, Americas, Asia and Europe. Input will be solicited around 4 working group themes and cross-cutting topics. The output will be a global vaccine action plan.

The four working groups are: (1) Public & Political Support, (2) Delivery, (3) Global Access and (4) Research & Development (R&D).

The charter of the Working Group “Public & Political Support” is to:

Strengthen public and political support for vaccines.

Its scope is to:

- Facilitate networking for the academic and advocacy communities around a shared agenda
- Synthesize key foci related to the existing evidence base, identifying gaps and essential policy research questions
- Advise other DoV Collaboration working groups by applying an advocacy filter to technical products

The charter of the Working Group “Delivery” is to:

Prevent, eliminate or eradicate diseases by means of achieving high and equitable coverage with effective and safe immunization along with other essential healthcare interventions.

Its scope is to:

- Build upon the current Global Immunization Vision and Strategy (GIVS)
- Help ensure country consultation and engagement
- Develop recommendations for improving immunization systems as a platform to prevent mortality and morbidity
- Create estimates of costs and financing for delivery

The charter of the Working Group “Global Access” is to:

Develop an action plan that helps to ensure global access to an adequate supply of high quality affordable vaccines with formulations and presentations that meet the needs of all countries.

Its scope:

- Efficient and effective supply procurement strategy
- Affordable pricing strategy
- Comprehensive financing strategy
  - Approaches to meet projected financing needs
  - Approaches to get greater return on available financing
- Improved demand forecasting methods and tools
In the following, the focus will be on the R&D working group.

Its scope is to:

- Understand the landscape to perform R&D prioritization, based on a review of previous prioritization exercises
- Identify and evaluate innovative ideas and processes which could contribute to overcome barriers related to near term, middle term and long term vaccine research
- Analyze available technology and process engineering solutions and technology solutions as well as regulatory pathways to accelerate the scale up of affordable vaccines for those that need them the most

The traditional approach on prioritization of disease may not be the best approach for strategic planning. Prioritization of diseases on the basis of their burden does not fit into timelines and such an approach may fail with regards to the feasibility for successful product development. Therefore, the R&D working group opted for a time-based approach, categorized into short-term, middle-term and long-term using probability of success as an arbiter. Each of the three R&D Working Group categories is organized by different Task Teams, composed by R&D core members and additional engaged experts. Meeting two to three times over the course of this time limited effort, each Task Team will look at different themes related to the main topic of interest and, once work is completed, will integrate Task Team deliverables into the overall global vaccine action plan.

- Short term: transformational research
- Middle term: translational research
- Long term: vaccine immunology

Transformational research deals with issues that overlap with the delivery and global access working groups. It will include operational research; it aims at innovations in communications, and investigates issues related to ‘knowledge, attitudes and practice’ amongst others. The sub-stream on translation research will focus on the production cost reduction through process engineering, thermostable vaccines, new vaccine combinations, new delivery systems and new adjuvants.

The sub-stream on long term research will focus on more high-risk long-term research such as nanotechnology and immunology.

R&D Task Teams have been created and coordinators for each sub stream have been nominated with the sub-streams covering the short-term, middle-term and long-term research.
Time-based approach of the R&D working group:

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<td>Stability- thermostable vaccines</td>
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In conclusion, the global vaccine action plan will incorporate input from the consultation process and build on current work and include recommendations around:

- Expanding the delivery and use of new under-utilized vaccines
- Forging mutually beneficial alliances with the private sector to develop and deliver vaccines
- Cultivating a robust scientific enterprise to discover and develop new vaccines
1.1 Burden of disease update  
Saladin Osmanov

The number of adults and children living with HIV in 2009 amounted to 33.3 million, out of which 2.5 million children under 15 years of age. 2.6 million people were newly infected in 2009 and 1.8 million died of AIDS. As in previous years, sub-Saharan Africa bore the brunt of HIV infections and AIDS deaths, with 1.8 million and 1.3 million respectively. Encouragingly, the incidence of HIV infections appears to have passed its peak sometime in the second half of the 1990s and is now in some countries is on an, albeit very slow decline. This fall in incidence has been followed, with a time-lag of about 5 years by a fall in AIDS mortality. This is due to both the falling HIV incidence, as well as better access to ARV of an increasing number of people living with HIV. Significant decreases, i.e. over 25% between 2001 and 2009, in HIV incidence have by and large been limited to sub-Saharan Africa. While the decline over the same time period has been slow in East and South Asia, admittedly from a lower baseline level than in sub-Saharan Africa. The HIV incidence has remained almost stable in the Americas and in Western Europe. Most worryingly, during those same years the incidence of HIV infections has sharply risen in Eastern Europe and Central Asia, followed by a rise in HIV prevalence, in children in particular as well as in AIDS mortality.

Genetic variability of HIV represents a particular challenge for HIV vaccine development, since cross-protection among HIV subtypes is expected to be very limited. The situation is relatively clear in the Americas and Western Europe where the HIV epidemic is dominated by B subtype, in the southern cone of Africa, India and Ethiopia, where an almost pure subtype C HIV epidemic is encountered. The Eastern Europe and Central Asia, epidemic is dominated by subtype A with a smaller fraction of subtype B infections. However, the molecular epidemiology of HIV-1 demonstrates increasingly complex patterns, with a clear shift from pure subtypes to recombinants, so-called "circularizing recombinant forms" (CRF). This co-dominance of many different subtypes and CRF is particularly evident in Western and Central Africa and in some countries the majority of circulating virus is no longer pure subtypes, but recombinants. The present HIV-1 classification is becoming more and more complicated and does not necessarily predict the immunology and biology of the virus. Therefore, it is necessary to critically assess the relevance of genetic subtypes and CRF of HIV-1 by appropriately designed vaccine efficacy trials.
1.2 RV144 prime boost trial - update & next steps  

_Supachai Rerks-Ngarm_

The RV144 study was the first HIV vaccine clinical efficacy trial to provide evidence that protection against HIV infection using a vaccination strategy may be possible. The study was performed in Thailand, using a community-based, randomized and double-blinded placebo-controlled design involving 16,000 HIV-negative males and females, 18-30 years of age. The study vaccination strategy was based on a prime-boost combination of:

- ALVAC-HIV - a recombinant Canarypox-vectored vaccine expressing HIV-1 envelope glycoprotein gp120 (subtype E, predominant in Thailand) linked to the transmembrane portion of gp41 and HIV-1 gag and protease (subtype B) produced by Pasteur Mérieux, given at 0, 4, 12 and 24 weeks
- AIDSVAX B/E, a bivalent HIV-1 recombinant gp120 protein subunit vaccine containing one protein of ach subtype B and subtype E, which was produced by VaxGen and given to volunteers at the 12 and 24 week time points.

The vaccine regimen was safe and well tolerated. In just under 53,000 person-years of observation, 125 HIV infections were observed, 51 among vaccines and 74 in the placebo group. In a modified intention-to-treat analysis, this resulted in an estimated vaccine efficacy of 31.2% at month 36 months after the last injection. Virus load was almost identical in the placebo group and in breakthrough infections in the vaccinated group, i.e. the vaccine had no effect on viraemia. Moreover, the vaccine’s efficacy appeared to wane over time after the last injection.

The results described above, in particular the low - and waning- efficacy of 31% as well as the absence of an effect on HIV viral load in vaccines led to the following conclusions regarding the utility of these vaccine trial results:

- for RV144 volunteers in the placebo group: no obligation to provide the vaccine
- for public health authorities: no sufficient scientific information to support a decision to license this vaccine strategy
- for use of the vaccine as controls in future vaccine trials: not warranted, i.e. placebo control still ethically acceptable

In a series of consultations following the analysis of the RV144 trial a number of follow-up studies of RV 144 were recommended, with the aim of:

- Determining correlate(s) of protection for use in future HIV vaccine approaches and optimizing the regimen;
- Confirming the results and demonstrate efficacy in different target population with potential for licensure;
- Describing and formally testing for differences between HIV-infected subjects who received either vaccine or placebo in RV144, in clinical or biomarker-based events, e.g.
  - occurrence of AIDS-defining events, initiation of ARV treatment, CD4 counts, plasma viral load, etc.
1.3 RV144: Post-trial scientific analysis

_Punnee Pitisuttithum_

A surrogate endpoint of protection, sometimes loosely referred to as a correlate of protection, reliably predicts the efficacy of a vaccine - while the biomarker(s) determined may or may not be protective itself. For obvious reasons of efficiencies of time and resource savings as compared to the need of waiting for and reliably determining clinical endpoints in vaccine trials, these surrogate endpoints are generally considered the “Holy Grail” of vaccine evaluation. Since a surrogate endpoint needs to be validated in a successful vaccine efficacy trial before being used in another vaccine efficacy study, the RV144, as the first successful HIV vaccine trial offers a unique opportunity to identify such a surrogate measure of protection. A study has therefore been initiated that involves 35 investigators from 20 institutions working on 32 different assays. In a first phase, specimens were evaluated and compared in a broad survey of innate, humeral, systems biology, genetic, and cellular assay. In a second, on-going (May-July 2011) phase a case control study using selected assays is being performed.

An important finding of these studies was that both the gp120 molecules contained in AIDSVAX, the protein subunit component used in the RV144 trial, as well as ALVAC-HIV, the canarypox-vectored priming vaccine in RV144, have unique antigenic properties. Thus, the gD tag of gp120, a HSV-derived protein sequence used for purification of the vaccine, positively affects antibody reactivity with conformational, but not with linear epitopes. Moreover, the specific structure of ALVAC exposes an important known site responsible for antibody-dependent cellular cytotoxicity. However, it is unknown how these antigens affected the induced immune responses nor if there were responses that allow to differentiate between the (modestly successful) RV144 and the (completely unsuccessful) Vax003 trial which used the same AIDSVAX antigen. Most importantly, it would be important to learn if the moderate protection observed in RV144 was due to any of the features described above and this question will be a main focus of the on-going correlates analysis.

1.4 Strategy for changing the landscape for HIV vaccine trials: optimizing trial design for the HIV vaccine pipeline

_Glenda Gray_

The pace of human efficacy trials of HIV vaccines is slow by any standards: trials run from 3-5 years; post trial analyses add at least another year. Therefore, a new paradigm is required to efficiently conduct large scale efficacy trials while at the same time exploring correlates of protection. Trial designs adaptations such as the ones listed allow to shorten or eliminate the gap between the trial phases described above:

- a “drop-the-loser / pick the winner” design, typically a two stage design whereby at end of first stage the inferior arms are dropped
- an adaptive dose finding
- a biomarker-adaptive design, to select right patient population and detect disease early
- an adaptive treatment switching design
• a hypothesis-adaptive design
• an adaptive seamless phase II/III trial design comprising a two stage design, “learning stage” (phase IIB) and “confirmation phase” (phase III)
• a multiple adaptive design

The result of the RV144 HIV vaccine trial provides the opportunity to alter the landscape for performing efficacy trials through a two track program: a series of sequential/iterative research trials, the goal of which is (a) to improve upon the RV144 results and attempt to define a correlate of acquisition and (b) a standard licensure trial to define the utility of the ALVAC gp120 combination in populations of public health relevance.

Sequential adaptive design phase 2B trials are proposed as another opportunity to accelerate HIV vaccine evaluation. These consist in a series of coordinated phase 2B trials that are conducted in same population/geography over time using similar entry criteria and follow up. The goal is to define as quickly as possible a regimen that appears better than placebo (40% reduction in acquisition) or to eliminate a regimen that is not better than placebo. Elements that are proposed to be adapted include the alteration of the regimen or trial based upon the initial data, alteration of trial timeframe to ask about durability in protection or whether a boost should be initiated. The merits of evaluating more than one regimen at a time consist in accelerated identification of promising vaccine candidates. In addition, they yield information on correlates of immune protection to be further pursued in subsequent trials. For trials with multiple vaccine arms, pooled analyses provide greater sample size and greater heterogeneity in immune responses and hence greater power.

1.5 HIV neutralizing antibodies and prospects for vaccine development

_Eva Maria Fenyo_

Other virus infections teach us that antibodies are important for protection. In monkey models, passive transfer of simian immunodeficiency virus (SIV) neutralizing antibodies protects against SIV, a viral infection closely related to HIV. Moreover, HIV-1 neutralizing antibodies protect against infection with a chimeric SIV with HIV-1 envelope (SHIV). However, it is not clear to-date which antibodies are neutralizing in humans or which structural properties a protective neutralizing antibody should have. It is clear, however, that in view of the enormous genetic variability of HIV, such antibodies should have broad neutralizing capacity.

A main difficulty in determining whether such broadly neutralizing antibodies against HIV exist lies in the unknown relevance of the assays used to demonstrate neutralization. Therefore NeutNet, an international network for comparison of HIV neutralization assays – has been organized. In two phases, laboratories were running pseudovirus (PSV) or virus infection (VI) assays. Viruses of different subtypes and biological phenotypes were tested against monoclonal antibodies (TriMab, 4E10, 447D) and sCD4 (phase I) or 10 polyclonal reagents (phase II).

No single assay was capable of detecting the entire spectrum of neutralizing activities.
Since it is not known which in vitro assay correlates with in vivo protection, the study concluded that a range of assays should be used for the ex vivo detection of neutralizing antibodies.

Recently monoclonal antibodies were derived by selecting for neutralization capacity. These neutralizing antibodies react with quaternary structures, i.e. epitopes that are created by protein–protein interactions that occur during multimerization. It is as a result of such reorganization that many proteins (such as enzymes and the trimetric gp120 spike of HIV-1) carry out their physiological function. Examples of monoclonal antibodies that react with quaternary epitopes are 2909 and PG16, which react with the trimetric form of gp120 on the surface of HIV-1 virions or env-transfected cells, but not with monomeric gp120. Interestingly, PG16 is broadly neutralizing but 2909 is not. These antibodies are reacting with different but overlapping epitopes and share structural similarities, usually involving V2 and V3 loops of the gp120 molecule. Most importantly, it is currently unknown how frequent this type of antibody is in HIV-1-infected individuals and even more importantly, what a vaccine should look like that induces this type of antibodies.

1.6 AAVP and the African HIV Vaccine Agenda – What next?

Chidi Nweneka

There is a striking disconnect between countries and regions with an important burden of HIV and AIDS and those where the biggest public sector investments into preventive HIV vaccine research and development are made. In Africa, which bears the highest burden of HIV/AIDS, only South Africa can be found among the 10 largest sponsors of HIV biomedical prevention research. This imbalance prompted, in the year 2000, the “Nairobi Declaration - An African Appeal for an AIDS vaccine”, which called, inter alia, upon African Heads of States and Governments as well as regional and political bodies to strengthen individual and collective efforts towards directing resources in support of an African Strategy for an HIV Vaccine and, requesting WHO and UNAIDS to facilitate the establishment of a mechanism for translating the African strategy for an HIV vaccine into tangible and deliverable outputs.

Within less than a year, the latter request of the Nairobi declaration was translated by WHO, UNAIDS and African and other international partners into the establishment of the African AIDS Vaccine Programme (AAVP), the mission of which is “to promote HIV vaccine development for Africa through research, advocacy, partnership and contribution to capacity strengthening and policy development”. During its first decade, the AAVP was housed in WHO/IVR and supported by a Steering Committee and 4 centres of excellence. The AAVP’s work was based on 5 work areas comprising (a) country-based strategic planning, (b) biomedical research, (c) communications and media, (d) regulatory issues and (e) ethics, law and human rights. In these five areas, AAVP’s strategic approach comprised capacity strengthening, advocacy, policy development, networking and community involvement. During this period, AAVP has built up an extensive network of partners, funders & other key stakeholders and achieved high level of visibility, acquiring the status of the ‘voice of the African continent in the global HIV vaccine agenda’. Moreover, AAVP has spearheaded the creation of national AIDS vaccine plans in many African countries and facilitated south-south collaboration between researchers and R&D networks. AAVP has held four bi-annual forums that provided a platform for networking among African scientists and between African scientists and scientist from other parts of the world.
In 2006, an external review of AAVP was commissioned, which identified strengths, weaknesses, as well as opportunities and threats to AAVP. While overall very positive, the review found that in order for AAVP to prosper, it was necessary to increase African ownership of and contribution to all phases of development of an effective HIV vaccine suitable for use in Africa. It concluded that in order to fulfil this goal, AAVP needed to become an independent African organization, based in Africa under African leadership, promoting and advocating for the African HIV vaccine agenda.

After an extended transition period, this goal has now been reached: with the Uganda Vaccine Research Institute, a respected African research institution has been identified as a future host of the AAVP. International as well as local AAVP boards have been installed and in June 2011 a new Executive Director has taken office. AAVP’s new programme approach is the promote the African HIV vaccine agenda through resource mobilization for vaccine R&D, capacity building, HIV vaccine advocacy, and strengthen AAVP’s partnership support programme.
2.1 Reaching adolescents with sexual and reproductive health services—implications for HPV vaccine delivery

Venkatraman Chandra-Mouli

Adolescent girls deserve particular attention. There are 600 million adolescent girls in the developing world. By virtue of gender and other social inequalities, many adolescent girls in developing countries are at risk from violence, forced early marriage, HIV/AIDS and other sexually transmitted infections – especially among the poor. Such adolescent girls may be excluded from schooling, fair employment and access to good health care. Achieving 6 of 8 MDGs (including those related to reducing childhood mortality, maternal mortality and HIV) requires concerted attention to adolescent girls.

HPV vaccination is seen as an effective tool for the prevention of cervical cancer. However, the challenge is to deliver the vaccine to girls between the ages of 9-13. Schools are an excellent setting to reach girls with HPV vaccine. But to achieve this, two conditions must be in place: girls must be in schools and functional systems must exist to deliver the vaccine. Some countries have high school enrolment and effective school health programmes. Such countries could deliver HPV vaccine as a school-based programme. However, other countries have low school enrolment and weak school health services, and therefore school-based approaches will not achieve high vaccine coverage rates.

We must reach girls as early as we can for several reasons. The proportion of girls in school starts to fall towards the end of primary school and dramatically falls after that. However, girls who are not in school are more likely than those in school to initiate sexual activity early. Globally, one in ten girls initiate sexual activity before the age of 15; 90% of the about 16 million pregnancies under the age of 19 occur in developing countries.

There are now many initiatives under way to provide adolescents with health services. The priority for the future is to ensure that each country, state and locality has a policy and support to encourage provision of innovative and well-assessed youth-friendly health services. The evidence for the effectiveness of interventions to increase young people’s use of health services was sufficient to recommend that interventions that include training for service providers, making improvements to clinics and using activities in communities should be widely implemented with careful monitoring of quality and coverage, and those that involve other sectors should also be cautiously implemented, provided they include a strong evaluation component.
In conclusion, HPV vaccine is an effective & safe tool to protect girls from cervical cancer. But it is much more than that. It provides a valuable opportunity to strengthen efforts to draw attention to their needs & to reach them with a wider range of proven sexual & reproductive health information & services.

2.2 HPV vaccination—what are the barriers to access?

*Emmanuel Mugisha*

Here we briefly summarize the experience of a pilot project for HPV vaccination in Uganda as part of PATH’s formative research into HPV vaccine introduction in countries. Two vaccine delivery strategies were employed:

- **Strategy 1**, Nakasongola District, **Child Days-based**: Vaccine delivered during Child Days Plus to 10-year-old girls both in and out of school.
- **Strategy 2**, Ibanda District, **school-based**: Vaccine delivered through schools and outreach to girls attending Primary 5, or 10 years of age if out of school.

In the study areas the vaccination achieved high coverage and good acceptance. The reasons for the acceptability included the information that this vaccine was against a cancer. Intensive efforts at communication were made which included public messages, interpersonal communication between families, health workers and other key groups such as teachers.

The pilot introduction highlighted several issues: (1) adding HPV vaccination had minimal impact on other services; (2) service providers reported benefits (e.g., opportunity to be involved in health activities, increased knowledge base, and being able to offer valuable health information to others), and (3) there is the potential to integrate HPV vaccination with other school health programs. However, it also highlighted the importance of coordinated efforts between health and education sectors for school-based immunization.

However, introducing HPV in schools was not without challenges. They include the relatively high cost of providing school health services, reaching all girls particularly where school enrolment is not optimal, and the issue of denominators for estimating coverage for a multi-dose vaccine such as HPV.

2.3 Social mobilization and logistics: yellow fever campaigns

*Edinam Agbenu*

Yellow fever campaigns are an excellent example of the complexity of social mobilization and logistics. Effective and quality logistics services are necessary to ensure that a vaccine gets to where it is needed and that the vaccine is administered in the safest manner possible. To do so requires trained staff, materials, transport and fuel for transport. In addition it is important to pay attention to the logistics needed to ensure a functioning adverse events monitoring system to pick up any AEFI and respond effectively. Injectable vaccinations are waste-producing. Therefore, logistics management must include consideration for the collection, transport and destruction of these wastes so that they do not pose any threat to human health.
2.4 School-based immunization

Rudi Eggers

The WHO/UNICEF GIVS provides the strategic framework for reaching more people through immunization beyond the infant age group. A survey of school-based immunization was conducted coupled with special in-depth analysis for select countries. A standardized questionnaire was sent to countries through WHO and UNICEF regional offices in 2006, with follow-ups to non-responders in 2007 and 2008. Clarifications were requested where information was unclear. Finally the replies received from 143 countries were collated and analysed.

This survey shows that globally school enrolment is high except in the Sub-Saharan Region. Vaccination given to a school-aged target group, using the school as venue to deliver the vaccine should be viewed as a strategy and not as a separate program. While it is easy to reach school children, a school-based programme will miss out those children not in school. More importantly, for a successful school based programme, the involvement and collaboration of the Ministry of Education is vital to the implementation of a broad-based integrated school health programme.

The result of the survey showed that 61 countries (31%) reported some form of school-based vaccination. In 85% of these countries, the approach is implemented nation-wide (note: pilot phases were included in the analysis), 97% of countries with school-based vaccination target boys and girls. And the timing was mainly at school-entry (79% of countries with school-based vaccination target grade 1), but in some cases also in secondary school. Tetanus-toxoid containing vaccines are core to school-based vaccination; in about half the countries also polio and/or measles-containing vaccines are delivered.

Some salient characteristics of School-based Vaccination Programmes include:

- Sometimes the target group is defined as age-based rather than grade-based
- Net female primary school attendance in countries with a school-based programme ranges from 28% to 99%.
- Limited information on the size of school-based vaccination: Only 52% of countries have information size of the target group, and only 49% have some information on the number of children reached.
- Figures are difficult to interpret for lack of standardization
- Coverage is sometimes reported as a % of enrolled population with no estimate of age-specific population coverage (estimated range of 30% to > 200%)

From the five-country in-depth analysis one of the key findings is that the programmes which are functioning well and providing a broad range of services are those that are nationally owned, and developed.

In conclusion, school-based vaccination is a promising delivery method that reaches enrolled children and should be explored further.
3.1 Why and which protein-based pneumococcal vaccines?

Data from high-income countries show that indirect effects have been very substantial for the reduction of invasive pneumococcal disease (IPD) for vaccine serotypes following introduction of pneumococcal conjugate vaccine (PCV). The vaccine effect on nasopharyngeal carriage appears to drive this indirect effect at least for some serotypes. The programmatic experience of PCV7 in USA shows that indirect benefits are about twice as great as direct benefits, and include unimmunized age groups. Herd protection has been established with 50% efficacy against carriage.

However, the efficacy against carriage and the reduction in serotype-specific IPD following the introduction of conjugate pneumococcal vaccines have been partially offset by serotype replacement disease. In general, total reductions in IPD have been smaller than vaccine-serotype specific effects, because of variable increases in IPD related to non-vaccine serotypes. The UK Health Protection Agency data represents a rather extreme example, whereby the vaccine-serotype reductions are almost matched by non-vaccine serotype increases in IPD. However, data need to be analysed with great care.

Conjugate pneumococcal vaccines are therefore associated with the following shortcomings: serotype specificity associated with serotype restriction and serotype replacement disease; and furthermore, these vaccines are associated with complex manufacturing and high cost.

Common protein vaccines may overcome (or complement) the serotype restriction of PCV, and may possibly be cheaper to manufacture.

Several pneumococcal proteins have been identified with a pattern of age-dependent antibody responses that suggests a role for these antibodies in protection from infection. A subgroup of these proteins have been shown to be highly conserved among pneumococcal strains, to have very low homology to human sequences, and to be protective in animal protection models following challenge with pneumococcal bacteria – these proteins are being developed as candidate vaccine antigens.

Which proteins should the Pneumococcal protein field focus on?

This R&D field is largely driven by animal models and assay system data. In general, combinations of proteins are superior to single proteins. There is considerable amount of redundancy in adhesion mechanisms and rapid recombination within and between species suggesting that multiple proteins/alleles will need to be combined.
The PCV experience shows that the carriage effect is a driver of efficacy against disease. Recent modelling work supports a strategy targeted at elimination of carriage. Licensure pathways for an anti-carriage vaccine would be simpler as they would not require head-to-head comparisons with conjugates or the need to demonstrate IPD effect against non-vaccine types. Examination of a carriage effect in a setting with introduced PCVs should also be possible with quite small studies, although considerable uncertainty exists with regards to highly ‘invasive’ serotypes e.g. 1, 5. Here there is less evidence that a carriage state precedes invasive disease.

Protein combinations targeting carriage are therefore an attractive option, most likely associated with lower R&D costs, with the idea to be additional to, rather than compete with, the successful PCVs.

### 3.2 The vaccine pipeline

*Mark Alderson*

There are various possible pneumococcal protein vaccine (PPV) strategies including proteins alone (with or without adjuvants), adding PPV to PCV, PPV as carriers for PCV, whole cell vaccine and heterologous vectors expressing relevant proteins. Several lead candidate antigens have varying degrees of sequence polymorphism and different degrees of supportive data from animal models and assay systems. The consensus is that combinations of proteins will be needed; single proteins tend to show less protection in animal models compared to conjugate vaccines and different proteins serve different and complementary functions. Recent data on a combination protein vaccine with GSK’s proprietary oil-in-water emulsion, AS02, in a non-human primate model was said to look promising. Several different animal model systems were presented.

Animal model protection from whole cell vaccine is both antibody and T-cell mediated. This presents a challenge as traditionally there are more antibody-related assays than T cell assays in the pneumococcal vaccine field. Whole cell vaccine has the benefit of inherent adjuvant properties. Intranasal challenge of whole cell vaccine has shown IL-17 dependent partial protection against carriage and protection has also been seen in a sepsis model.

With regards to clinical studies, there is a single candidate PPV plus PCV vaccine in Phase 2 trial, a candidate by GlaxoSmithKline (GSK). One of the readouts in this candidate’s evaluation is to demonstrate impact on carriage. Sanofi Pasteur is developing another PPV candidate, currently in Phase 1 trials, and to-date their results have been presented at conferences, but not yet published. Intercell’s candidate is discussed below.

Arizona State University is conducting a Phase 1 evaluation of a salmonella vector expressing pneumococcal proteins.

A hybrid strategy was raised for discussion. This would be to use a common protein as carrier for a limited valency conjugate vaccine, designed to meet the WHO/GAVI Alliance target product profile (TPP) for the advanced market commitment (AMC), with licensure based on non-inferiority to licensed PCV.
3.3 Target product profile from an industry perspective

Andreas Meinke

Intercell’s approach starts with identification of epitopes recognised by sera from exposed humans. They have thereby identified 100 proteins and tested 20-30 antigens in models for sepsis and pneumonia. Three proteins, PsaA, PcsB, StkP, were selected and are all highly conserved. The first Phase 1 clinical trial of this vaccine candidate known as IC47 showed safety and tolerability in two dose groups with and without adjuvant. An adjuvant effect was seen only for PsaA. There was a >= 2-fold increase of IgG ELISA for each individual antigen in 85-100% of the high dose group. Antibodies induced by IC47 in this clinical trial did not protect in passive transfer models in mice. The company is planning to substitute or add other proteins to IC47, with different functions in pneumococcal virulence pathways and/or mechanisms of protection.

Intercell’s perspective on a TPP for PPV: the target age group is similar to that stated in the AMC TPP for PCV i.e. young children in developing countries. In terms of safety, the profile would need to be at least comparable with other protein vaccines, and averting any self-homology by eliminating any regions known to have similarities with self-protein sequences.

The following lessons have been learned: conserved proteins do not necessarily always induce cross-reactive responses for all serotypes; highly protective antigens are often not genetically conserved; broad protection can only be achieved by a combination of several pneumococcal proteins; protective immunity for PPV is not only mediated by antibodies: and proteins must be devoid of epitopes inducing immune responses to human antigens.

3.4 Clinical trials and demonstration of public health benefits

Claire Broome

The potential public health benefit of pneumococcal protein-based vaccines (PPVs) rests on their potential protection against serotypes not covered by PCV, protection in age groups not traditionally targeted by PCV, improved protection against syndromes such as non-bacteraemic pneumonia and otitis media, and lower costs compared to PCV. GAVI aims to accelerate access to 10 and 13 valent PCV. The current constraint on clinical evaluation of PPV is that the best-defined correlate of protection is anti-polysaccharide antibody but this is not relevant for PPV. The target of PPV evaluation should be clinical protection.

The decision about which clinical evaluation strategy would be most appropriate for a given PPV would be greatly facilitated by preparatory longitudinal epidemiological studies of age-specific incidence of non-PCV serotype IPD.

An illustrative sample size calculation for a trial comparing PCV to PCV plus PPV using the baseline incidence of IPD for types not in the vaccine in the Prevenar-9 group from a previous Gambian trial is given: With an α of 0.05 and 1-tailed significance testing such a trial would be possible with a sample size for each group of less than 10,000 if 80% power and 90% efficacy against all IPD were assumed. Numbers quickly escalate if observed vaccine efficacy point estimates are lower than 90%.
What if a PPV including PCV were to be licensed using PCV criteria? The public health impact could then be demonstrated by performing Phase 4 case control effectiveness studies post introduction. In terms of nasopharyngeal carriage there is currently not sufficiently good rationale to assume that the reduction in carriage would translate to public health impact to justify licensure based on carriage alone. Studies could potentially be conducted on immunogenicity of PPVs in non-traditional target populations such as neonates and the elderly, and if these look promising clinical efficacy studies could be performed in such age groups. Animal models could inform the question of whether PPV show promise for non-bacteraemia pneumonia or otitis media compared to PCV control. Another illustrative sample size calculation for radiological pneumonia endpoint indicated that greater than 10,000 trial participants per group would be needed for a superiority trial of PPV + PCV vs. PCV alone in infants unless high incidence settings and >15% reduction in radiological pneumonia were expected.

Preparatory studies are key to defining likely benefits before pivotal clinical efficacy studies are finalized. A global collaborative approach could facilitate an efficient and transparent progress. High risk groups such as those HIV infected are potential populations for clinical efficacy evaluation due to high incidence rates for various disease manifestations, but the downside is the known lower vaccine efficacy in this group.

Individuals who have recovered from previous IPD were raised as a possible group worthy of further study of their immune responses to common protein antigens. So far, little work has been conducted in this area, though there is known to be a degree of serotype-specific deficiency in the antibody response corresponding to the previous infecting invasive serotype. A further WHO meeting is planned to discuss the issues relating to possible licensure of PPV based on a carriage primary endpoint.
4.1 Epidemiology and burden of dengue

Luiz da Silva

Dengue is caused by four dengue virus serotypes (DENV-1 to DENV-4) which are transmitted by mosquitoes of the *Aedes* genus, mainly *Aedes aegypti*. The predominant transmission cycle is between mosquitoes and humans in urban environments. Sylvatic cycles in non-human primates and transovarial transmission in mosquitoes have also been observed, which may contribute to persistence of the virus. In the last decades, the global incidence and geographic distribution of dengue has increased significantly. At least 2.5 billion people in more than 100 countries are now estimated to be at risk of dengue infection. Tropical and subtropical regions in Southeast Asia, Central and South America and the Caribbean are particularly affected. While many countries have reported increasing numbers of dengue cases in recent years, the case fatality rates have generally remained stable or declined, reflecting improved clinical management.

The two main factors driving increased incidence and geographic expansion of dengue are urbanization and globalization. Rapid urbanization in less developed countries, often without adequate housing and infrastructure, creates favourable breeding conditions for *Aedes aegypti*. In a recent study in Brazil, the average duration of dengue outbreaks was found to correlate with the size of urban populations, with outbreaks in large cities lasting more than six months. Globalization has facilitated international travel and migration and thereby leads to geographic dissemination of the four different DENV serotypes. In most dengue endemic areas, co-circulation of several DENV serotypes is observed, which has been associated with increased severity of disease.

Dengue places a significant disease and economic burden on endemic countries, and dengue outbreaks can have overwhelming effects on health care systems. In contrast to many other diseases, the impact of dengue is not necessarily diminished by economic growth, as shown by the increasing importance of dengue in emerging economies such as Brazil. In the absence of a licensed vaccine or specific therapeutics, dengue control efforts tend to focus on vector control measures. However, vector control is very costly and labour-intensive, requiring a large and well-trained workforce. Success of vector control measures in the past, for example in the American tropics, has been difficult to maintain. The development of a dengue vaccine therefore represents an important approach to more effective disease control in the future.
4.2 Clinical diagnosis and case classification

Vinh Chau Van Nguyen

Clinical evolution and outcome of dengue infections are often difficult to predict. Dengue infections may remain asymptomatic or lead to various clinical presentations ranging from self-limiting febrile illness to life-threatening conditions. Clinical management can be facilitated by appropriate case classification systems. The WHO dengue case classification system was last revised in 2009 ([link](http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf)).

The previous version of the case classifications published in 1997 categorized symptomatic dengue infections into “Dengue Fever (DF)” and “Dengue Haemorrhagic Fever (DHF)” characterized by plasma leakage that may lead to “Dengue Shock Syndrome (DSS)”. These case classifications were widely adopted and implementation of the accompanying management guidelines has contributed to the decrease in case-fatality rates. However, the changing epidemiology of dengue in recent years has resulted in changes in clinical manifestations, including shifts in the age of dengue patients and an increase in clinically severe cases which do not fulfil the criteria for DHF. In response to requests for reconsideration of dengue case classifications, WHO/TDR supported a prospective clinical multicentre study across dengue-endemic regions (DENCO) to collect evidence about criteria for classifying dengue into levels of severity. Several expert consensus groups convened by WHO recommended a revision of the classification, which was adopted in 2009.

The current WHO dengue case classification system categorizes symptomatic dengue infections into “dengue” and “severe dengue”. Severe dengue is characterized by at least one the following three criteria: severe plasma leakage, severe haemorrhage and severe organ impairment. Triage and case management are further facilitated by the definition of warning signs, resulting in three groups of patients: dengue cases without warning signs to be treated as outpatients; dengue cases with warning signs to be referred for in-hospital care; and severe dengue cases requiring emergency treatment. A recent multicentre study in 18 countries concluded on high acceptance and applicability of the current case classification system, particularly with respect to triage and case management. In addition to clinical management, the classification system can be adapted to dengue surveillance and to measurement of clinical endpoints in dengue vaccine and drug trials.

Laboratory assays to confirm clinical diagnosis of dengue use direct (virus isolation, RNA detection, antigen detection) and indirect detection methods (IgM/IgG serology). Diagnostic assays differ by the level of confidence in test results, the accessibility of technologies and the application time window with respect to the course of infection. Various dengue diagnostic kits are now commercially available, and WHO/TDR has established a network of laboratories to evaluate these tests by criteria such as sensitivity, specificity and ease of use.
4.3 Immune responses to dengue vaccines: implication for safety and efficacy

Alan Barrett

DENV infection has been shown to confer long-term immunity against re-infection by the same serotype, but only short-term immunity against a secondary infection by one of the three heterologous serotypes. Dengue vaccine development efforts therefore aim for a tetravalent vaccine which simultaneously provides long-term protection against all four DENV. Tetravalent vaccine development is complicated by the fact that the four DENV are genetically and serologically quite distinct. For example, amino acid homology in the E protein, a major immunogen for protective immunity, ranges from 62 to 77% between the four DENV. In addition, immune interference between the individual components of a tetravalent formulation poses a challenge for live-attenuated dengue vaccines.

Mechanisms of protective immunity against dengue infection are poorly understood. There is currently no consensus on immunological correlates or surrogate markers of protection against dengue, and it appears increasingly likely that correlates of protection will only be determined in efficacy trials. For licensed vaccines against other flavivirus diseases (yellow fever, Japanese encephalitis and tick-borne encephalitis), it is clear that neutralizing antibodies are critical component of protective immunity, and neutralizing antibody levels are used as surrogate markers of protection. Maternal antibody and passive protection studies indicate that humoral immune responses also play a major role in protection against dengue. Moreover, induction of high titre neutralizing antibodies appears to provide indication of protective responses in monkeys, and studies with chimeric dengue vaccine candidates suggest that neutralizing antibodies against the E protein are a major determinant of protective immunity. However, it is currently unclear what threshold level of neutralizing antibodies is required for protection. Furthermore, measurement of tetravalent antibody responses is complicated by cross-reactivity of antibodies as well as by differences in immune responses between flavivirus-naive and previously infected individuals. In addition to the important role of neutralizing antibodies, there is indirect evidence suggesting that other immune mechanisms such as cytotoxic T cell responses may also be involved in protective immunity.

Dengue immunological studies and vaccine development have been hampered by the fact that unlike for other flaviviruses, there is no animal model for human disease in which candidate vaccines could be evaluated for protective efficacy and safety. Moreover, immune responses to DENV are more complex than for other flaviviruses due to the potential role of immune enhancement in dengue pathogenesis. There is evidence that both innate and adaptive immune responses, including non-neutralizing antibodies, T cell responses and cytokines, play a role in immunopathologically mediated disease. Antibody-dependent enhancement (ADE), whereby pre-existing non-neutralizing or sub-neutralizing antibodies enhance uptake of virus-antibody complexes into FcγR-bearing cells, has been proposed as the primary mechanism for immune enhancement. ADE has been observed in cell culture studies and would be consistent with the increased risk of severe disease observed in secondary heterotypic DENV infections as well as in infants with waning maternal DENV antibodies. However, other studies have found that enhancement is not observed for all DENV strains and that levels of enhancing antibodies observed in cell culture assays do not predict viral burden or clinical severity in subsequent secondary dengue infections.
There are theoretical concerns that dengue vaccines could induce imbalanced or short-lived antibody responses, resulting in low antibody titres which are not protective and may even enhance disease upon subsequent infection. However, dengue vaccine trials to date have found no evidence of increased susceptibility to subsequent DENV infections.

4.4 The YF-dengue chimeric vaccine candidate

Jean Lang

The current dengue vaccine lead candidate, which has been developed by Sanofi Pasteur, is based on replacement of the prM/E genes of the live-attenuated YF17D vaccine strain with the prM/E genes of DENV. The tetravalent formulation consists of four chimeric YF-DEN (CYD) viruses containing the YF17D replication machinery surrounded by an envelope corresponding to the respective DENV serotype. Antibodies induced by the tetravalent vaccine have been shown to neutralize a large number of DENV strains from different endemic regions.

The candidate vaccine has already been evaluated in 6000 subjects, 70% of which were children in endemic countries in Asia and Latin America. Phase I and II trials so far have shown a satisfactory safety profile. Reactogenicity tends to decrease with successive doses, and no increase in reactogenicity was observed in individuals with pre-existing dengue antibodies compared to dengue-naïve individuals. Seropositivity rates were found to increase and become more balanced with successive doses, with seropositivity rates of more than 90% against all DENV serotypes post dose three.

A first efficacy trial (phase IIb) is being conducted in about 4000 Thai children aged 4-11. The primary endpoint is efficacy after three doses in preventing virologically confirmed dengue disease of any severity due to any of the four serotypes. Preliminary efficacy results are anticipated by the end of 2012, based on 27 expected dengue cases post dose three (assuming 70% efficacy and an attack rate of 1.3%). In follow-up studies lasting three years post-vaccination, laboratory diagnosis of dengue will be performed in all hospitalized febrile illness cases. Phase III studies to evaluate commercial scale lot consistency, extended efficacy and large scale safety have already been initiated in six countries. Efficacy studies include two multi-centre trials aiming to enrol more than 30 000 children aged 2-16 years from multiple Asian and Latin American countries.

According to the current target product profile, the vaccine will be administered subcutaneously in a three dose schedule at 0, 6 and 12 months, starting from two years of age. Submissions for licensure will be primarily targeted at high disease burden endemic countries. Scale-up of manufacturing capacity, including construction of dedicated facilities, is under way in order to minimize the time from vaccine licensure to availability. If results of clinical trials continue to be favourable, availability of the vaccine could be envisaged within the next four years. Continued development efforts may result in further improvements of the product profile, including additional target groups such as children below the age of two, or a more compressed regimen which would make the vaccine more suitable for travellers.
4.5 The dengue vaccine pipeline - opportunities and challenges

Anna Durbin

In addition to the chimeric YF17D dengue vaccine candidate by Sanofi Pasteur, three other live attenuated tetravalent dengue vaccines are currently in clinical development. A vaccine candidate attenuated by serial cell passage developed by GSK has completed phase II trials, but further development is currently not planned. Live attenuated recombinant candidates based on DENV intertypic chimeras and/or targeted mutagenesis have been developed by NIH and are undergoing phase I/II clinical evaluation. Another live attenuated recombinant candidate based on serial cell passage and DENV intertypic chimeras, which has been developed by Inviragen, is in phase I clinical evaluation.

Characteristics of an ideal dengue vaccine include induction of long-lived protective immunity already after one dose and safety for both vaccinees and the environment. Current LAV candidates appear to require multiple doses in order to achieve a balanced tetravalent immune response. This is thought to be due to immune interference between the individual live attenuated viruses in tetravalent mixtures, whereby some strains “outcompete” others in terms of immunogenicity. Selection of individual viral strains based on infectivity, as well as multidose schedules with interdose intervals of several months has been shown to improve the induction of a balanced immune response. Threshold antibody levels required for protective immunity against the different DENV serotypes remain to be determined, and long-term persistence of vaccine-induced antibody titres is not yet clear. With respect to safety, LAV candidates have so far shown an acceptable short-term safety profile in the post-vaccination period, and no evidence for vaccine-related dengue-like illness has been observed. However, long-term safety remains to be evaluated, including theoretical concerns about immune enhancement of disease in vaccinees with subsequent wild-type DENV infections, which may occur many years after vaccination. Data from trials so far do not show any evidence of immune enhancement or of other, LAV-specific theoretical safety concerns such as transmission to mosquitoes, reversion to virulence or recombination with wild-type flaviviruses.

Various nonliving dengue vaccines are also being evaluated. Phase I proof-of-concept trials with monovalent candidates have been completed for a subunit vaccine developed by Merck and a DNA vaccine developed by NMRC. In addition, vaccine candidates based on purified inactivated DENV, VLPs and various viral vector systems are in preclinical development. One advantage of nonliving vaccines over live vaccines is the lack of replication competition between the individual components of tetravalent mixtures, which may facilitate induction of a balanced immune response. Moreover, some nonliving vaccine candidates are designed to express only those DENV antigens thought to induce potent neutralizing antibodies, rather than cross-reactive, potentially disease-enhancing antibodies. Nonliving vaccine candidates are also evaluated in heterologous prime-boost approaches together with live-attenuated candidates, which may allow for combining advantages of different technologies.

In summary, the current dengue vaccine pipeline is advanced and diverse and appears to have high potential for giving rise to a first generation of vaccines and possibly second generation vaccines with improved product profiles. As the first dengue vaccine may be licensed within the next few years, delivery issues such as supply and demand, affordability and introduction in the context of national immunization programmes are receiving increasing attention in the dengue vaccine community.
4.6 Long-term safety evaluation

Donald Burke

While clinical trials so far have shown no evidence for an increased risk of severe disease in vaccinees, evidence of immune enhancement from natural dengue infections makes it seem prudent to proactively develop a careful long-term safety analysis plan for dengue vaccines. The Vaccine Modelling Initiative (VMI), in collaboration with the WHO and the Dengue Vaccine Initiative, is exploring the potential of mathematical modelling to improve understanding of hypothetical risks and to guide risk mitigation strategies, pharmacovigilance programmes and phase IV study designs. A first joint WHO/VMI dengue modelling workshop in 2010 brought together mathematical modellers and dengue epidemiologists, clinicians and vaccine developers, in order to review current dengue transmission models and determine future priority research questions related to dengue vaccination.

A key parameter for dengue transmission models is the basic reproductive number $R_0$ that characterizes DENV transmissibility. Epidemiological data on the incidence of severe dengue in Thailand are consistent with spatial variation of $R_0$, leading to an epidemic wave structure, i.e. waves of severe disease emanating from Bangkok (where $R_0$ is highest), which reach more distant provinces up to several months later. However, use of a single value of $R_0$ may not sufficiently reflect complex dynamics between different serotypes. Therefore, more elaborate version of the S-I-R (susceptible-infectious-recovered) model of dengue epidemics incorporate interactions between the four DENV serotypes such as short term cross-protection and potential later enhancement of disease.

Modelling of vaccine introductions is based on current concepts of dengue dynamics. For example, the duration of short term cross-protection observed in natural infections provides an estimate for how long vaccines could have broadly protective antibodies which may wane at a later stage. In one preliminary dengue vaccination model, protective serotype-specific immunity, cross-serotype immunity and herd immunity were found to collectively overwhelm enhancement of disease in most (but not all) simulations. Modelling was based on various assumptions, e.g. related to vaccine efficacy. It will be important to measure the key immunological parameters needed for vaccination modelling in on-going clinical trials. In this respect, increasing contacts and informal collaborations between modellers and investigators of dengue cohort studies and vaccine trials are very promising.

In addition to safety, several other priority questions can be addressed by dengue vaccine modelling, such as the optimal age of vaccination or changes in the patterns of epidemics after widespread immunization. To complement simulations based on mathematical equations, individual-based simulation approaches are being developed, which enable spatial and temporal visualization and tracking of individuals and may make modelling easier to understand.
5.1 Influenza vaccine production technology transfer

Jan Hendriks

A WHO initiative exists to increase global and equitable access to influenza vaccine in the event of a pandemic by supporting developing country production capacity through technology transfer. TRIPS Art 66.2 obliges developed countries to promote technology transfer.

In cooperation with WHO, the former Netherlands Vaccine Institute (NVI) has established since early 2008 an expertise and training center for influenza vaccine production for technology transfer to manufacturers in lower- and middle income countries.

As of January 2010, this expertise centre for influenza vaccine production was, together with the Research and Development Unit of the former NVI, re-integrated into the Infectious Diseases Unit of the National Institute for Public Health and the Environment (RIVM). This Unit reflects more than 100 years of extensive knowledge and experience gained through vaccine research, development, production and technology transfer. RIVM functions as a training centre and as resource institute for WHO’s Global Learning Opportunities on Vaccine Quality and for manufacturers in low- and middle-income countries.

The Developing Countries Vaccine Manufacturers (DCVM)-Network is a voluntary public health driven alliance of vaccine manufacturers from developing countries aiming at consistent supply of quality vaccines accessible to developing countries (www.dcvm.org).

NVI/RIVM has established and optimized (since early 2008) an in-house and egg-based pilot seasonal influenza vaccine production process suitable for up scaling, training and technology transfer to DCVM-Network members. The process to produce seasonal vaccine can be applied to potential pandemic vaccines (in particular H5N1) for public use when appropriate reference strains become available. The process is at pilot-scale (10,000 eggs), using semi-automated equipment to produce whole cell vaccine and follows WHO guidelines (as outlined in the recommendations for the production and control of influenza vaccine inactivated, WHO TRS 927, 2005).

NVI/RIVM runs generic international influenza vaccine production courses, which also include aspects of cGMP, Quality Control, Quality Assurance and regulatory affairs.
Candidates for these courses were selected through WHO/IVR and the Developing Countries Vaccine Manufacturing Network (DCVMN). Preference was given to candidates coming from institutions or companies from low and middle-income countries that had received through WHO/IVR a seed grant to establish influenza vaccine manufacturing capabilities within their organization.

Bilateral agreements exist with Vacsera (Egypt), IVAC (Viet Nam) and UNIL (Switzerland). For example, the collaboration on technology transfer with UNIL provides training and technology transfer for dose-sparing adjuvants for influenza vaccine to DCVM countries. RIVM is consultant to UNIL on GMP and training to establish oil-in-water production at BioFarma (Indonesia). Tailor-made courses are being conducted for National Regulatory Authorities (NRA). Such an establishment of a ‘hub’ for influenza is an important capacity-building tool.

Interested recipient-parties are advised to consult viability criteria established previously by WHO. The viability of local vaccine production requires various critical elements, including GMP, quality control, adequate management structure and legal status.

5.2  Open platform for key technology: adjuvants

*Martin Friede*

Adjuvants play a critical enabling role in vaccinology for the following reasons:

- Inducing cell mediated immunity to non-live vaccines
- Enhancing immunity to recombinant antigens
- Dose reduction of pandemic influenza vaccines
- Increasing the breadth of immunity
- Increasing speed of seroprotection / reducing doses
- Inducing immunity in non-responding populations

Adjuvants tend to be proprietary, therefore there is limited access to researchers and little know-how on transfer agreements to researchers and manufacturers alike. These problems resulted in the use of available but often inappropriate adjuvants. Aluminum based adjuvants for example are widely used and acceptable, but are still one of the most difficult adjuvants to use as they are weak adjuvants. In contrast, water-in-oil emulsions are strong adjuvants, but are associated with more reactogenicity.

Therefore, R&D of vaccines requires access to know-how and appropriate adjuvants. Two public-sector adjuvant centers have been established to address this need.

1. The Infectious Diseases Research Institute (IDRI, Seattle, USA) conducts research, development and supply of adjuvants to the vaccine community, in particular for GLA (synthetic TLR4 agonist) and squalene emulsion.

2. The Vaccine Formulation Laboratory at the University of Lausanne (UNIL) serves as a centre that offers open provision of formulation services and generic adjuvants (EU), training on vaccine formulation and adjuvants, and harmonization of assays and kits, and technology transfer of processes and supply of generic adjuvants.
For example, IDRI provided technology transfer to the Cantacuzino Institute (Romania) for H5N1. UNIL established a technology transfer hub for oil-in-water emulsions. UNIL did a technology transfer to BioFarma (Indonesia) for adjuvanteion of H5N1. Other examples for open-platform activities are the establishment of a preclinical dossier with commercial adjuvant by UNIL to achieve a dose reduction of IPV with an adjuvant. In preclinical studies, a >10-fold dose reduction with oil-in-water emulsion was shown.

Open access centers are critically important to facilitate vaccine development. But open-access can be associated with risk of inappropriate use of adjuvants in clinical research, and controlled access to qualified users may be necessary.

5.3 Cholera vaccine technology transfer

Rodney Carbis

WHO estimates that only 5-10% of cholera cases are reported. The burden of cholera is likely to exceed 1 million cases annually with an estimated number of 120,000 deaths. This translates into 330 deaths per day. Therefore there is a need for a safe, high quality affordable vaccine. In order to make the vaccine available to impoverished communities, technology transfer needs to be done.

The International Vaccine Institute (IVI) Korea has the following vision statement: “To promote the health of people in developing countries by the development, introduction and use of new and improved vaccines”

IVI has established several requirements to perform technology transfer:

- Manufacturer operates in compliance with WHO cGMP standards
- Manufacturer has the capacity to achieve WHO pre-qualification
- NRA in the country of the manufacturer needs to have met WHO requirements
- Manufacturer should have capacity to produce or acquire bulk components
- Demonstrated capacity to scale up process from pilot scale and convert into a product
- Commitment to public health and to supply market demand

There are 3 models for vaccine development at IVI: using (1) the technology from existing manufacturers (2) the technology from the inventor (universities, small companies, NIH) and (3) the technology developed in house at IVI.

An example for a successful technology transfer by using the technology from an existing manufacturer is the inactivated whole cell vaccine for cholera, where transfer occurred from a Vietnamese manufacturer to an Indian manufacturer, facilitated by IVI.
A vaccine against cholera (Dukoral; Crucell/SBL Vaccin AB) was licensed and WHO prequalified, but very expensive (>40 Euro for 2 doses). In contrast, ORC-Vax from Vietnam VaBiotech was not WHO prequalified, but was priced at only US $1.00 per dose. ORC-Vax (VaBiotech) has inactivated Inaba and Ogawa (O1) plus O139 cells, is an oral vaccine, and was first licensed in 1997. Steps were taken to make ORC-Vax suitable for transfer and to address cGMP issues. After successful transfer, clinical studies were conducted. High level of process control and lot release assays were in place, with detailed SOPs for production and quality control. Phase II studies showed that the vaccine was safe and had immunogenicity with superior vibriocidal responses compared to existing Vietnamese vaccine and the internationally licensed Swedish vaccine with results similar in non-endemic and endemic settings. The vaccine provided 70% protection for at least 3 years in a Phase III trial conducted in Kolkata, India, with 65,000 subjects aged one year and older. Scaling up was conducted at Shantha, India.

5.4 Perspectives from a technology recipient

Suresh Jadhav

The vaccine industry faces various challenges such as competitive differentiation to balance the need of stakeholders, fill technology gaps, unpredictable markets, ever changing regulatory scenarios and intellectual property issues. Technology transfers are an integral component of the options to build, buy and partner. The success of any tech transfer depends on financial issues, the viability and sustainability of the project, the adaptability for the recipient to absorb new technology [existing infrastructure/human resources and prior experience, and future incentive] Technology transfer can be classified into: a) Embodied technology transfer: Flow of knowledge embodied in new products, materials, tools, machines and similar equipment. b). Disembodied technology transfer: other forms of flow of technical knowledge.

Technology transfer may include:
- Sales/purchase of results oft he R&D work
- Turnover of licenses, patents, utility models and know-how
- Sales/purchase of production techniques, means of automation etc
- Technological advisory/consulting
- Technical staff training

Tech transfers have played an important role in capacity building of Developing country vaccine manufacturers. Here we present the role of tech transfer at the Serum Institute of India Ltd (SIIL). Founded in 1966, SIIL is India’s biggest biotech company and the world’s 5th largest vaccine producer with installed capacity of over 1 billion doses of different vaccines. SIIL is partner to international agencies such as WHO, PAHO, UNICEF and GAVI. The operations began in 1967 with tetanus antitoxin and toxoid. Important milestones are the fact that by 1999 SIIL was the world largest producer of measles and DTP vaccines, by 2001 it launched indigenous manufactured recombinant hepatitis B vaccine, 2004 liquid human diploid cell rabies vaccine, 2005 DTP-Hepatitis B combination vaccines, 2007 Hib Vaccine, 2008 the pentavalent vaccine, and in 2010 it achieved WHO prequalification of the pentavalent vaccine.
In 2010-2011, SIIL launched H1N1 and Men A conjugate vaccine with WHO prequalification for Men A conjugate Vaccine. Its evolution and success was closely related to technology transfer. For example, for the Meningitis conjugate A Vaccine, the know-how was transferred from CBER, FDA, USA and SynCo Biopartners. SIIL is now able to produce the vaccine for sub-Saharan Africa at a special introductory pricing of less than 50 cents/dose. The vaccine is WHO pre-qualified and production target is 50 million doses per year. Furthermore, SIIL was a major contributor of MR, MMR and Rubella vaccine and contributed significantly to the vaccine requirements in the Americas. SIIL now belongs to the top ten suppliers of PAHO.

International agencies such as WHO, NVI, PATH, US NIH played an important role in successful technology transfers. Political will and NRA support is equally important for such technology transfers.

5.5 Conjugated Meningococcal A Vaccine

Jean-Marie Préaud

A good example of efficient technology transfer is the development of the conjugate serogroup A meningococcal vaccine for Africa (MenAfriVac).

Because of the advantages of the conjugate meningococcal over the polysaccharide meningococcal vaccine, the Epidemic Vaccines for Africa (EVA) project was established at WHO by Dr Luis Jodar. In-depth discussions with vaccine manufacturers ensued in 1999 and 2000 that resulted in the development of costing models for conjugate vaccines and the evolution of a collaboration between WHO and CVP/PATH. In June 2001, funded by a grant from the Bill & Melinda Gates Foundation, a 10-year partnership between WHO and PATH was created, called, Program for Appropriate Technology in Health. Its mission was to eliminate epidemic meningitis as a public health problem in a sub-Saharan Africa through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines. By the end of 2001, beginning 2002 discussions took place between African public health officials and WHO/AFRO. Because the cost of conjugate vaccines was the main limiting factor on the background that the meningitis belt countries are the poorest in the world, any success of a meningitis vaccine project (MVP) would only be possible unless vaccines were priced less than US$ 0.50 per dose. After extensive discussions a decision was made to pursue the development of a monovalent A vaccine because the biggest proportion of meningococcal isolates from Africa is Neisseria meningitidis serogroup A. A monovalent serogroup A conjugate vaccine has the advantage of simplicity, low price-sustainability and lower risk and would therefore result in a solid public health impact.

Because no agreement could be reached with major vaccine manufacturers, negotiations ended in March 2002. MVP decided to pursue the development of a Men A conjugated vaccine using a different strategy by creating a consortium to do the following:

- Identify sources of raw materials (Men A PS and tetanus toxoid)
- Identify a conjugation method
- Identify a vaccine manufacturer willing to accept technology transfer (fermentation and conjugation) and make the conjugate vaccine at a price less than $US 0.50 per dose.
SynCo BioPartners in Amsterdam agreed to provide polysaccharide for the project. Conjugation method was developed at CBER/FDA, Bethesda, USA and transferred to Serum Institute of India, Ltd (SIIL). The production process and analytical methods were transferred to SIIL team after a three-week intensive training at CBER, Bethesda, including the preparation of lab-scale batches. Biocomparability protocols have shown that the materials produced at lab scale, then pilot scale, and industrial scale were qualitatively comparable to the material produced by Synco.

Subsequently, the lots produced at industrial scale have been tested and used for the Phase II and Phase III clinical trials. The formulation and lyophilization of the MenA conjugate vaccine was developed at Aérial, Illkirsch, France.

South/South transfer of a vaccine product as shown in the above example occurred at an affordable price. The end result was capacity building for the Indian manufacturer (SIIL) and for Indian and African clinical investigators. This could serve as a model for other vaccines/products.

5.6 African network for drug and biologicals innovation

Solomon Nwaka

There is an increasing emphasis on pharmaceutical R&D and manufacture in Africa. The AMCOST Cairo Declaration of 2006 stated the intent to promote R&D and develop innovation strategies for wealth creation and economic development. But existing capacity is not coordinated or leveraged to solve African health challenges, and the focus remains on external collaborations. This is seen in the fact that only 5% of research articles are in collaboration between two or more African countries. However, African research capacity is increasing as shown by increasing presence of research centers.

The African network for drug and biologicals innovation (ANDI) was founded to address these issues. ANDI was launched in Abuja in 2008. Its goal is to promote and sustain African-led product R&D innovation through the discovery, development and delivery of affordable new tools, including those based on traditional medicines. ANDI will also support capacity and infrastructural development. The Secretariat and Central Office of ANDI is now hosted by the United Nations Economic Commission for Africa (UNECA) in Addis Ababa, Ethiopia. The ANDI Board membership comprises representation from each of the 5 subregions of Africa, leading health experts, a representative from the African Diaspora, and key institutional partners - UNECA (legal hosts for ANDI), the World Health Organization (WHO), and the African Development Bank (AfDB).

The mission statement is “To promote and sustain African-led health product innovation to address African public health needs through the assembly of research networks, and building of capacity to support human and economic development."

The vision is to create a sustainable platform for R&D innovation in Africa to address Africa’s own health needs.
To achieve this, a business model has been developed with core R&D activities, network support and brokerage (advocacy and public/private partnerships). ANDI’s sees it’s key roles in project identification and support, support on project management, building up centres of excellence, infrastructural support, IP management (including licensing and technology transfers) and advocacy (stakeholder involvement, increased funding, regulation/validation, access etc) as well as brokerage of partnership and public and private collaborations. A trust fund at UNECA has been set up with the intent to grow to $30 M p.a. in regular contributions in 5 years. Additional trust funds with other partners and endowment funds are being explored. There is also potential to leverage financing for projects through national resources, governments and development agencies, trade banks, foundations and others.

To-date, 207 project applications have been received by region for R&D activities for drugs, vaccines, diagnostics, medical devices and technologies.
Session 06:
Report from satellite workshops

Moderator: N. Ganguly
Rapporteur: U. Fruth

6.1 Report from Workshop on maternal immunization
Rapporteur: Marc Steinhoff

Significant neonatal, young infant, and maternal morbidity and mortality still occur, mostly in low-resource countries, despite the fact that many causes of these deaths are vaccine preventable. Immunization against selected infectious diseases during pregnancy is a potential strategy to reduce severe disease in mothers and their newborn infants, all the more since even in low income countries, antenatal care frequently reaches pregnant women.

In a number of diseases, there is demonstrated benefit of maternal immunization. Thus, vaccination with tetanus vaccine to prevent neonatal tetanus is a well-established strategy that has had significant impact on the reduction of deaths due to neonatal tetanus in developing countries. Seasonal influenza vaccine was recommended for pregnant women as early as 1960 in the US and, even in the current WHO recommendation, pregnant women are included as target for influenza vaccination. Pertussis disease is predominantly in young children, particularly infants less than 3 months of age. Recently CDC recommended pertussis vaccination in late pregnancy to prevent the disease in neonates.

*Streptococcus pneumoniae* (pneumococcus) is an important cause of childhood pneumonia. While the safety of repeat doses of 23-valent pneumococcal polysaccharide vaccine (PPV23) needs study, maternal PPV23 may be more useful than neonatal immunization with PCV because of the serotypes not contained in the conjugate vaccine causing disease in early infancy. Thus, maternal PPV23 vaccination could potentially be beneficial to mother, fetus, neonate or the infant. Although Hib vaccine too may have a role to protect the neonate or the young infant through maternal immunization, given its high herd immunity, it is felt that probably this is not needed. There are other respiratory diseases such as RSV, *Group A Streptococcus*, *Group B Streptococcus*, against which vaccines are being developed and, in future, they may become candidates for maternal immunization when vaccines become available. At present the only other bacterial disease against which large scale immunization campaign is being rolled out is that of conjugate meningitis A vaccine across the meningitis belt of Sub-Saharan Africa and, even though clinical trial did not include pregnant women, the Global Advisory Committee on Vaccine Safety (GACVS) recommended that pregnant women should not be excluded from receiving it.
While all of these are truly exciting and promising for future childhood deaths as well as protect the pregnant woman, there are also many challenges. The meeting dealt at great length on some of the key challenges. They include:

- Safety considerations, such as the (theoretical) risk to a developing fetus from vaccination of the mother during pregnancy
- Affordability and access, with vaccines such as the ones to protect against seasonal influenza or pertussis bearing price tags beyond what low income countries can afford to pay
- Logistics and implementation challenges, even where services are reached relatively better, monitoring coverage and measuring impact remain stumbling blocks.
- Lack of inclusion of pregnant women in pre-licensure clinical trials as an impediment for getting the indication for use in pregnant women into the product monographs.

The group listed several future research topics/agenda for consideration to strengthen the evidence base for the use of vaccines in pregnancy, including, but not limited to (a) performance of detailed, age-specific burden of disease studies in various settings and, particularly focusing around the neonatal and young infant age group, (b) conduct of large-scale efficacy trials of maternal immunization powered to assess laboratory-confirmed clinical outcomes in young infants, (c) operational research to determine the feasibility and cost of delivering influenza vaccine to pregnant women, (d) operational research into the feasibility of including specific vaccines into routine antenatal care and (e) cost/benefit and cost effectiveness analyses including infant effects.

6.2 Report of the workshop on virus-like particle (VLP) technologies

Stanley Plotkin

Virus-like particles (VLP) are a way of constructing viral particles composed of viral protein antigens needed for protection, without chemical inactivation and without sufficient genomic material to allow for replication. Thus, it has none of the safety issues of live viruses, it allows for presentation of unchanged epitopes. The basic discovery was that under certain conditions, some viral proteins found in regular array on the surface of the virus, self-assemble in solution. The power of the approach is that viruses and VLPs are of the size 20-100 nm that penetrate vessels and are carried to lymph nodes where B cell responses can be induced. In addition, they can elicit T cell responses because they are taken up by dendritic cells and macrophages, which again carry them to the lymph nodes, where they are more immunogenic for T cells than soluble antigens.

The workshop reviewed a number of different VLP-based vaccine development approaches in a variety of diseases:

Human papillomavirus: Prophylactic HPV vaccine is the most successful example of VLPs. Their immunogenicity is better than nature, because in nature HPV antigens never get beyond the basement membrane to the lymph nodes and thus there is no immune response. The vaccine has already decreased precancerous dysplasia in Australia.
Influenza: NA, HA, and M1 proteins of the virus are needed to assemble VL particles. The VLP are highly immunogenic in mice and ferrets. Their immunogenicity is similar to inactivated virus, but in addition they generate T cell responses.

Noroviruses: are the 2nd most important viral cause of diarrhea in children and adults, after rotavirus. There are two genotypes, G1 and 18 different G2. Four G2 genotypes are now most prevalent and cause 80% of disease. VLPs are produced using alphavirus replicons to express the proteins. In mice given multivalent vaccine there is some heterogenotypic protection, but it is not yet certain that this approach will work in humans.

Rotavirus: There are two live vaccines, but they are not as effective in developing countries as in developed countries. VLP might help overcome these problems, but so far there is a big problem with rotavirus VLP yield and VLP work against this pathogen is currently on hold.

HIV: VLP allow the presentation of HIV Env protein in increased density as compared to the native virus. In guinea pigs VLPS were far more immunogenic than the native virus and three doses resulted in neutralization of tier 2 viruses. Virosome approaches are also being tested to develop an HIV vaccine.

Hepatitis B: VLP are being developed as a therapeutic vaccine in infected individuals. A phase 1 trial showed safety and immunogenicity, breaking tolerance. A placebo controlled efficacy trial is currently being conducted in Bangladesh.

Chikungunya: a VLP vaccine is being developed based on envelope antigen, which has been shown to be protective in monkeys after high dose challenge. Passively transferred antibodies were also protective.

The workshop concluded that VLPs can represent an exciting new platform for vaccine candidates, but since some proteins assemble “naturally” and others do not, the effort required to properly “engineer” the desired VLPs may not always warrant the effort. There are possibilities to prepare complex VLPs, e.g. including adjuvants, in particular mucosal adjuvants and those with the potential of increasing cross-protection. Safety seems appropriate in general, but caution needs to be exerted if the VLP contain adjuvants, particularly for the nasal route. In general, the effort should be considered in the light of the difficulty to produce the VLP, the time involved as well as the target pathogen, e.g. HIV, for which producing a good vaccine is a major challenge.

6.3  Report on the workshop on group A streptococcal vaccines

F. Schödel

Group A streptococcus (GAS) infection is a frequent disease, the occurrence of which peaks between 5 and 15 years of age. It shows many relatively benign manifestations, with the primary infections being pharyngitis and impetigo. However, the latter can lead to very serious consequences such as invasive disease, acute rheumatic fever, rheumatic heart disease and acute glomerulonephritis. It is these latter that are all associated with excess morbidity and mortality, the biggest impact stemming from rheumatic heart disease. Estimates of the global mortality burden of severe GAS associated disease range from 500,000 to 1.15 million deaths/year. Since GAS affects young people in their twenties and thirties, it has a major societal impact.
Stumbling blocks for vaccine development include multiplicity of serotypes as well as perceived safety concerns. These barriers can, however, be addressed. Thus, safety concerns were not reproduced in studies, which is at least in part due to the fact that epitopes cross-reacting with human self-structures were removed from all potential vaccine constructs. In order to address the multiplicity of serotypes, a 30-valent 4-protein vaccine for M protein variable epitopes has been created and work is on-going to demonstrate cross reactivity of additional serotypes/emm types. Furthermore, there is research being undertaken to combine these with conserved epitopes or proteins.

The group developed a number of recommendations for research and development:

- **Preclinical testing:** the breadth of isolate coverage by the 30-valent vaccine as well as the added protective effect of conserved protein candidates need to be established and a high throughput bactericidal assays representative of major clinical isolates needs to be developed.

- **Clinical testing of vaccine candidates:** there was consensus that the first clinical endpoint for efficacy should be prevention of strep throat. This is feasible in relatively small clinical trials because of high attack rates and would enable licensure of a vaccine that could eventually be tested for other disease endpoints.

- **Collaborations to establish clinical endpoints and to train sites for studying prevention of acute rheumatic fever and RHD:** intervention studies, cluster randomized trials and/or effectiveness approaches.

Finally, it was recommended that in a next steps a small team should be set-up to define urgent research gaps, in particular in the areas of (a) updating disease burden estimates, (b) development of tools for clinical testing of vaccine candidates (especially high throughput bactericidal assay) and (c) the development of a high level road-map for further vaccine development. Considering the disease burden and availability of candidate vaccines, the group called upon WHO to make GAS a WHO priority. WHO could be instrumental in advocacy as well as coordination and facilitation of research and development.
Session 07: Update on priority vaccine-preventable diseases

*Moderator: Terbi Kilpi*
*Rapporteur: Carole Tevi-Benissan*

### 7.1 Meningococcal A conjugate vaccine: first introduction experience in West Africa
*Richard Mihigo*

The Meningitis Vaccine Project (MVP) is a 10 years partnership between WHO and PATH, created through core funding from the Bill & Melinda Gates Foundation, with the goal to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa. A new, affordable Group A meningococcal conjugate vaccine (MenAfriVac®) was developed, licensed in December 2009 and prequalified by WHO in June 2010. A study on antibody persistence will take place in the fall 2011 to measure the duration of protection, 4 to 5 years after receiving the vaccine.

The vaccine is being introduced progressively in the Meningitis Belt through a comprehensive strategy, approved by the GAVI Alliance in June 2008. In September 2010, pilot introduction was conducted in a few districts in Burkina Faso, Mali and Niger, prior to scale-up to the mass campaign in December 2010. Burkina Faso, Mali and Niger launched the large-scale introduction campaign with a non-precedential attendance of high level states representatives. Burkina Faso had opted for a nationwide introduction, whereas Mali and Niger opted for a phased introduction. Almost 20 million people were vaccinated in the three countries and the vaccination coverage rate was around 95%. The preliminary surveillance data from the 2010 - 2011 meningitis season showed a dramatic decrease in the number of meningitis A cases, ever seen in these countries. However, these are preliminary results after only one year post introduction, which should be taken cautiously. To measure the real impact of the introduction, data from several years post introduction should be analysed. Regarding the post marketing surveillance, MenAfriVacTM introduction was not associated with serious safety concerns according to the AEFI surveillance system put in place (only 7/19,529,810 vaccine related cases were detected representing 0.35/1,000,000).

The success of the introduction has been due to early planning, providing timely financial resources, well planned social mobilization and a good communication plan. In addition, strengthening capacities at all levels was crucial, as well as regular coordination meetings.

However, many challenges and constraints were faced during this campaign. The vaccine was prequalified in June and pilot introduction started in September, which gave a short time for the preparation. As well as competing priorities, polio H1N1 and measles campaigns were conducted at the same time,
Also cold chain constraints and weak waste management in some areas needed to be overcome.

The mobilization of the age group 15-29 years old was very weak. There is a need to target this group in future campaigns through appropriate communication messages.

In conclusion, due to the limitations of spontaneous reporting, implementation of active surveillance is required in subsequent campaigns in order to further reassure the populations about the safety of this new vaccine. The discussion raised the essential need to assess duration of clinical protection through rigorous Phase 4 effectiveness studies. Lessons learnt from this first introduction will improve the quality of the roll out in the other countries with Nigeria, Chad and Cameroon planned in 2011 and Benin, Senegal, Ghana and Sudan planned for 2012.

7.2 Rotavirus Vaccines: what's in the pipeline?  

_Duncan Steele_

It is estimated that each year, rotavirus (RV) causes 527,000 deaths predominantly in developing countries. Introduction of Rotavirus vaccine in routine use has shown a remarkable impact on diarrhoeal hospitalizations and mortality. From July 2002 - May 2009, a 41% reduction in deaths among children of 59 months or younger was demonstrated in Mexico. The vaccine efficacy against severe rotavirus gastroenteritis in the first year of life was estimated around 50-60 % in Africa and Asia and as the impact was so significant, SAGE recommended the incorporation of Rotavirus in EPI.

Several efforts were put in place to measure and understand the performance of the rotavirus vaccines, for example the Accelerated Vaccine Initiative Technical Advisory Consortium (AVI TAC), the Rotavirus Vaccine Impact (PATH), the Optimization of Immunization Schedules (WHO IVR) and PROVIDE group to study the biological aspects of the immune response to Rotavirus and OPV. Soon, new rotavirus data will emerge over the next 1-3 years (dosing schedules, impact studies particularly on HIV infected infants, and need for enhancing the immunogenicity either with a booster doses or Zinc and probiotics supplementation, and safety results related to intussusception).

At present, 28 countries have introduced rotavirus vaccines and 25 countries have applied for Rotavirus introduction in the GAVI May 2011 round. Several new live, oral Rotavirus vaccines are in the pipeline:

The Indian neonatal Strain 116E is a naturally reassorted human-bovine rotavirus strain, causing asymptomatic infection in neonates in Delhi, with good immune response and protects children from severe RV disease on infection. In phase II clinical trial, 116E was safe and immunogenic after three doses. Subsequently, a phase III randomized, double blind clinical efficacy trial has started in 3 sites across India with results expected in 2013-2014. EPI vaccine non interference study is planned.
The Human Neonatal Strain RV3 is a naturally attenuated strain in maternity units. Infants were followed up for 3 years and no diarrhoeal symptoms in siblings aged 1-2 years were detected. This vaccine showed poor immunogenicity with low titer vaccine in early study. Currently, there is an improved RV3 vaccine (RV3-BB) production and manufacturing on going (with a higher vaccine titer, after technology transfer to Biopharma). The RV3-BB vaccine is currently under early clinical development with a Phase I trial safety in adult, toddler and infant on going in Melbourne, and a Phase II trial planned in New Zealand, for proof of principle of immunogenicity at higher titer. Next steps will include Phase IIb immunogenicity study in infants and Phase III efficacy study in Indonesia.

The Vietnamese Rotavirus Vaccine, developed by Centre for Vaccine Research and Production of Vaccines and Biologicals (PolyVac), NIHE, has been evaluated in Phase I Safety study in adults, in Phase II immunogenicity study in infants at 2 concentrations and in various dosing schedules. The immunogenicity was similar to the GSK Rotarix.

The UK Bovine-human Rotavirus Reassortant Vaccine is a tetravalent vaccine tested in US and Finland. The suggested neonatal immunization schedule at 2 months avoids age dependant risk for intussusception. Clinical development showed safety and non-reactogenic effect in phase I as well as satisfactory immunogenicity in phase II trials. The vaccine was also safe and well tolerated when administered concomitantly with childhood vaccines. When compared to the licensed RotaShied, immunogenicity and efficacy were similar. The NIH office of Technology has licensed out the reassortant strains to several vaccine manufacturers in Brazil, China, India and USA and some manufactures are well advanced in the production of the BRV vaccines candidates.

The Rhesus Reassortant Rotavirus Vaccine is currently evaluated in a Phase IIb immunogenicity study in Ghana. Study results should be available by end of 2011.

There is new interest in non - replicating Rotavirus Vaccine (NRRV) approaches by different groups or institutions. However, funds are limited to support/evaluate this approach.

7.3 Pneumococcal immunization

Doug Holtzman

The pneumococcal conjugate vaccine (PCV 7) was introduced in the United States of America in the early 2000’s, with more than 30 million children safely and effectively vaccinated. The routine use of PCV in US has virtually eliminated serious childhood pneumococcal disease caused by serotypes included in the vaccine and indirect effects are pronounced among adults and children.

The impact of the pneumococcal vaccine has been demonstrated in Gambia through an RCT with 7 deaths prevented for every 1000 children vaccinated. Currently, India, China, Nigeria, Ethiopia, Bangladesh, Pakistan, Uganda and Democratic Republic of Congo have the highest burden of the disease.
There is assurance that the introduction of the PCV vaccine will have an impact on the disease. To allow this introduction, the Advanced Market Commitment (AMC) was created to help transform the pneumococcal vaccine market that was historically focused on high-income markets. Key donors made an advanced market commitment in order to scale up production capacity, with the purpose to meet developing country needs and accelerate uptake. AMC is therefore a pool mechanism to create economic incentive for new producers willing to jump on pneumococcal vaccine markets. AMC provides suppliers with $1.5 billion subsidy in return for 10-year volume commitments at a fixed price. AMC-registered suppliers agree to a legally binding peak annual volume commitment for at least 10 years; manufactures will receive a portion of the total $1.5 billion. The AMC target product profile must include serotypes 1, 5 and 14 which are the most frequently occurring serotypes in GAVI-eligible countries. In addition to the 3 serotypes, the product should also include serotypes that account for at least 60% of invasive pneumococcal disease isolate among children in the region for which the proposed pneumococcal vaccine will be used. The first AMC-supported introduction of pneumococcal occurred in Nicaragua at the end of 2010. Up to date, 7 GAVI eligible countries have introduced PCV, 11 countries were approved for PCV introduction in 2011 and more than 30 countries are expected to introduce PCV by 2015.

However, many issues and challenges are still to be resolved; at the level of impact in the developing countries or how the prevention of the major cause of pneumonia will affect the health care utilization and system, and how fast the serotype replacement will occur in developing countries. Evaluation of vaccine impact and serotype replacement requires population based data on incidence of invasive pneumococcal disease in a system which is consistent before and after vaccine introduction. An effective surveillance system to determine impact following vaccine introduction will also be useful, especially in some of the developing countries for which there is virtually no data.

7.4 Measles eradication: A research agenda

David Brown

With progressively increasing coverage with measles vaccination coverage, mortality and number of cases have been reduced from 1980 through 2009. Each of the six WHO regions has set an elimination date. In 2010, a global consultation meeting has looked at the feasibility of measles eradication, taking in consideration many factors such as biology, vaccine market and economic analysis, impact on health systems, global context and political feasibility. The results were presented to SAGE in Nov 2010, who acknowledged the remarkable progress made in reducing deaths from measles worldwide. SAGE requested that processes were established to develop and oversee the research agenda required for eradication. In May 2011, at the Global Measles and Rubella Research meeting, a range of programmatic issues were identified: epidemiology, vaccine efficacy and immunogenicity, immunization strategies, laboratory and surveillance, mathematical modelling and economic analysis and rubella. Issues related to the epidemiology of the disease included: causes of outbreaks in post SIA and high vaccination coverage settings, disease burden and risk factors by age group, economic cost of measles outbreaks and response in low and middle income countries, and the potential role of waning immunity and HIV in sustaining the transmission of the virus.
Alternative routes for measles vaccination are currently studied with variable effects (oral, intranasal, conjunctival) but the most promising methods are subcutaneous, intradermal and through aerosol.

The Measles Aerosol project’s goal is to license at least one method (vaccine and delivery device) for respiratory delivery of currently licensed measles vaccines. This method can be used by trained volunteers (non-medical personnel), is safe and effective and does not generate unsafe waste. Phase II/III clinical trial is completed but the results are not yet available. The use of Dry Powder Measles Vaccine with different devices is also currently evaluated.

Several laboratory tools for surveillance of measles exist (IgM/avidity assays in case of acute infection, IgG assays to guide vaccination and during the serosurveys and RT, PCR for molecular epidemiology). However, there is potential value of improved laboratory surveillance to rapidly identify outbreaks, and distinguish between importation and indigenous circulation of genotypes. The Point of Care Tests (PoCT) can be used by members of a healthcare team or by non-medical staff, and present ideal features including high sensitivity and specificity, simplicity and rapidity, storage at room temperature and low cost. PoCTs are already available for many pathogens (virus, bacteria, protozoa and biological threats). The evaluation of measles IgM PoCT for serum, and PoCT for oral fluid has demonstrated high sensitivity and specificity. Finally the molecular detection and characterization of measles strains directly from PoCT has shown appropriate performance for programme.

7.5 Polio research agenda
Roland Sutter

Currently, there are different priorities in research and product development to accelerate polio eradication, to assess the risk of vaccine-derived poliovirus emergence after OPV cessation and to secure eradication for future generations. Tremendous progress has been made in countries to accelerate the eradication of polio. India is on the verge of eradication and Nigeria is on a similar path. However, Pakistan and Chad have reported an increasing number of cases during the last 4 months.

In order to accelerate eradication, there is a need (1) to develop appropriate polio vaccines; (2) to assess the immunogenicity of polio vaccines by studies conducted a short-interval periods between rounds of mOPV1 vaccination; (3) to formulate higher-potency mOPV1 and (4) to address potential impact of micronutrients (zinc, Vit A, iron etc) on vaccination. Since 2005, several polio vaccines were developed and prequalified. Vaccines that are licensed and prequalified are mOPV1, mOPV3 and bOPV. Presently only mOPV2 is licensed. Regarding vaccine performance, susceptibility gaps need to be evaluated and potentially closed by conducting seroprevalence surveys and evaluating the use of IPV and fractional-dose of IPV. Concerning epidemiologic understanding, research should (1) look at the contribution of a specific population (adolescents, adults and migrant population) to the transmission of the disease, (2) assess the mucosal immunity (waning and boosting immunity); (3) investigate the outbreaks by determining the causes and build on the lessons learned. Program performance should also be reviewed by monitoring SIAs, assessing and improving programme communication and social mobilization. Finally, efforts should be put on surveillance in supporting environmental surveillance in Pakistan, India,
and Northern Nigeria, in evaluating and improving the reverse cold chain and evaluating the mobile phone reminders to health care focal points. Analysis of genomic data should be conducted in order to maximize the use of surveillance data.

The elimination of Sabin-derived poliovirus will occur on one hand by assessing the risks of VDPV through surveillance data, iVDPV studies, cVDPV outbreak investigations and the iVDPV surveillance project in Egypt. On the other hand, this elimination will use modelling to evaluate the risk of cVDPV emergence and circulation and to define vaccination options and associated costs and disease burden. The switch from OPV to IPV will also be evaluated through (1) the change in routine schedule in Mexico, (2) the IPV demonstration projects in Indonesia and Cape Verde and (3) the change from OPV to IPV in Malaysia.

To secure eradication, it is essential to provide appropriate products with the development of Sabin-IPV, or of alternate seed strain for future IPV and of non-infectious approaches to IPV production. Facilitating IPV production in developing countries through Sabin-IPV technology transfer and availability of master seeds. IPV should also be made affordable by reducing the schedule (1-2 versus 3-4 doses). Three major priorities should facilitate this: (1) fractional dose wild-type IPV administered with needle-free devices; (2) adjuvanted Sabin IPV and (3) combination vaccines with the hexavalent vaccines. Regarding the development of needle-free devices, progress was made in 2010 with the availability of appropriate (spring-powered) devices for developing countries, the establishment of WHO-prequalification criteria and the scientific evidence of the feasibility of this method. The next steps will include the development and the production of intradermal devices for IPV, a pilot introduction with ergonomic studies and technology transfer. An innovative approach is also considering the development of antiviral compounds against polioviruses with the capsid-binding inhibitor and the protease inhibitor. Promoting the development of new diagnostic tests for surveillance purpose and of appropriate policies will contribute to securing eradication.

At present, major programmes are working towards accelerating eradication, eliminating Sabin derived poliovirus and securing eradication. These programmes have a track record of all their accomplishments, but finally to improve the chances of eradicating polio, continued innovation is needed.
1. Maternal Immunizations

*Chair: Mark Steinhoff*

**Maternal Immunization Landscape Review**

*Kathy Neuzil*

A report commissioned to PATH by BMGF was completed in September 2010; it summarizes the available evidence to inform policy decisions for maternal immunization in low-resource settings, and identifies gaps and key recommendations. The review highlighted the significant neonatal, young infant and maternal morbidity and mortality in low-resource countries. Given that pregnant women are accessible even in the most difficult countries and that many causes of death are vaccine preventable, immunization against selected infectious diseases during pregnancy is a potential strategy to reduce severe disease in mothers and their newborn infants.

**Figure 1: Global cause of child deaths**

![Pie chart showing global causes of child deaths with neonatal deaths accounting for 41%, pneumonia accounting for 14%, and other non-communicable diseases accounting for 4%*.

Source for Fig 1: Black RE et al. Lancet 2010; 375 (9730): 1969-87
Maternal immunization with tetanus vaccine to prevent neonatal tetanus is a well-established strategy that has had significant impact on the reduction of deaths due to neonatal tetanus in developing countries. Dr Ahmadu Yakubu showed that even in the low income countries 69% of pregnant women receive at least one antenatal care, 39% at least four times, and that overall estimated TT2+ coverage is 80%. At the same time significant challenges till persist in reaching all prenatal women with TT vaccine.

**Influenza maternal immunization in Bangladesh**

*Mark Steinboff*

Seasonal influenza vaccine was recommended for pregnant women as early as 1960 in the US, and WHO recommendations include influenza vaccination for pregnant women. A recent randomized control trial in Bangladesh (N Engl J Med 2008; 359:1555-64) clearly showed the efficacy in both mother and infant in the reduction of flu-like illness. There were other studies (Zaman 2008 in Bangladesh, Poehling 2011, Eick 2011 & Benowitz 2010, all in the US) that also reviewed the effect of maternal influenza vaccination which confirmed the Bangladesh findings. North American studies showed the beneficial effects, be it ILI, hospitalization or lab positivity for influenza virus. Data also suggests that flu vaccine is associated with improved foetal growth as maternal seasonal flu infection has negative impact on foetus. It seems that maternal influenza vaccine protects mother, foetus, and infant up to 5-6 months. A study to confirm and to replicate in other settings was started in Nepal. If this study confirms that maternal flu is a preventable cause of reduced birth weight, it would have important implications for future strategies for antenatal maternal immunization with flu vaccine.

**Pertussis maternal immunization**

*Scott Halperin*

US and Canadian data on pertussis mortality show that the disease is predominantly in young children, particularly infants less than 3 months of age. In Canada, a case control study from 1991-2002 showed that all 16 fatal cases of pertussis were infants 6 months of age or younger, and that 15 were 2 months of age or younger, with mean age 6.5 weeks. Similarly in California, from Jan-Sept 2010: 4,017 cases of pertussis were reported and, again the majority were infant cases <3 months of age with 9 deaths, all in infants <2 months of age. The US data from 2000-2009 showed that 78% of the pertussis deaths were in <1 month age infants. Based on these, the CDC recently recommended pertussis vaccination in late pregnancy to prevent the disease in neonates.

**Maternal Immunization with Hib and pneumococcal vaccines**

*Kim Mulholland*

*S. pneumoniae* (pneumococcus) is an important cause of childhood pneumonia and the experience with pneumococcal vaccination is mainly with the polysaccharide vaccines (23, 14 & 9 valent) although an incomplete study was also carried out with the 9-valent conjugate pneumococcal vaccine.

The use of maternal PPV23 may be more useful than neonatal immunization because of the non-PCV serotypes causing disease in early infancy. Further, there is no data on the safety of repeat doses of polysaccharide PPV23 vaccine and this needs study. However, maternal immunization is a feasible approach to protect young infants and
if a PS vaccine is to be used a single dose with or following 1st pregnancy is probably the most appropriate strategy.

Although Hib vaccine too may have a role to protect the neonate or the young infant through maternal immunization, given its high herd immunity, it is felt that probably this is not needed. There are other respiratory diseases such as RSV, Group A Streptococcus, Group B Streptococcus, against which vaccines are being developed and, in future, they may become candidates for maternal immunization when vaccines become available. At present the only other bacterial disease against which a large-scale immunization campaign is being rolled out is that of conjugate meningitis. A vaccine across the meningitis belt of Sub-Saharan Africa and, even though clinical trials did not include pregnant women, the Global Advisory Committee on Vaccine Safety (GACVS) recommended that pregnant women should not be excluded from receiving it.

**Safety and safety standards for maternal immunization**

*Hans Spiegel*

Safety is of paramount importance and it central to any study of or the use of vaccines in pregnancy. Current ACIP recommendations as well as FDA Regulation and Evaluation of Vaccines offer recommendations on vaccination during pregnancy as well as ethical codes and rules/regulations that govern both the principles of conducting clinical studies in pregnancy and the practice of immunization during pregnancy and breastfeeding periods. There are mechanisms and networks in place to ensure early and timely recognition of safety signals and appropriate responses in the event of adverse events following immunization. *Guidelines for Neonatal and Maternal Immunization in Clinical Trials* are currently in development.

**Maternal Immunization strategy at the Bill & Melinda Gates Foundation**

*Angela Hwang*

The Bill & Melinda Gates Foundation (BMGF)’s vision is to see the expansion of maternal immunization as a strategy to prevent infections in infants given that 10% or more of childhood deaths are due to infections during the neonatal period, the time when infants are most vulnerable and most difficult to reach. One of the key challenges, particularly in developing countries, is the lack of disease burden and vaccine efficacy data in specific circumstances that are important in leading towards an evidence-based policy decision. The Foundation is working to address these gaps for influenza vaccination in pregnancy by supporting efficacy/burden studies in Nepal, Mali and South Africa. There are also other studies looking at the aetiology of disease. They include Pneumonia Etiology Research for Child Health (PERCH) study in Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, Zambia, and a cohort study in South Africa (Drakenstein Child Lung Health Study), and the ANISA study or the Aetiology of Neonatal Sepsis in South Asia in Bangladesh, India, Pakistan; these are community-based studies in infants from birth to 2 months.

Many studies have shown that pregnant women are at greater risk in H1N1 pandemic. Moreover there is now growing data on the burden of influenza in the tropics with improved influenza surveillance following the recent pandemic occurrence. There is also evidence of the indirect protection of infants when pregnant women are immunized with influenza vaccine. However, in most developing countries there is no seasonal
influenza vaccination policies and no specific efforts to prioritize pregnant women as target for influenza immunization.

Delivering influenza vaccines to pregnant women will be a challenge given that it is a multi-dose vaccine. The vaccines need to be formulated annually as circulating virus strains may differ from season to season, or even from region to region. Generally pregnant women are excluded from clinical studies of new vaccines and therefore such vaccines are not evaluated and approved for use in pregnancy. Despite the above issues, there are positive changes in the approach towards maternal immunization with influenza vaccines. At least 17 PAHO countries have already put in place policies for vaccinating pregnant women with seasonal influenza vaccine; WHO is currently steering a SAGE Flu Working Group to evaluate the relevance and safety of flu vaccines in pregnancy, technology transfer to developing country manufacturers is ongoing which would, in future, potentially increase availability and reduce cost of vaccines. However, further research to assess the most suitable operational strategies for specific regions or countries as well as behavioural studies to enhance acceptance and understand better the financial implications to develop a realistic investment case are needed.
2. **Virus like particles (VLPs) satellite workshop**  
*Chair: Stanley Plotkin*  
*Rapporteur: Teresa Aguado*

2.1 **Technologies to make VLPs**  
*Martin Bachmann, Cytos Biotechnology, Schlieren, Switzerland*

Virus like particles (VLP) are a way of constructing viral particles composed of viral protein antigens needed for protection, without chemical inactivation and without sufficient genomic material to allow for replication. Thus, it has none of the safety issues of live viruses and it allows for presentation of unchanged epitopes.

The basic discovery was that under certain conditions, some viral proteins found in regular array on the surface of the virus, self-assemble in solution.

The power of the approach is that viruses and VLPs are of the size 20-100 nm that penetrates lymphatic vessels and are carried to lymph nodes where B cell responses can be induced. They are effective immunogens because they present repetitive epitopes: that is, multiple copies of the same organized protein. They have relatively large surfaces and are hydrophobic. In addition, they can elicit T cell responses because they are taken up by dendritic cells and macrophages, which again carry them to the lymph nodes, where they are more immunogenic for T cells than soluble antigens. Part of the reason may be that they stimulate Pathogen-associated molecular patterns (PAMPs) and therefore innate immune responses. The responses in turn generate durable B cell responses.

VLPs are constructed in eukaryotic expression system, yeast, insect cells using baculovirus or in plants and in general they are very stable. VLPs typically contain multiple copies of a single subunit, but more complex VLPs are based on multiple copies of different subunits and therefore able to simultaneously induce immune responses against several proteins/pathogens. VLPs can also be assembled to contain adjuvants such as certain TLR agonist sequences.

Therefore, this technology offers a great opportunity for designing particles to suit particular needs of a given vaccine, however there are limitations in the individual assembling properties of different proteins.

**Human papilloma virus (HPV)**  
*Margaret Stanley, Cambridge, UK - HPV*

A most successful example of VLPs is the prophylactic HPV vaccine. Human papillomaviruses are responsible for 5% of all cancers. The VLPs are 50 nm particles composed of L1 protein, which in nature is present in loops on the virus. Their immunogenicity is better than nature, because in nature HPV antigens never get beyond the basement membrane to the lymph nodes and thus there is no immune response. Prophylactic HPV L1 VLP vaccines circumvent the viral epithelial evasion strategies since they are delivered by intra-muscular injection. The stromal dendritic cells of the muscle that encounter the highly immunogenic repeat structure of the VLP then migrate with their cargo to the lymph node initiating an immune cascade that results in a robust T cell dependent B cell response generating high levels of L1 specific serum neutralizing antibody and crucially strong immune memory. The antibody induced is present at basement membrane when there is a tear in the epithelium and
neutralizes virus.

The ability to generate HPV virus like particles (VLPs) by the synthesis and self-assembly in vitro of the major virus capsid protein L1 has transformed our prospects for preventing cervical carcinoma in women. There are two commercially available VLP vaccines, showing remarkable efficacy, strong immunity and a good safety profile. In addition, very recent preliminary results in Australia indicate the decline in high-grade pre-cancerous lesions (precancerous dysplasia), following introduction of the vaccine in 2007.

The L1 VLPs seemed to have the optimal geometry to achieve the objectives for the individual oncogenic types; however a vaccine based on L2 protein would be the ideal, as in principle it would confer cross-protection. Unfortunately, L2 VLPs have been difficult to prepare and the required “engineering” may not be possible, therefore this remains an experimental approach.

**Influenza**

*Theodore Ross, University of Pittsburgh, USA*

There has been lately high interest in exploring the potential of VLPs while designing strategies to enhance immune responses both for pandemic as well as for seasonal flu.

Influenza VLPs were engineered based on the seasonal and pandemic isolates and purified from the supernatants of insect cells or mammalian cell-culture based systems following infection/transfection of expression cassettes comprised of only three influenza virus structural proteins, haemagglutinin (HA), neuraminidase (NA), and matrix (M1). All three proteins were needed to assemble particles.

Adult or aged mice or ferrets were vaccinated intramuscularly or intranasally with VLPs and the immune responses were compared to responses elicited in animals vaccinated with recombinant HA (rHA):

All vaccinated animals had high titer anti-HA antibodies regardless of the vaccine immunogen. In addition, VLP elicited a broadly reactive set of T cell responses in both the lungs and spleen. These VLPs elicited antibodies that recognized a broader panel of antigenically distinct viral isolates compared to rHA.

Following challenge, all mice vaccinated with VLPs were protected against influenza challenge, however, the use of a toll-like receptor TLR-3 agonist during VLP vaccination improved the protection levels and it was necessary to elicit complete protection in aged mice. Interestingly, influenza VLPs can be given intranasally.

Although the results are encouraging, these are so far animal studies; also, the speed and expense of VLP production must be compared with alternative methods to make influenza vaccines.
Norovirus
Ralph Baric, University of North Carolina, Chapel Hill, NC, USA

Noroviruses are an important cause of food-borne gastroenteritis and outbreaks occur in many settings, with higher risks in the developing world and in aged, immunosuppressed, infants and young children. In fact, they are the second most important viral cause of diarrhea in children and adults, after rotavirus. There are approximately 200,000 deaths per year in children.

However, norovirus are very heterogeneous in nature which poses a challenge to vaccine design. There is a 1-2% genetic change per year in the most varying strains. There are two genotypes, G1 and G2. G1 infection may induce some persistent immunity, but there are 18 different G2 genotypes and they cause 90% of disease. Within those, the G2.4 genotype is the most prevalent, causes 80% of disease and are undergoing antigenic variation like influenza virus. The receptors for the virus are the ABO blood group antigens.

Using mouse and human monoclonal antibodies, major epitopes associated with protective immune responses were identified and VLPs produced using alphavirus replicons to express the proteins.

The group compared the efficacy of monovalent and multivalent vaccines in mouse models of human disease, demonstrating that adjuvanted multivalent vaccine platforms not only elicit immune responses against the expressed proteins in the VLPs, but more importantly, also some heterogenotypic protection. Recent NoV VLP trials in humans are promising, providing protection from clinical disease. One key for vaccine development is the development of multiple human challenge inocula.

Rotavirus
Philip Dormitzer, Novartis, Cambridge, MA, USA

Today there are two live rotavirus vaccines in use, but they are not as effective in developing countries as in developed ones. So there is an increased interest in developing non-replicating rotavirus vaccines that could complement those currently in use.

Rotavirus structural proteins self-assemble into virus-like particles, which have vaccine potential. Particles composed of the rotavirus inner and middle capsid proteins, vp2 and vp6, are readily made and very stable, but they have modest protective potential, showing efficacy when used as the sole immunogen in small animal models of rotavirus infection and the ability to boost immunity from a live virus vaccine in the gnotobiotic pig model of disease.

However, one could hang vp7 and vp4 on the VLPs, but the particles are then unstable and the yield poor. vp7, the rotavirus outer shell protein, is the determinant of G serotype and an important target of neutralizing antibodies. VLPs incorporating vp7 are also readily made. Unlike vp2/6 VLPs, vp2/6/7 VLPs elicit neutralizing antibodies, but they are somewhat less stable. Authentic rotavirus virions have a second neutralization antigen, the spike protein vp4, which is also a target of neutralizing antibodies. Under experimental conditions, vp4 can be incorporated into VLPs, but the efficiency of making properly assembled vp2/4/6/7 VLPs appears to be too low at present for practical vaccine production. The difference in protective efficacy between vp2/6/7 VLPs and well-assembled vp2/4/6/7 VLPs is unknown.
Because rotavirus can be readily grown and inactivated, the merits of VLP approaches should be compared to those of inactivated virus approaches. This may be another case of a formulation that does not necessarily represent an advantage over killed virus vaccine, and more evaluation is required.

**HIV**

*Richard Compans, Emory University, Atlanta, GA, USA*

VLPs are attractive as candidate antigens for HIV vaccines designed to induce neutralizing antibodies, because the Env protein is presented in its native oligomeric, membrane-anchored form. However, in the native HIV virus the expression occurs only at low levels.

In contrast, the surface glycoproteins of many other enveloped viruses, including some retroviruses, are incorporated into virions at 10-20 fold higher levels. Substitution of the membrane-anchor sequences of HIV Env with those of other retrovirus glycoproteins resulted in a dramatic increase of Env incorporation into VLPs.

To further enhance VLP immunogenicity, especially for mucosal immunization, the Emory group incorporated membrane-anchored forms of the TLR5 agonist flagellin into the chimeric VLPs.

HIV-specific immune responses induced by the resulting VLPs were determined in a guinea pig model. The chimeric VLPs induce enhanced systemic antibody responses by either systemic or mucosal vaccination as well as enhanced mucosal immunity by a mucosal immunization route, as demonstrated by levels of HIV-specific serum IgG and mucosal IgG and IgA.

These results indicate that HIV VLPs incorporating high levels of Env and a molecular adjuvant have excellent potential for further development as a prophylactic HIV vaccine.

Among the conserved neutralizing epitopes of Env the Membrane-Proximal External Region (MPER) of gp41 is widely recognized as a promising target for vaccine development. Sera from guinea pigs vaccinated with especially designed VLPs expressing this protein, but not the standard HIV VLPs, were found to neutralize HIV pseudovirions.

Although interesting results, these have been obtained so far only in animal studies. The potential in humans need to be explored.

**HIV- virosomes**

*Sylvain Fleury, Mymetics Corporation, Epalinges, Switzerland*

The ideal vaccine to prevent sexual transmission of HIV-1 should obviate entry and very early infection of HIV-1 at mucosal sites, otherwise it may be too late.

The Mymetics approach is to construct a virosome particle consisting of HIV proteins embedded in influenza membranes. This looks like a VLP particle in size and the lipid may improve the antigen presentation. The antigens incorporated are from gp41 and a Membrane-Proximal External Region (MPER) peptide called P1. P1 is a lipopeptide
containing the Membrane-Proximal External Region (MPER) and the galactosyl ceramide mucosal receptor binding motif.

The group previously demonstrated that mucosal IgAs/IgGs induced by vaccination with those virosomes, protect non-human primates (NHP) against vaginal heterologous SHIV challenges, in the absence of serum neutralizing antibodies. At present they are investigating if mucosal antibodies with similar antiviral properties can be induced in women during a Phase I trial. The design is injecting virosomes IM at 0 and 8 weeks, followed by IN immunization at 16 and 24 wks.

Preliminary results show safety of the virosomes. The immunogenicity results are also confirming the previous data obtained on non-human primates, and the anti-HIV-1 mucosal responses elicited are an indication of the potential of this approach.

Hepatitis B therapeutic vaccine

Gerardo Guillen, Center for Genetic engineering and Biotechnology, Havana, Cuba

Despite prophylaxis, 370 million people worldwide are still chronically infected with hepatitis B, remaining a serious public health problem. The limitations of the current available therapies underline the need for alternative therapies, including a therapeutic vaccine.

Specific immunotherapeutic strategies target the stimulation of CD4(+) and CD8(+) T-cell responses and the induction of pro-inflammatory cytokines capable of controlling viral replication.

The decision to develop a new therapeutic vaccine including HBsAg and HBcAg VLPs has resulted in a novel liquid formulation. HBsAg was made in yeast (Pichia pastoris) and HBcAg in E coli. A simple mixture of particles in phosphate buffer, sterile and non-pyrogenic, is to be administered in repeated doses by intranasal and subcutaneous routes.

The nasal vaccine candidate called NASVAC proved to be safe and immunogenic first in transgenic mouse models and then in a Phase I, randomized, double blinded and placebo controlled clinical trial in healthy volunteers.

Safety and efficacy results (all the patients had ALT sustained normalization and 50% of patients remained negative 48 weeks after the end of treatment) from a Phase I-II trial in 20 chronic patients have supported the approval of a Phase III controlled clinical trial in Bangladesh, using 5 intranasal doses followed by 5 doses both intranasally and intramuscularly.

Chikungunya virus

Wataru Akahata, VCR, NIH, Bethesda, MD, USA

Chikungunya virus (CHIKV), an alphavirus, is epidemic in Africa and Asia, and has also produced foci in Europe, representing a serious public health threat. It is now adapted to Aedes albopictus. The Chikungunya VLP vaccine is based on envelope antigen.
The group developed a new vaccine CHIKV VLP vaccine that protects against CHIKV infection in nonhuman primates. Monkeys immunized with VLPs produced high titer neutralizing antibodies that protected against viremia after high-dose challenge. When antibodies were transferred into immunodeficient mice, they protected against subsequent lethal CHIKV challenge, indicating a humoral mechanism of protection.

Also, similar vaccines have been constructed using envelope from Western Equine, Venezuelan Equine and Eastern Equine Encephalitis. A quadrivalent mixed vaccine produced high titer neutralizing antibodies in mice and monkeys, without competition, therefore indicating that this approach could potentially be utilized for the development of a pan-alphavirus vaccine.

CHIKV VLPs were also modified to present other vaccine antigens. The group used them as a vehicle for HIV proteins: HIV-1 outer domain envelope (CHIKV-OD) and they elicited antibodies against the CD4 binding site in non-human primates, demonstrating their potential.

Interesting approach, particularly for the alphaviruses, but so far results obtained only in animal models. Human studies are awaited.
3. Group A Streptococcal (GAS) Vaccines for the Developing World

Moderator: Florian Schödel
Rapporteur: Ana Maria Henao Restrepo

The workshop provided a forum for overviews of group A streptococcus (GAS) disease burden and epidemiology, updates on GAS vaccine candidates and strategies for clinical evaluation, and discussions of the opportunities, challenges and critical next steps to accelerate development of safe and effective GAS vaccines.

Disease burden and potential global impact of GAS vaccines

Group A streptococci (GAS) are important causes of morbidity and mortality worldwide. Recent population-based estimates indicated that there are at least 517,000 deaths each year due to severe GAS diseases (eg, acute rheumatic fever (ARF), rheumatic heart disease (RHD), acute post-streptococcal glomerulonephritis (APSGN), and invasive infections) (1). The greatest burden of GAS disease is due to RHD, with a prevalence of at least 15.6 million cases, with 282,000 new cases and 233,000 deaths each year. The global burden of invasive GAS diseases is unexpectedly high, with at least 663,000 new cases and 163,000 deaths estimated each year (1). In addition, there are more than 111 million prevalent cases of GAS pyoderma, and over 616 million incident cases per year of GAS pharyngitis.

Epidemiologic data from developing countries for most GAS diseases is poor. Emerging data from a number of developing countries indicate that the disease burden figures outlined above are likely to be underestimates. Mortality estimates based on recent studies in developing countries suggest that the excess mortality from RHD may approach 1.15 million deaths/year, approximately 5 times the rate estimated in previous studies (2, 3). Additional detailed data are needed from developing countries to confirm these figures. There are a number of challenges to estimating GAS disease burden in low and middle income countries, including a lack of uniform methodology across studies, poor access to laboratory diagnosis, limited access to health care services for some high risk groups; inadequate medical records and no vital events registration system. In an effort to remedy some of the problems, standard protocols for GAS burden estimation were developed in 2005 (http://www.niaid.nih.gov/TOPICS/STREPTOCOCCAL/Pages/protocols.aspx). Although these protocols have been used at a number of sentinel sites (Mali, Nicaragua, Fiji), there is a need to implement these protocols more widely and for other sentinel sites to be established. Nonetheless, extrapolation to age specific excess cardiac mortality suggests a significant disease burden impact. These data underline the need to enhance control strategies, collect better evidence from developing countries, and develop new primary prevention strategies.

Vaccine prevention of GAS infections and their immunological complications has been a goal of researchers for decades. An ideal GAS vaccine would prevent colonization, carriage, symptomatic and asymptomatic infection, invasive disease, toxin mediated complications, ARF, RHD and APSGN. The socio-economic burden, public demand, and public health priorities for a GAS vaccine differ in various parts of the world. In industrialized countries, the factors driving the development and deployment of GAS vaccines are a reduction in the number of cases of GAS pharyngitis and prevention of invasive GAS disease. Prevention of GAS pharyngitis would translate into a marked reduction in the number of antimicrobial prescriptions for sore throat symptoms...
and time spent away from school or work. Prevention of invasive GAS cases would translate into reductions in severe morbidity and mortality (4). In contrast, in the developing world, the drivers are the high burden of ARF/RHD, invasive disease, and APSGN with its potential for contributing to chronic renal disease in adulthood (5). Prevention of ARF/RHD would translate into a significant reduction in global mortality and morbidity as well as a considerable socio-economic impact with reductions in RHD–related health care costs associated with chronic cardiac failure and expensive cardiac surgery.

Molecular epidemiology of GAS infections and implications for vaccine development

A systematic review of the global distribution of GAS emm types was presented. Emm sequence typing is the most widely used method for defining GAS strains. Most of the available data are from high-income countries (84%), with limited data from low-income countries (6). The epidemiology of GAS disease in Africa and the Pacific region appears to differ from that in other parts of the world, especially when compared to high-income countries. In Africa and the Pacific, there appear to be no dominant emm types, a higher diversity of emm types, and many of the common emm types found in industrialized countries are far less common (including emm 1, 4, 6, and 12). These differences may be due to the high prevalence of GAS impetigo found in many resource poor settings. The implication of these data is that that the current formulation of the 26-valent M protein-based vaccine would provide good coverage in high-income countries, particularly USA, Canada, and Europe, but poor coverage in Africa and the Pacific, and only average coverage in Asia and the Middle East. However, recent data from both whole M protein sequencing and from further multivalent vaccine studies (see below) indicate that M protein-based vaccines may evoke cross-protective antibodies that would broaden their potential efficacy (7, 8). Although there are many different emm types associated with skin disease, these emm types are often highly related at a more detailed genetic level and antibodies against some of these emm types may provide cross protection against other emm types. These data clearly have significant implications for multivalent M protein vaccines and are the subject of ongoing investigation. Molecular epidemiologic data relating to other vaccine targets are limited. Some data are available for the J8 vaccine antigen, which has been found to be highly conserved among GAS strains in a limited number of tropical settings (9).

Current status of GAS vaccine development

An optimal GAS vaccine would prevent colonization, carriage, symptomatic ad asymptomatic infection, invasive disease, toxin mediated complications, ARF, RHD and APSGN. Several vaccine candidates against GAS infection are in various stages of preclinical and clinical development (Table 1). Only one candidate vaccine, the multivalent N-terminal M protein-based vaccine, has entered clinical trials.

Type specific M protein–based vaccines. These vaccines consist of short peptides from the N-terminal region of M proteins from multiple different GAS emm types strains fused together in tandem to form larger vaccine proteins. A 26-valent vaccine has been constructed that includes 80%–90% of serotypes that caused invasive infections or pharyngitis, as demonstrated by recent surveillance in North America (10). The vaccine also includes one conserved epitope; a protective antigen (Spa) that is expressed in
several serotypes. This vaccine underwent clinical evaluation in adults, with evidence indicating that it is safe and induces immune responses to all component antigens (11). This is the only GAS vaccine that has been in human trials.

A new 30-valent M protein-based vaccine is currently in the pre-clinical stage of development (8). This vaccine contains protective M protein peptides from serotypes of GAS that account for 98% of all cases of pharyngitis in the US and Canada, 90% of invasive disease in the US and 78% of invasive disease in Europe. Pre-clinical studies to date have shown that the vaccine evokes bactericidal antibodies against all 30 vaccine serotypes. In addition, significant levels of cross-opsonic bactericidal antibodies have been observed against 24 of 40 non-vaccine serotypes tested to date (8). These results suggest that the potential efficacy of the 30-valent vaccine may extend well beyond the constituent M peptides.

Other vaccine candidates containing conserved GAS antigens. Additional antigens shared among many or all serotypes of GAS have been identified as candidates for vaccine development. These include 1) conserved regions of the M protein, and 2) non-M protein common antigens. Table 1 summarizes the research and development phase of vaccine candidates, but it should be noted that this list is not exhaustive. While in vivo evidence of protection against GAS has been demonstrated with many of these vaccine candidates, none has been evaluated in clinical trials. The J8 vaccine, a conserved M protein vaccine, is scheduled to enter Phase 1 clinical trials in Australia during 2012 (personal communication, Michael Good, Griffith University).

Near-term research and development

There was general consensus that the majority of potentially protective antigens of GAS have been identified. It is also apparent that most of the candidate vaccine antigens have been tested in pre-clinical studies in isolation and not in combination. Preclinical testing of the 30-valent vaccine will continue in order to establish the breadth of serotype coverage, with particular attention to GAS isolates from studies conducted in developing countries where the prevalence of RHD is high. Some experts argue that current knowledge is adequate to guide the formulation and test combination GAS vaccines containing M-protein and common (shared) antigens. Complex multivalent M protein-based vaccines may or may not have predicted efficacy that is sufficient for global application. Protective efficacy in humans of candidate GAS vaccines will need to be assessed in clinical trials and efficacy studies will inform the definition of immune correlates of protection. The perceived clinical risks can be evaluated through additional clinical development with carefully designed protocols.

Vaccine assessment challenges and regulatory considerations

In discussing the regulatory pathway for GAS vaccines, it must be acknowledged that there is no regulatory consensus and only general observations are possible. This is influenced by the fact that it is not yet clear what the antigen and/or adjuvant content would be, the intended indication of the various candidate vaccines (may differ worldwide) and the targeted age groups.
The standard regulatory expectations include: “proof of principle”: details of immune response; doses, schedules, adjuvants; efficacy (or prediction of efficacy); host factor effects; extrapolation to other populations; safety in target populations. The regulatory support data regarding doses, schedules, amount of antigen per dose; contribution of an adjuvant; timing of first dose (especially in infants); dose intervals; number of doses; need and timing for further doses.

Moreover, studies should consider that the worldwide need is prevention of RF/RHD, invasive streptococcal infections, and possibly APSGN. However, these would not be feasible primary endpoint(s) in pre-licensure efficacy studies. The consensus among participants was that the first clinical endpoint for efficacy should be prevention of GAS pharyngitis which would require relatively small clinical trials because of high attack rate and would enable licensure for prevention of GAS pharyngitis. Efficacy in preventing impetigo could follow as a subsequent study, which would also be relatively small because of the high attack rate in a number of populations, particularly in tropical countries. Less common but more serious complications of GAS infections would follow later in large-scale population-based studies.

An additional challenge is the availability of clinical and laboratory infrastructures to optimise case ascertainment and of standard antibacterial regimens for breakthrough GAS infections. Minimum diagnostic criteria are therefore needed. Studies may be conducted in populations with high rates of GAS infections and low risk of ARF or APSGN and then extrapolate the results to populations at higher risk. Moreover, study designs need to account for the potential of limited serotypes in circulation during study period. A rationale would be needed to generalize the results beyond population and strains in the study site. Once efficacy has been demonstrated, the possible use of comparative immunogenicity to assist bridging to other populations (may not have immune correlates of protection but can still compare) should be considered together with the conduct of extensive serologic and functional assays to establish the potential for cross-protective immunity in populations where the epidemiology of GAS infections may differ from that of the original field trials.

The incidence of APSGN and ARF are important factors to consider when assessing safety and efficacy of candidate vaccines and to ascertain vaccine-associated streptococcal sequelae versus sequelae of undetected GAS infection. Provisions should be made to establish baseline attack rates of ARF and APSGN prior to and during large scale field trials to differentiate breakthrough cases from vaccine-associated complications.

It is important to note that initial safety concerns have not been supported by the results of subsequent studies. Since 1923 there have been 19 clinical trials of GAS vaccine candidates – only one of which, significantly flawed in design, appeared to suggest an increased risk of ARF in vaccines. Cross-reactive epitopes were removed from the 26-valent vaccine and the vaccine was shown to be safe, well-tolerated and immunogenic in phase I/II clinical studies. Pre-clinical evaluation of the 30-valent vaccine has also shown it to be free of human tissue cross-reactive epitopes (8).

In summary, there is not yet regulatory consensus regarding minimum data required pre-licensure for GAS vaccines evaluation. The submission of specific proposals to relevant regulatory bodies will help to advance the current guidelines as many critical questions may have to be answered after initial approval. Cumulative regulatory experience may lead to re-assessment of risk-benefit in specific populations.
Next steps

The primary aim is to undertake a single proof-of-concept clinical trial of a promising GAS vaccine, demonstrating protection against pharyngitis. It is hoped that such a trial would stimulate interest among many individuals, institutions and companies contemplating involvement in further GAS vaccine development.

The next steps should be to include the establishment of a small team of experts to define urgent research gaps, updated disease burden estimates and, develop or improve tools for clinical testing of vaccine candidates (especially high throughput bactericidal assay, multiplex ELISAs and automated assays for tissue cross-reactive antibodies). More importantly this team should be challenged to prepare a high level and detailed road-map for further vaccine development.

To support the development of a GAS vaccine as a public health priority and provide a foundation for cost-effectiveness of a vaccine for developing countries, the following is proposed:

1) To update global disease burden estimates, using mortality data, disability-adjusted life year measurements (DALYs) and other related statistics and define gaps for additional studies.

2) To identify sentinel sites for disease burden studies using already established surveillance protocols to conduct additional studies as needed and prepare for vaccine trials.

3) To more clearly define the global molecular epidemiology of GAS as it relates to vaccine development.

4) To support the development of improved tools for clinical testing of vaccine candidates including a high throughput bactericidal assay.

5) To develop protocols for the testing of GAS vaccines to support a clinical development plan and regulatory requirements.

6) To develop a Target Product Profile for a GAS vaccine to be modified as new data is available from research and clinical studies.

7) To explore collaborations with academia, industry, public health agencies/institutions, for sharing resources.

8) To involve vaccine manufacturers in global GAS vaccine development efforts.

9) To develop a road-map for further vaccine development with the immediate aim of a clinical trial using pharyngitis as the endpoint.

10) To plan and coordinate large funding applications to support the above initiatives.
References


Table 1. Candidate GAS vaccine antigens.

<table>
<thead>
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<th>Vaccine class</th>
<th>Vaccine epitope</th>
<th>Development stage</th>
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<td>M protein: Type-specific region</td>
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<td>Completed phase I and II clinical trials Preclinical</td>
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<td>Non M protein: Surface proteins</td>
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<td>Nine common antigens</td>
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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.