

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

**Bamako, Mali
6-9 December 2009**

Immunization, Vaccines and Biologicals



**World Health
Organization**

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Abbreviations and Acronyms

AE	Adverse event
Aeras	Aeras Global TB Vaccine Foundation
AIDS	Acquired Immunodeficiency Syndrome
APC	Antigen-presenting cell
ARI	Acute respiratory infection
BCG	Bacillus Calmette Guérin (vaccine)
CDC	Centers for Disease Control and Prevention (Atlanta, GA, United States of America)
CHAVI	Centre for HIV Vaccine Immunology
CIN	Cervical intraepithelial neoplasia
CMI	Cell-mediated immunity
CSF	Cerebrospinal fluid
CTB	Cholera Toxin B subunit
CTL	Cytotoxic T lymphocyte (CD8+)
CVP	Children's Vaccine Program (United States of America)
DALY	Disability-adjusted life year
DHF	Dengue haemorrhagic fever
DHHS	Department of Health and Human Services (United States of America)
DNA	Deoxyribonucleic acid
DOMI	Diseases of the most impoverished (Program)
DOTS	Directly-observed treatment short-course (TB)
DTP	Diphtheria-Tetanus-Pertussis vaccine
EC	European Community
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GMP	Good manufacturing practices
GMT	Geometric mean titer
GSK	GlaxoSmithKline

HA	Haemagglutinin
Hib	Haemophilus influenzae type B
HIV	Human Immunodeficiency virus
HPV	Human Papillomavirus
IAVI	International AIDS Vaccine Initiative
ID	Intra-dermal (route)
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intra-muscular (route)
IP	Intellectual Property (rights)
IPV	Inactivated polio vaccine
IVI	International Vaccine Institute (Seoul)
IVR	Initiative for Vaccine Research (WHO)
JE	Japanese Encephalitis
MAb	Monoclonal antibody
Men A	Meningococcus serogroup A
Men B	Meningococcus serogroup B
MDR	Multiple drug-resistant (TB)
MHC	Major Histocompatibility Complex
M tb	Mycobacterium tuberculosis
NA	Neuraminidase
NAb	Neutralizing antibody
NGO	Non-governmental organization
NIAID	National Institute of Allergy and Infectious Diseases (United States of America)
NIH	National Institutes of Health (United States of America)
OPV	Oral polio vaccine
PAHO	Pan-American Health Organization
PATH	Program for Appropriate Technology for Health (United States of America)
PEP	Post-exposure prophylaxis (rabies)
PPD	Purified protein derivative
PS	Polysaccharide (capsular)
QC	Quality control
R&D	Research and Development
RIG	Rabies Immunoglobulin G
RV	Rotavirus
SARS-CoV	SARS coronavirus
SBA	Serum bactericidal antibody

SCID	Severely compromised immunodeficient
STI	Sexually-transmitted infection
TB	Tuberculosis
TOC	Test-of-concept (trial)
TT	Tetanus toxoid
UNAIDS	United Nations Programme on AIDS
UNICEF	United Nations Children's Fund
VLP	Virus-like particle
VRC	Vaccine Research Center (NIH, United States of America)
WHA	World Health Assembly
WHO	World Health Organization
YF	Yellow Fever

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1. Session I: Seasonal and Pandemic Influenza Vaccine Research and Development

Moderator: Abraham Hodgson and Kathy Neuzil
Rapporteur: Laszlo Palkonyay

Pandemic influenza vaccine research and development has been a hot topic during the year 2009, after the emergence of the pandemic A (H1N1) 2009 influenza virus. Besides a global H1N1 pandemic update and summaries on particular aspects of current pandemic vaccine development issues, the session focused on diverse related themes such as the status of the WHO sponsored programme of influenza vaccine production capacity building in developing countries, the prospects for the development of a universal seasonal influenza vaccine in the future, an update on the burden of illness of infectious respiratory diseases in Africa, and the presentation of an ongoing influenza vaccine effectiveness trial in Senegal.

1.1 Avian and pandemic H1N1 threats: the current situation *(Sylvie Briand)*

Zoonotic and pandemic threats from the avian H5N1 virus still exist as the virus continues to circulate actively in poultry in several countries. Although reassortment of the avian H5N1 virus with pandemic H1N1 or other animal or human influenza virus is possible, the likelihood of such an event is unclear, and the pathogenicity or transmissibility of the resulting reassortants cannot be predicted. Therefore, continuing the current WHO-coordinated virological monitoring of poultry remains of prime importance. The past few years confirmed that better control of poultry decreases the risk of zoonotic infection. Reducing disease in animals is of benefit to human public health: there was no new case of H1N1 infection in humans in 2009.

Altogether, on November 27, 2009, the number of WHO-confirmed human H5N1 cases was 444 with 262 deaths, which represents an extremely high case fatality rate (61.5 %). One should not forget, however, that, besides the current H1N1 pandemic and avian H5N1 viruses, other influenza viruses such as H2, H3, H5, H7 or H9, also pose zoonotic and pandemic risks.

Regarding the current pandemic, there is evidence that, as of December 5, 2009, every country in the world had been affected by the 2009 H1N1 pandemic, and the global number of cases was in the order of millions. As most countries have stopped counting individual cases, the number of cases officially reported to WHO is definitely and significantly lower than the actual number of cases. Pandemic H1N1 influenza has been predominant during the year in most countries, up to the point that, in some countries, no seasonal H1N1 or H3N2 influenza cases have been reported. Regarding age groups affected by the pandemic, it has been determined that i) older teens and young adults have the highest attack rates (median 12-28 years), ii) the less than 5 years-old cohort has the highest rate of hospitalization, although, due to population distribution, the absolute number of hospitalizations is higher in the slightly older age group, and iii) mortality is highest in the 50-60 years-old group.

The H1N1 pandemic has placed a significant burden on health care systems worldwide with notably increased rates of outpatient visits in many places. The overall hospital admission rate has been very high in specific age groups. Utilization of intensive care units (ICU) has been about 4 to 15 times higher than in normal influenza seasons. The very intensive use of ICU was challenging from the resource point of view, as severe acute respiratory distress symptom (ARDS) cases, mainly in young, previously healthy adults, required intensive treatment that could at times last as long as 4 weeks to 2 months!

Due to the relatively short period of time elapsed since the initiation of the pandemic on April 2009, current conclusions on the novel pandemic H1N1 infection and disease should be considered as temporary. Still, what has been observed is that the pandemic presents with a wide spectrum of infections from symptomless cases to fatal disease, with most people developing self-limited upper respiratory tract illness. However, some groups are more prone for severe disease, such as pregnant women, patients with chronic conditions such as cardiovascular or respiratory diseases, diabetes, immunosuppression, and possibly, obesity. Also, 20 to 40 % of the deaths due to ARDS occurred in young healthy adults with no underlying conditions

1.2 The burden of respiratory diseases in Africa (*Claire Cutland*)

Dr Clare Cutland from the University of Witwatersrand, South Africa, in a co-authored presentation with Dr Shabir Madhi, presented data on the burden of respiratory diseases in Africa with a special focus on influenza disease. It was clear, through diverse African publications from the past two decades, that, despite of a general paucity of influenza data from most African countries, influenza causes significant morbidity and mortality on the continent, as observed every time it was investigated systematically.

Based on South African morbidity and mortality data from various years, diverse age groups and different locations one can conclude that i) similarly to temperate climate countries, influenza shows evident seasonality in South Africa, ii) a clear connection exists between peak influenza activities and school absenteeism, and iii) seasonal influenza-related excess mortality is mostly observed in the population older than 65 years.

The timing of the novel H1N1 pandemic in South Africa has provided special insight into the natural history of the virus. After an early peak of predominantly H3N2-related influenza activity in May, a second peak of disease followed in July and August due to the novel H1N1 pandemic virus, which replaced almost entirely all seasonal influenza strains. Between June 8, when the first H1N1 virus was isolated, and December 1, 2009, 12 631 H1N1 cases were confirmed through laboratory testing. Out of the 92 deaths officially registered, 28% occurred in pregnant women, 95% of whom were in their third term of pregnancy, and 50 % in HIV positive patients. In 23 % of the cases, no co-morbidity could be identified.

Additional relevant influenza information was gathered from vaccine trials carried out in Africa, both with influenza and other vaccines. In a recent prospective, double blind, randomized, placebo-controlled Phase IV trial in HIV-positive adults of a single dose trivalent inactivated seasonal influenza vaccine given prior to the anticipated onset of the influenza season, a 75.4% efficacy level was documented.

Recent trials with pneumococcal conjugated vaccines (PCV) in children 6 to 48 months of age, demonstrated that under real life situation in Africa, influenza virus infection did predispose to pneumococcal co-infections resulting in severe pneumonia that required hospitalization. In the non PCV-immunized study participants, the incidence of hospitalization for confirmed influenza-associated lower respiratory tract infections was between 75 and 180 per 100 000. The negative effect of concomitant HIV infection was clearly demonstrated, as the incidence rate for hospitalization for HIV-positive infants and toddlers was up to 1200 cases per 100 000 population. Influenza vaccination should therefore be encouraged in Africa, including in HIV-positive persons.

1.3 Seasonal influenza vaccine effectiveness in Senegal (*Aldiouma Diallo*)

A seasonal influenza vaccine effectiveness study was organized in the Niakhar district in Senegal, in the form of an observer-blind, cluster-randomized, controlled (IPV), parallel group trial, which was organized in partnership between the Institut de Recherches et Développement (IRD), Dakar, Sénégal, the Institut Pasteur, Dakar, PATH, and the US Centers for Disease Control and Prevention, to evaluate the total effectiveness of a trivalent inactivated seasonal influenza vaccine (TIV) administered in two doses before the rainy season to children six months to 10 years of age. Historically the rainy season is the period of peak influenza activity in the study area.

The study-linked surveillance program was conducted as part of routine public health influenza monitoring. The study field staff was blinded to the vaccine status of the participants in the study. Two types of surveillance were carried out, covering the entire 39 500 population of the district:

- Enhanced passive surveillance *in health posts*:
 - All persons with self-reported subjective fever or measured fever were referred for assessment to study staff by the health post nurses,
 - Informed consent was obtained,
 - Specimens (nasal and throat swabs) were collected from those with influenza like illness (ILI),
 - Persons reporting difficulty breathing were further assessed by study physicians,
 - Febrile subjects meeting the ILI case definition were enrolled even if they tested positive for malaria
- Active surveillance *in the community* (20 villages):
 - Field workers conducted weekly visits to all compounds in the study area,
 - Informed consent was obtained,
 - Clinical data were collected by field worker,
 - Technicians were dispatched to collect nasal and throat swab specimens,
 - Persons reporting difficulty breathing were further assessed by study physicians.

Up to November 22, 2009, a collection of 4897 clinical specimens had been collected. One quarter of them had gone through testing for influenza, of which 22.4% (311 specimens) scored positive for the A/H3N2 subtype, demonstrating the total absence of the pandemic A/H1N1 virus in the region at a time as late as the end of November 2009. This observation is in line with the conclusions of the WHO global pandemic monitoring that West Africa was one of the last regions to be reached by the circulating pandemic virus.

1.4 Pandemic influenza vaccine production in the United States of America (*Michael Perdue*)

The Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services (HHS) has been in charge of the coordination of the 2009 H1N1 influenza vaccine production, control and delivery in the United States of America since 2004. Back five years ago, only two inactivated influenza vaccine and one live attenuated vaccine (LAIV) were licensed. Currently, in addition to LAIV, five inactivated split vaccines have been licensed and four additional vaccines are in clinical development. In 2009, pending FDA approval, the cell-based manufacturing technology became available in the country in addition to the traditional egg-based manufacturing technology. One inactivated split virus pandemic H1N1 vaccine has been licensed and numerous adjuvanted formulations that exhibit antigen-sparing properties are in clinical trials, not to mention cross-protective formulations which are also under development. In collaboration with the National Institute of Health (NIH) a specific BARDA pandemic evaluation approach was initiated in 2009, the so called “Mix N Match” trials, where vaccine antigens are matched with different adjuvants in clinical trials in the search of the best potential antigen-sparing combination. During the last five years the influenza vaccine production capacity increased significantly in the country: 90 million doses egg-based trivalent inactivated vaccine, 50 million doses cell-based trivalent inactivated doses and 15 million doses LAIV are available for use, not to mention adjuvants available for dose-sparing interventions if needed. In contrast, the domestic vaccine production capacity in 2004 was limited to 30 million trivalent inactivated doses produced in one single plant.

In 2009 BARDA provided funds through production contracts to five manufacturers to perform clinical trials with pandemic H1N1 vaccines, which resulted in 13 trials in the United States of America and Costa Rica including more than 11,000 study subjects from 6 months to over 65 years of age. The overall conclusions of the trials were that: i) split vaccines without an adjuvant elicited potentially protective antibody levels (FDA criteria) with 15 µg HA per dose, often as early as 8-10 days post-vaccination with one dose in persons above 10 years of age and two doses in children below 10 years of age; ii) the same vaccines in combination with adjuvants were even more immunogenic, albeit also more reactogenic at both the local and systemic levels; and iii) all safety results were consistent with those of seasonal vaccine clinical trials, and no severe adverse event was reported.

HHS and BARDA also supported international vaccine development against pandemic influenza through a series of grants: a US \$24.4 million to WHO in support of vaccine production capacity building in developing countries; a US \$1 million to Valbiotech in Viet Nam to develop a cell-based influenza vaccine; a US \$3.5 million grant to support international development of LAIV technology; and a US \$8 million award to PATH for conducting clinical trials in Viet Nam with pandemic vaccine candidates.

The US government will also donate 10 per cent of its domestically produced H1N1 vaccines to the WHO for utilization in developing countries.

1.5 Influenza vaccine production capacity building in developing countries: Example from the Serum Institute of India (SII) *(Suresh Jadhav)*

The WHO influenza vaccine production capacity building programme in developing countries was designed to increase developing country response capacity to pandemic threats, in line with the recommendations of the WHO Global Influenza Action Plan to increase vaccine supply in the case of pandemic influenza.

Since early 2007 the WHO has been sponsoring 11 developing country vaccine manufacturers through “seed” grants in support of influenza vaccine production capacity building as part of their country pandemic preparedness activities. Six grants were attributed in 2007 to Bio Farma (Indonesia), Birmex (Mexico), Butantan (Brasil), GPO (Thailand), IVAC (Vietnam), and the Serum Institute of India (SII). Five additional grants were attributed in 2009.

Two main development lines were used by the different companies: the fill/finish approach (Birmex, Bio Farma’s first approach), which implies to have the vaccine bulk provided by an established influenza vaccine producer; or the complete production technology development approach (Bio Farma’s more recent approach, Butantan, GPO, IVAC and Serum Institute of India), that necessitates the help of established producers or advices from experts. As far as vaccine technologies are concerned, both inactivated and live attenuated influenza vaccines (embryonated hen’s egg based) were developed. All six manufacturers made significant progress, as assessed by independent technical experts and as demonstrated by the approval of a new seasonal vaccine by a National Regulatory Agency and the production of clinical grade inactivated or live pandemic H1N1 vaccine candidates by several companies, which were ready to enter clinical trials at the time of the meeting in Bamako.

In 2009, SII was able to respond to the challenge posed by the novel H1N1 pandemic virus. The company developed an egg based, whole-virion, alum-adsorbed pandemic H1N1 vaccine candidate. A first clinical trial batch was produced by the time of the meeting in Bamako and, pending regulatory approval, clinical studies were planned to start in January 2010.

The company also obtained a sub-license for developing the Russian live attenuated influenza vaccine (LAIV). SII’s pandemic H1N1 LAIV candidate is based on a reassortant working seed lot produced at the Institute of Experimental Medicine, Saint Petersburg, Russia, starting from the A/17/California/2009/38 (H1N1) pandemic strain and the A/Leningrad/134/17/57 donor strain. The reassortant strain was provided, through the WHO, by the original developer of the master donor strain. A GMP batch of the H1N1 LAIV candidate vaccine was already produced by the time of the meeting in Bamako, and, pending regulatory approval, clinical studies were planned to start in January 2010, using a small spray device provided with the vaccine.

1.6 Is a universal influenza vaccine feasible? (*Rick Bright*)

Influenza viruses cause significant morbidity and mortality (up to 500 000 deaths per year world wide). The disease is particularly severe in very young and very old individuals, in individuals with chronic cardio-pulmonary conditions, in pregnant women and in the immunocompromised. Albeit vaccination is the cornerstone for influenza prevention and all current vaccines are safe and efficacious, seasonal vaccines are only about 30% to 50% effective in older adults and early candidate vaccines against H5N1 viruses remain poorly immunogenic without the addition of adjuvants.

Influenza vaccine effectiveness is based primarily on the induction of neutralizing antibodies that target highly variable regions of the virus hemagglutinin (HA). Protection following infection or vaccination is strain-specific, implying that emerging new influenza virus strains cannot be covered by the vaccine. There is therefore a need for constant reformulation of the vaccine for the yearly immunization campaigns both in the Northern and the Southern hemispheres, to cope with the constant drifting or shifting of HA or NA antigenicity, as little or no cross-protection exists against drifted strains. Another problem is that current vaccines are predominantly produced in embryonated hen's eggs and the inherent surge capacity in the case of a pandemic outbreak is relatively limited.

A theoretical "universal" influenza vaccine should be able to elicit long-lasting protection against any given subtype of influenza A virus. This would allow one to eliminate annual "guesswork" for strain selection, reduce vaccine production costs, eliminate vaccine "mismatches" with circulating viruses -an occasional phenomenon observed with current seasonal vaccines-, reduce the potential for vaccine shortages and increase the global supply of vaccines. Such a vaccine could be stockpiled for future epidemics/pandemics.

Broader and longer-lasting immunity could be obtained by incorporating highly conserved proteins into novel influenza vaccine candidates that would elicit both cellular and humoral immune responses to conserved proteins or cross-reactive epitopes. This implies to identify perhaps less immunodominant, but more cross-reactive B and T cell epitopes on HA, NA and conserved viral proteins to "engineer" those sequences into a vaccine that would optimize expression and delivery / uptake of the antigen. The M2e protein, a fairly conserved viral membrane protein, as well as the M1 and NP proteins are conserved viral antigens that fulfill at least part of these criteria.

Some of the vaccine candidates that could meet these attributes are LAIVs, DNA vaccines made with plasmid-based single or multiple gene combinations, recombinant subunit expression systems (baculovirus, yeast, other fungi, tobacco plants), virus-like particles (VLPs) produced through lentiviral, baculoviral, fungal or tobacco plant systems, live recombinant vaccines using adenovirus or alphavirus vectors, or multigenic synthetic peptides with conserved CTL epitopes, to only name a few. Candidate subunit vaccines that are at an early pre-clinical / clinical development stage include flagellin-fused M2e or M2e-HBc conjugate, M2e encapsulated in liposomes, VLP candidate vaccines made with both the M2e and the M protein, candidate DNA vaccines expressing M2e alone or in combination with NP or NP and HA. It is too early to attempt a detailed description of the characteristics of each of these products.

Significant challenges are also to be overcome, such as establishing immune correlates of protection, threshold antibody levels synonymous with protection, how to measure significantly cellular immune responses, to name a few. How to assess the potential protective efficacy of new concept-based vaccine candidates remains an immensely challenging and complex task. The question of an appropriate animal model (ferrets, non-human primates?) to measure efficacy is also to be solved. Large efficacy trials aiming at identification of correlates of protection are urgently needed, as they will pave the way to the ultimate goal, the regulatory approval of universal influenza vaccine(s).

In spite of all these considerable challenges, the licensure of a universal influenza vaccine would make an important contribution to epidemic and pandemic preparedness, so continued research in this area should be encouraged, accelerated and funded.

2. Session II: Measles and Rubella

Moderators: Inacio Mandomando and Mike Levine
Rapporteur: Peter Strebel

2.1 Recent success in reducing measles mortality (*Peter Strebel*)

Between 2000 and 2008, global mortality due to measles was reduced by 78% from an estimated 733 000 deaths in 2000 to 164 000 deaths in 2008. All WHO regions, with the exception of the South East Asia Region, have now achieved the 2010 global goal of reducing measles mortality by 90% compared to estimated 2000 levels. Challenges to achieving the 2010 global measles mortality reduction goal include weak immunization systems, reduced financial and political commitment to measles control (in part due to recent successes), and incomplete implementation of recommended strategies in India. If the program to accelerate reductions in measles mortality cannot be sustained, there will be a resurgence in measles cases and deaths, resulting in a slowing down of progress towards reaching Millennium Development Goal 4.

Recent progress in reducing global measles mortality has renewed interest in measles eradication. Measles eradication is generally considered to be biologically and technically feasible because humans are the sole pathogen reservoir; accurate diagnostic tests exist; and an effective intervention (measles vaccine) is available. The challenges to achieving measles eradication are likely to be political, social and managerial.

2.2 Priorities for measles control and research (*William Moss*)

Broadly, control of measles can strive to achieve mortality reduction, regional elimination or global eradication of the disease. Mortality reduction has been achieved through efforts to increase coverage of the routine first dose of measles-containing vaccines (MCV) and through a second opportunity for measles vaccination, largely through supplemental immunization activities (SIAs). Operational and research priorities for achieving high levels of first-dose coverage include: 1) improvements in routine vaccine coverage in Africa and South East Asia; 2) assessment of the impact of measles control activities on health systems; and 3) assessment of potential synergies with rubella and polio control programs. Operational and research priorities for improving access to a second measles vaccination include: 1) developing evidence-based guidelines for the optimal interval between SIAs, when and how to transition from SIAs to routine 2nd dose and the optimal age of routine 2nd dose; 2) assessment of the impact of other interventions linked to SIAs; and 3) assessment of the market supply of MCVs. Measles control programs require effective and efficient surveillance programs to detect and document outbreaks and to identify high risk areas. Operational and research priorities for measles surveillance include the need to: 1) develop point-of-care diagnostic test for measles and rubella; 2) develop novel methods to estimate measles mortality in the face of successful mortality reduction; 3) re-evaluate surveillance indicators; 4) validate vaccine coverage figures to identify low coverage areas; and 5) develop immunization registries.

Recent progress in reducing global measles mortality has renewed interest in measles eradication. The challenges for measles eradication can be conceptualized as challenges to achieving high levels of vaccine coverage, high levels of population immunity and sustained measles elimination. Challenges to achieving high levels of vaccine coverage include: 1) the sustainability of current measles mortality reduction strategies, particularly SIAs; 2) conflict and political instability; 3) population growth and demographic changes; and 4) public perceptions of vaccine safety. Challenges to achieving high levels of population immunity (with high vaccine coverage) include: 1) waning immunity; 2) heterogeneities in vaccination and clustering of susceptibles; and 3) the HIV pandemic. Challenges to sustained measles eradication include the use of measles virus as an agent of bioterrorism.

2.3 Measles aerosol vaccine project update (*Ana Maria Henao Restrepo*)

Aerosol delivery to the respiratory mucosa is the natural route of transmission for measles virus, and the most promising non-injectable method of vaccination studied so far. Its efficacy is estimated to be comparable to that of parenteral administration of the vaccine. Indeed, in previous studies aerosolized measles vaccine appears to be equally or more immunogenic than subcutaneous vaccine in children aged 10 months and older. Aerosol delivery devices are available that could be used in low resource environments by lay people with limited training and would avoid issues related to injection safety.

Administration of the current measles vaccine via the respiratory route is being comprehensively studied. An animal safety and immunogenicity study and a GLP toxicity study reported good immunogenicity and lack of evidence of local or systemic toxicity. A Phase I trial including 145 measles immune healthy volunteers was completed (2007-08) in India. Results suggested no vaccine related adverse events and good immunogenicity results. A Phase III clinical trial involving 2,000 subjects 9-11, 9 months of age has been launched in India to complete the dossier for licensure in compliance with international standards. Under the auspices of the WHO's Measles Aerosol Project the goal is to achieve licensure by 2011.

2.4 Measles DNA vaccine priming for infants (*Marcela Pasetti*)

Despite the overall progress achieved with mass immunization campaigns, measles mortality in young children remains a significant public health problem in several countries in sub-Saharan Africa. Approximately 30% of infants 2 months of age have protective levels of measles antibodies acquired through maternal breast-feeding, but the proportion falls down to about 4% by 6-8 months of age. Measles DNA vaccine candidates are being developed to specifically target infants who are too young to receive the current licensed measles vaccines. These DNA vaccines are plasmids that express either the H or the H and F MV proteins. Both are well tolerated and highly immunogenic in animal models, including cotton rats, newborn and adult mice, and juvenile and very young infant rhesus monkeys using different routes and modes of immunization. Immune responses were further increased when a 2-dose DNA priming series was followed by a mucosal or parenteral boost with live attenuated EZ measles vaccine. DNA vaccines have also been found to be safe and well tolerated when administered to healthy adults using a 2-dose regimen. Since routine infant immunization in sub-Saharan Africa involves contacts at 6, 10 and 14 weeks of age, the ultimate goal is to administer one of these DNA vaccines at 6 and 10 weeks of age as the priming immunogen, followed by a dose of currently licensed attenuated measles vaccine as the boosting immunogen at 14 weeks of age.

2.5 Global control of rubella and congenital rubella syndrome (CRS) (*Carlos Castillo*)

The first stage in rubella elimination was the recognition of the disease as a public health problem. To better define the scope of the problem, available data from outbreaks and literature reviews were analyzed, operational studies such as retrospective searches were implemented, and burden of disease studies were conducted. It was estimated that in 1999 more than 20 000 infants were born with congenital rubella syndrome (CRS) in Latin America and the Caribbean.

In 2003, PAHO Member States adopted the goal of eliminating rubella and CRS by 2010. In order to reach this goal, PAHO/WHO developed a rubella control and CRS prevention strategy that included: 1) the accelerated implementation of rubella vaccination; 2) the integration of measles/rubella surveillance; 3) the implementation of a CRS surveillance system and; 4) viral detection and isolation. Furthermore, rubella elimination strategies were aligned with those for measles elimination through the use of the combined MR vaccine which contributes to achieving and maintaining the elimination of both diseases. Measles and rubella vaccination strategies include “catch-up,” “keep-up,” “follow-up,” and “speed-up” campaigns targeting adolescent and adult men and women.

Rubella elimination strategies have been highly successful in the Region of the Americas. Endemic rubella virus circulation was interrupted in 2005 and the last rubella case (genotype 2B virus) was reported in January 2009. Endemic virus circulation in the Region is limited to one country (Argentina). Countries that reported the last endemic rubella and CRS cases are implementing active case searches and monitoring of virus excretion from confirmed CRS cases, in order to document and verify the interruption of endemic virus transmission.

3. Session III: Malaria Vaccines

Moderators: Odile Leroy and Ogobara Doumbo
Rapporteur: Vasee Moorthy

The session brought together overviews of malaria epidemiology, field trial design and analysis, updates on recent consultative processes and state-of-the-art presentations on malaria vaccine candidates under clinical evaluation. During 2009 the malaria vaccine field reached a major milestone: the start of a pivotal Phase III multi-center trial of the most advanced candidate vaccine, RTS,S/AS01, in 7 countries in sub-Saharan Africa.

3.1 Overview of malaria epidemiology (*Philip Bejon*)

Malaria disease burden is decreasing in some locations around the edge of the endemicity map in Africa with total mortality annually estimated at 863 000 for the year 2008. The reasons for such a decrease in some locations are not entirely clear but are often temporally related to scaling up in new effective treatment regimens and vector control programs. *P. falciparum* accounts for the vast majority of deaths, but in some dually endemic settings, *P. vivax* disease is becoming more apparent as control measures differentially impact *P. falciparum* burden. Recent prospectively conducted epidemiological studies in dually endemic areas have characterized severe *P. vivax* malaria as an important disease entity that is under-recognized.

There are two approaches to global disease burden estimation, one based on health system reporting and the other on endemicity maps. Global disease burden estimates vary between 243 million (2008 WHO estimate) and 451 million cases (2007 mapping estimate), with the disease burden in India, the Democratic Republic of Congo and in Nigeria representing a substantial amount of the uncertainty. A non-linear relationship between malaria transmission and morbidity was described.

Implementation of successful malaria control in some settings has led to very large reductions in total child mortality. For example, in Equatorial Guinea, annual all-cause under-5 mortality dropped from 152/1000 during the period 1999-2004 to 55/1000 in the period 2004-2008, coinciding with intensive malaria control. These and other data suggest that the total contribution of malaria to child mortality is higher than estimates derived from direct malaria-related deaths. Child mortality is obviously strongly linked to malaria incidence, providing an imperative to continue with recent gains in malaria control and develop a highly efficacious malaria vaccine.

3.2 Current status of RTS,S/AS01 clinical trials (*Ally Olotu*)

Phase IIb efficacy data from a randomized, controlled study of the malaria vaccine candidate RTS,S/AS01 in 850 children aged 5-17 months at first immunization in Kenya and Tanzania demonstrated a 56% efficacy of the vaccine against all episodes of malaria over an average of 8 months of follow-up per child. A randomized, controlled Phase III trial of RTS,S/AS01 started in May 2009 and, as of December 2009, had enrolled over 6500 children at 10 of 11 sites in 7 countries in sub-Saharan Africa. These countries and sites are: Burkina Faso (Nanoro), Ghana (Kumasi and Kintampo), Gabon (Albert Schweitzer Hospital), Malawi (Lilongwe), Mozambique (Manhica), Tanzania (Korogwe and Bagamoyo), and Kenya (2 sites in Kisumu, and a third in Kilifi). The children are in two age groups: 5-17 months at first immunization and 6 weeks at first immunization, when the vaccine will be co-administered with routine EPI vaccines. The safety profile of RTS,S has been satisfactory to date, on a limited Phase II database of 1150 African children. Safety data in HIV-positive children will be available from a planned Phase II trial. The primary endpoint of the Phase III trial is efficacy against clinical malaria over 12-18 months after the third dose. Severe malaria efficacy data should be available from the Phase II data. The duration of benefit of RTS,S/AS01 is not yet known but will be assessed in the Phase III trial.

3.3 Upstream malaria vaccine candidates (*Christian Loucq and Mahamadou Thera*)

Two contrasting malaria vaccine approaches have demonstrated partial clinical efficacy during 2009 and both suggest scientific pathways forward to improve efficacy. The first approach is based on a new viral prime-boost delivery of a multiple epitope-TRAP (thrombospondin-related adhesion protein) construct developed in Oxford. The second is vaccination with a recombinant AMA1 (apical membrane antigen 1) vaccine construct which was tested in a Phase IIb trial in Mali. AMA1 is a highly polymorphic blood stage protein antigen and was formulated with GSK AS02A adjuvant for this trial.

The AMA1 field trial results from Mali showed promising results, pending a secondary analysis for allele-specific efficacy. The whole malaria *Plasmodium* vaccine approach is scheduled to complete initial sporozoite challenge trial evaluation during 2010. And, finally, PATH Malaria Vaccine Initiative have expressed their interest for pre-erythrocytic and transmission-blocking vaccines against *P. falciparum* as well as against *P. vivax*.

Basic and clinical malaria vaccine research thus continues to advance rapidly thanks to funding from governments, non-governmental organizations, industry and support from WHO. Important sources of funding have included the United States Agency for International Development, PATH Malaria Vaccine Initiative, the National Institute of Allergy and Infectious Disease, the Bill and Melinda Gates Foundation, European Union DG RTD, European Vaccine Initiative, European and Developing Countries Clinical Trial Partnership, the Wellcome Trust, the United States Department of Defense, Top Institute Pharma in the Netherlands and the African Malaria Network Trust. Malaria vaccine projects include recombinant proteins often requiring novel adjuvants, synthetic peptides, recombinant pox- and adeno-viruses, DNA vaccines and whole organism approaches. Comprehensive spreadsheets on projects are available through the WHO IVR website (www.who.int/vaccine_research/links/Rainbow/en/index.html.)

The Global Malaria Action Plan identified and endorsed the R&D need for a “next-generation, highly-efficacious vaccine that combines vaccine approaches and targets *P. falciparum*” (rbm.who.int/gmap/2-4a.html)

3.4 The role of vaccines in the malaria eradication process (*Chetan Chitnis*)

The malaria eradication R&D agenda process has been underway during 2009. The concept of vaccines that could have major indirect effects on transmission without a direct effect on morbidity is a subject for lively debate in view of the likely clinical and regulatory challenges that lie ahead for this approach. Vaccines are in pre-clinical development based on certain sexual stage mosquito antigens. The rationale is that it was demonstrated some time ago that antibodies raised against these antigens can block the mosquito stage of the malaria life cycle. Vaccines targeting pre-erythrocytic and blood-stages may also impact transmission if sufficiently efficacious. Indeed the impact of malaria vaccines on transmission, whichever the parasite stage they target, is felt to become the paramount concern in a hypothetical future where *P. falciparum* sustained control has been achieved across Africa.

R&D for eradication should not however detract from R&D for morbidity/mortality reduction as this would be counterproductive for public health in settings where mortality is high. Earlier malaria vaccine technology roadmap followed an inclusive, broad stakeholder-based approach. This community-based technology roadmap was endorsed by major stakeholders and still forms the framework for the vaccine R&D agenda for morbidity/mortality reduction. Landmark goals on the transition between the currently foreseeable morbidity reduction context in high transmission areas to a possible future elimination scenario in the same settings would be a beneficial utility for public health. For example, shifts away from *P. falciparum* R&D will be counter-productive until *P. falciparum* mortality is sustainably controlled.

3.5 Clinical endpoints in malaria vaccine trials to assess public health benefit (*Peter Smith*)

The extent to which a malaria vaccine delays the first episode of malaria following vaccination has been used as the primary endpoint in some vaccine trials. However, consideration of multiple episodes of clinical malaria, not only a first episode, is important for evaluation of the public health impact of vaccination. In addition, duration of protection following vaccination is important for the use of trial results for public health decision-making. The statistical methods used to analyse vaccine trials should be tailored to the likely mode of action of the vaccine under test. Two simple models are that a vaccine gives a certain level of protection to all vaccinated (the, so-called “leaky” model) or the vaccine gives complete protection to some and no protection to others (the “all-or-nothing” model). Different methods of analysis (and interpretation) are appropriate for these two models. Furthermore, heterogeneity in the risk of malaria in a trial population has the potential to bias efficacy estimates according to time since vaccination. Thus, in some circumstances, apparent waning of protection and heterogeneity effects may be indistinguishable. Although, efficacy trials are likely to focus mainly on efficacy against clinical malaria, because of the relative commonness of this endpoint in many communities, protection against severe malaria and mortality needs to be assessed, possibly post-licensure, to evaluate the full public health impact of a vaccine.

4. Session IV: Update on vaccines against GAVI priority diseases

Moderators: Mamadou Marouf Keita and Tony Nelson
Rapporteur: Carol Tevi-Benissan

4.1 Group A meningococcal conjugate vaccine as a tool for the elimination of epidemic meningitis from Africa (*Milagritos Tapia*)

Group A *Neisseria meningitidis* is the predominant pathogen causing epidemics in the countries of the so-called African ‘meningitis belt’ that stretches from Senegal in the West to Ethiopia in the East. More than 80 000 cases of meningitis A were reported in these countries in 2009. The Meningitis Vaccine Project (MVP) was established in 2001 through a public-private partnership that includes the WHO, PATH and the Bill and 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, which was tested in a Phase I clinical trial in India, a couple of Phase II trials in Mali and The Gambia, and a Phase II/III trial in several sites in India and Africa. The vaccine showed better immunogenicity and induced longer lasting bactericidal antibody responses than polysaccharide vaccines in volunteers 1-29 years of age. In addition, effective priming for immunological memory was demonstrated in toddlers 12-23 months of age. Currently, a Phase II clinical trial is ongoing among infants in Ghana, to determine the optimal dose and immunization schedule for infants. MenAfriVac® is expected not only to provide individual protection, but also to inhibit nasopharyngeal carriage and therefore decrease transmission of the pathogen, thus eliciting a herd immunity effect at the population level.

The vaccine introduction strategy has been presented and approved as an Investment Case to the GAVI Alliance in June 2008. This strategy is intended to rapidly protect the population and induce herd immunity through 1 single dose. Mass vaccination campaigns targeted at 1 to 29 years of age will be conducted in the African Meningitis Belt countries, starting in 2010 with Mali, Burkina Faso and Niger. Protection of new birth cohorts will be achieved through follow-up mass campaigns targeted at 1 to 4 years of age every 5 years and through introduction of the new vaccine in the EPI schedule. It is expected that MenAfriVac® will be made available at a price of US\$ 0.40 per dose.

High quality post-licensure studies should be designed to monitor vaccine safety and effectiveness, including validation of correlates of protection. This will require sustained surveillance efforts and the development of standard protocols in countries where the vaccine is introduced.

4.2 **Pneumococcus disease burden and the impact of conjugate vaccines** (*Anthony Scott*)

Streptococcus pneumoniae is a major cause of pneumonia, meningitis and sepsis in children worldwide, with an estimated 1 million deaths in children younger than 5 years of age every year. However, in many countries, few data are available on the actual incidence of serious invasive pneumococcal diseases and deaths, resulting in the absence of evidence upon which decisions on pneumococcal disease treatment and prevention could be based. To fill this gap and model disease burden, data were collected from surveillance systems and networks, research institutes, and vaccine trial analyses, with the objective to provide country-specific estimates of the disease burden attributable to pneumococcus, taking into account local infant mortality rates, HIV prevalence and local access to care.

Analysis of the available data showed that in 2000, there were 14.5 million episodes of serious pneumococcal disease worldwide, with pneumonia accounting for 13.8 million cases, sepsis for 538 000 cases and meningitis for 103 000 cases. Most of the resulting 826 000 deaths occurred in Africa and South East Asia. Stratifying the deaths by age showed that 11% of the deaths occurred in infants, toddlers and children 1-59 months of age, representing 7% of all deaths in children less than 5 years of age. Another 11% of the deaths occurred in HIV-positive individuals. A detailed analysis of available data, such as those from the Kilifi site in Kenya, showed that the highest risk of pneumococcal disease was in the first few months of life, especially in the first month of life.

The impact of pneumococcal conjugate vaccines depends on the serotype coverage of the formulation, the efficacy of the vaccine, the vaccination coverage and schedule, and the magnitude of indirect effects such as herd protection and serotype replacement. Two conjugate pneumococcal vaccines are now available, PCV 7 and PCV10. PCV7 (PrevnarTM), which covers about 66% of all strains globally, but only about 50% of the strains that are found in Africa and Asia, has recently been introduced in Rwanda and The Gambia. PCV 10 will cover more than 70% of all strains worldwide, but the total direct and indirect effects of the vaccine have not yet been evaluated. An effective surveillance system will be necessary following vaccine introduction, especially in some of the developing countries for which there is virtually no data in spite of systematic reviews of literature such as those done by the Global Serotype Project.

4.3 **Serotype replacement following introduction of pneumococcal conjugate vaccine** (*Cynthia Whitney*)

Over 90 distinct *Streptococcus pneumoniae* serotypes have been identified, whereas currently available conjugate vaccines cover only a limited number of serotypes (7, 10, or 13) and provide serotype-specific protection with limited cross-protection. Pneumococcus serotype distribution is affected by several factors including strain evolution and capsular switch, outbreaks and/or epidemics, impact of vaccination, population immunity status, use of antibiotics, age distribution, improved socioeconomic conditions, etc.

The pneumococcal conjugate vaccine (PCV 7) was introduced in the United States of America in the early 2000's, resulting in as much as 99% reduction in pneumococcal disease caused by the 7 serotypes contained in the vaccine and 79% decrease in overall pneumococcal disease among children <5 years of age, as determined by extensive surveillance carried out by the Active Bacteria Core Surveillance (ABCs) among 18.5 million people. However, a significant increase in pneumococcal disease caused by non-vaccine serotypes was also detected, especially among Alaska natives who showed a much increased prevalence of serotype 19A. Occurrence of type 19A as a replacement strain has been attributed to its potential to cause invasive disease, its common carriage in the nasopharynx, association with antibiotic resistance, emergence of new clones in the absence of vaccination and evidence of capsular switching. A different pattern may however be observed in other settings. Thus, no replacement disease has been observed in the Australian aboriginal population, and no prevalence of serotype 19A was observed in Navajo children.

Adults have also benefitted from vaccination, as observed in some populations. Thus the ABC data show a reduction of 36% of all pneumococcal diseases in adults >65 years of age, most likely due to a herd immunity effect. In Australia, vaccine serotype specific pneumococcal disease in adults decreased by 46% following the introduction of PCV7. Similar reductions were not however observed in Canada. Among U.S. adults 50-64 years of age, the benefit was only for healthy adults in this age group had a large degree of replacement disease, and that the degree of replacement disease varies with different syndromes.

In summary, vaccine benefits vastly outweighed the burden of replacement disease in the children population in the United States of America, Canada, and Australia, to the only exception of Alaska Natives living in remote areas. For adults, overall indirect benefits are mixed, with positive effects seen in the United States of America (including HIV positive individuals) and Australia, and no impact in Canada, in indigenous populations and in chronically ill US adults. Serotype 19A was the most significant replacement strain detected.

Further surveillance and analysis are required to determine what the status of replacement disease is in Europe and in developing countries, what will the impact of next generation conjugate vaccines be, and what is the true picture of replacement disease in different pneumococcal risk groups.

4.4 Rotavirus vaccines for children in developing countries: results of clinical trials (*Kathy Neuzil*)

It is estimated that each year, rotavirus (RV) causes 111 million cases of diarrheal disease, 25 million outpatient visits, 2 million hospitalizations and 527 000 deaths. Global surveillance shows that 40% of diarrheal hospitalizations in young children are due to RVs. There are currently two RV vaccines: a monovalent human vaccine, Rotarix™ (GSK Bio) and a pentavalent bovine reassortant vaccine, RotaTeq™ (Merck), that require two and three oral doses, respectively. The RV vaccines have so far been introduced into countries with a low burden of disease in North and South America, Europe and Australia, but not in Asian or African countries, although these bear the greatest burden of disease. In 2005 already, the Scientific Advisory Group of Experts (SAGE) had recommended the *“inclusion of rotavirus vaccination into the national immunization programmes of regions and countries where vaccine efficacy data suggest a significant public health impact...”* and because of concerns that *“live oral vaccines may not be fully effective in protecting the poorest children in developing countries,”* noted *“the need for urgently generating efficacy data in Asia and Africa, where the disease burden is very high.”*

Since 2005, however, randomized controlled trials of RV vaccines were conducted on more than 12 000 children in Mali, Ghana, Kenya, Malawi, South Africa, Bangladesh and Vietnam. Thus, a phase III clinical trial of the Rotarix™ vaccine was conducted in 2005 in South Africa and Malawi, involving 4941 infants who received either 2 or 3 doses of the vaccine or a placebo together with the EPI vaccines and were followed up until one year of age. The primary end-point of the trial was at least one episode of severe rotavirus gastroenteritis (RVGE). There were 5% RV diarrheal episodes in the control group and 2% in the vaccine groups, a pooled vaccine efficacy of 61% (CI: 44%, 73). The vaccine prevented more cases of severe diarrhea in poorer communities (3.9 cases prevented per 100 children in Malawi against 2.5 per 100 in South Africa). It also prevented 30% of episodes of gastroenteritis of any cause.

A Phase III clinical trial of the Rotateq™ vaccine took place in Ghana, Kenya and Mali involving a total of 5468 infants who received three doses of the vaccine at the same time as the EPI vaccines. The pooled efficacy of the vaccine against severe RVGE was 64.2% (CI: 40.2, 79.4) in the first year of life, and fell to 19.6% (0%, 44.4%) in the second year of life, with the number of episodes prevented falling from 1.5 per 100 children to 0.7 per 100. Overall efficacy during the total follow-up period was 39.3% (CI: 19.1%, 54.7%). Country-specific efficacy figures in the first year of life were: 65% (CI: 35.5, 81.9) for Ghana, 83.4% (CI: 25.5, 98.2) for Kenya. In Mali, because only 8 total cases were detected in the first year, the study was underpowered to demonstrate efficacy { 1.0% point estimate (CI: <0.0, 81.6) }. The low case count in Mali was, perhaps due to issues of surveillance and seasonality of RV diarrhea in Mali.

An efficacy trial of the Rotateq™ vaccine was also done in 2007 in Vietnam and Bangladesh, and lasted for 24 months. A total of 2036 infants were enrolled. The efficacy reported was 51.0% (CI: 12.8, 73.3) for the first year of life, 45.5% (CI: 1.2, 70.7) for the second year and 48.3% (CI: 22.3, 66.1) for the total 2-year follow-up period. Overall efficacy was 73% in Vietnam, but only 45.5% in Bangladesh. Similar to the experience in the GSK trial, however, because of the higher incidence of severe disease in poorer communities, more cases of severe diarrhoea were prevented in Bangladesh than Viet Nam. A randomized trial to look at possible indirect effects of the Rotarix™ vaccine is under way in Bangladesh.

Altogether, the RV vaccines have shown remarkable effectiveness against all RV strains, and no strain replacement phenomenon has been evidenced. As diarrheal diseases are an important co-morbidity factor in childhood and can act as a trigger to other diseases, the indirect effects of these vaccines, once introduced, is likely to be quite substantial. SAGE recommended the introduction of RV vaccines into the EPI. An estimated 5 500 000 infants died of RV diarrhea during the last decade (1999-2009): the introduction of RV vaccines will hopefully save many of these deaths in the future.

Several questions remain, however, that require further research, such as possible interference of RV vaccines with OPV, the effect of maternal antibodies on the effectiveness of the vaccine, optimal dosage and schedule, and effect of co-infections. Also, correlates of protection still remain unknown.

4.5 Haemophilus influenzae type B (Hib) vaccine: introduction in Mali *(Samba Sow)*

Mali, a 12.5 million inhabitant West African country, is the 4th poorest country in the world. Its infant mortality rate and Under-5 mortality rate are 120 and 218 per 1000 live births, respectively. Prior to the establishment of appropriate microbiology surveillance for bacterial disease, 71% of the pediatric admissions to Hôpital Gabriel Touré in Bamako had a presumed infection, 50% had a clinical diagnosis of malaria and 21% of the admitted infants died in the hospital. A Clinical Bacteriology Laboratory was established by the University of Maryland Center for Vaccine Development (CVD) in 2001 in Bamako. Staff was trained in clinical microbiology, GCP and data management. Subsequently, specimens were taken from all patients admitted with the following characteristics: age 0-15 years, temperature 39°C or above, and/or any clinical syndrome suggestive of invasive bacterial diseases. After 36 months of surveillance, data from this paediatric hospital showed a high incidence of Hib disease, which increased with age from 43 per 100 000 at 2-3 months of age to 376 per 100,000 population at 6 to 7 months of age. It was also shown that 12% of all hospital admissions of infants 4-11 months of age and 19.3% of deaths were due to Hib disease. These data served as a basis for the introduction of the Hib conjugate vaccine which occurred on July 2005.

The Hib vaccine introduction was done in a 3-step approach, starting with Bamako, the national capital, then extending vaccination to regional capitals and eventually to the rest of the country. The impact of the vaccine was monitored using the same hospital-based surveillance as above. Twenty-four months after the introduction of the Hib vaccine, Hib disease was reduced by as much as 88%, number of hospitalizations due to Hib disease fell by 75%, while that of all-cause hospitalizations fell by 29%. Serological survey for anti-Hib antibodies in infants 6-7 months of age showed progressive increase in the proportion of children with protective level of antibodies (at least 0.15 µg/ml), from baseline level at the introduction of the vaccine in 2005 to 70% 18 months later and to more than 80%-90% 30 months later.

The key lessons to be learned from the Mali experience, besides the impact on Hib disease and pediatric hospitalizations, include:

- Importance of credible local burden data for influencing decision makers and generating political will;
- Critical role of lab-based surveillance to demonstrate the impact of vaccine intervention;
- Partnership with local health department, generating a feeling of ownership and pride in the success of a public health project.

The Hib vaccine experience paves the way for similar endeavors with pneumococcal conjugate vaccines, RV vaccines, and Meningitis A conjugate vaccine. Introduction of the later in Mali is pending.

5. Session V: Pharmaco-vigilance in Low and Medium Income Countries (LMICs)

Moderators: Edwin Asturias and Peter Smith
Rapporteur: Pem Namgyal

5.1 The Brighton collaboration (*Odile Leroy*)

The Brighton Collaboration (BC) was founded in 1999 to facilitate the development, evaluation, and dissemination of high-quality information relative to the safety of human vaccines, starting from vaccine safety data generated by clinical trials and surveillance systems, and from epidemiological studies across different geographic regions. The aim of the BC is to develop and implement study protocols and guidelines for clinical trials and surveillance systems.

A standard terminology or a common “vocabulary” was lacking for adverse events following immunization (AEFIs), which hindered comparability of vaccine safety data across the globe. Thus, there was a need to develop standardized case definitions and guidelines for AEFIs, which would be useful for clinical trial safety monitoring and post-marketing surveillance of new vaccines.

The BC Process allows the prioritization of adverse event as defined by a scientific board. This involves six steps, which are: (i) search for available evidence, (ii) establishment of a working group, (iii) development of a draft of definitions and guidelines, (iv) review and evaluation of the draft, (v) review and endorsement by the CIOMS/WHO working group on vaccine pharmacovigilance, and (vi) finalization and dissemination of the document.

The BC involves a network of ~1500 volunteers from 91 countries, including 320 active working group members from 60 countries. More than 250 scientists from around the world have downloaded and used the Brighton case definitions. However, 80% of the participants are from the developed parts of the world, implying further efforts to involve also developing countries.

In terms of products, 27 BC Case Definitions & Guidelines have been finalized with at least three General Guidelines on AEFI definition and investigation. Further to five evaluation studies, the BC has produced at least five editorials and as many reviews, and developed an Automatic Classification Tool.

The BC is currently actively collaborating with INYVAX, to identify challenges in the implementation of vaccine safety standards in international clinical vaccine trials and to generate immediate “user-feedback” for the improvement of safety standards in clinical trials. It also participates in the Global Vaccine Safety Blueprint, which is a WHO project for a global plan to enhance vaccine safety monitoring, investigation and response. BC’s main roles is to assess needs and identify possible minimum capacity requirements for a global vaccine safety system

In the discussion that followed, appreciation was expressed on recognition of BC’s high quality work. A review of the challenges for implementation of safety standards in developing countries is being carried out, but there is much work left to be done. It was also highlighted that the aim of BC was not to make policy recommendations but to establish standards based on highest quality scientific evidence for defining adverse events following immunization

5.2 Yellow fever vaccine post-marketing studies in Brazil *(Reinaldo de Menezes Martins)*

Starting in 1997, there has been a progressive expansion of yellow fever (YF) in Brazil, which led the authorities to recommend YF vaccination in new areas, resulting in increased use of YF vaccine in the country. In 1998, the Brazilian Ministry of Health (MoH) National Immunization Program developed a national system for Surveillance of Adverse Events Following Immunization (AEFI). A manual on AEFIs was distributed to health workers and an electronic database was implemented into which more than 30 000 health workers across the country keep feeding data. In connection with the Ministry of Health and the Brazilian Regulatory Agency, the Pharmacovigilance Unit of the vaccine manufacturer, Bio-Manguinhos/Fiocruz, separately collects reports of AEFIs from Brazil and from other countries. And to support the surveillance system, five public health laboratories have been established across the country.

The detection and diagnosis of YF or YF-like illnesses is done at three levels: presumptive diagnosis at local level followed by confirmation of cases at state level, and final diagnosis at central level with the participation of experts. Cases are classified as confirmed, probable, suspect, discarded or inconclusive, according to CDC/WHO criteria. Sentinel hospitals are used for the surveillance of acute, febrile, ictero-hemorrhagic syndrome, which is an event requiring mandatory and immediate notification.

YF vaccine-associated viscerotropic disease (YFV-AVD) is a severe disease with a high case fatality rate (23 out of 26) that results from the dissemination of the YF vaccine virus in the body. It remains a rare event with a frequency of 0.02 cases per 100 000 doses of vaccine. Another severe adverse event is YFV-associated neurological disease (YFV-AND), which includes benign aseptic meningitis (1 case per 100 000 doses of vaccine), encephalitis, and autoimmune central (ADEM) or peripheral (GBS) disease. The incidence of Guillain Barré syndrome (GBS) is 1 case per 1 800 000 doses of vaccine. Other adverse events include hypersensitivity events (< 2 hours) and anaphylactic shock (>2hours). Despite the low rate of AEFI, the YF vaccine is still the most effective tool against YF and 90 million doses of vaccine have been used from 2000 to 2009 in Brazil.

Further studies of the vaccine are currently being carried out, such as low dose intra-dermal administration of the vaccine, needle-free administration, and improved purification of the attenuated virus. The relationship between AEFIs and virus titer is also being studied.

5.3 Update on new tuberculosis vaccine clinical trials (*Tony Hawkrigde*)

In spite of systematic vaccination with BCG at birth or soon after birth, tuberculosis (TB), a disease of poverty, still strikes an estimated 9 million people every year and causes around 2 million deaths per year. In addition, the emergence of multiple drug-resistant *Mycobacterium tuberculosis* (Mtb) strains (MDR-TB) and their spread is a dreadful menace, especially at a time when HIV/AIDS is a major facilitating factor for TB. The development of new TB vaccines has been focused on two types of products: priming vaccines and booster vaccines. Priming vaccines are to be given at or near birth, as is the case with the current BCG vaccine. They include both “improved”, genetically modified versions of BCG, and live attenuated versions of Mtb. Booster vaccines are protein subunit or virus-vectored TB vaccines, which may be given either “early”, during the first months of life, or “late”, for example at school entry, during adolescence or in adulthood. Numerous TB vaccine candidates are currently being developed, mostly by academic institutions and vaccine manufacturers in Europe and North America. All of these vaccines will eventually have to be tested for efficacy in the higher burden countries of Africa and Asia.

A priming vaccine candidate, VPM 1002 (rBCG ureC::hly::hyg), a genetically modified version of BCG, has so far been evaluated in a phase I safety trial where it was found to be safe in immunocompetent volunteers. Moreover, IFN- γ expression, a standard immunological readout in TB vaccine research and indicator of vaccine take, and the number of Mtb-specific CD4⁺ T cells, were found to be higher following VPM 1002 administration than after standard BCG.

Several booster TB vaccine candidates are currently undergoing clinical evaluation. The most advanced is MVA85A, a recombinant modified vaccinia Ankara virus expressing an immunodominant TB antigen, Ag85A, which has gone through numerous clinical trials including in HIV positive adults. Ag85A is a mycolyl transferase. MVA85A was shown to induce protection in small animal models and was safe and induced polyfunctional T cell responses in vaccinees. The vaccine is currently in a phase IIb, “test-of-concept” trial in 2784 BCG-vaccinated infants in the Western Cape province of South Africa. Another viral vectored TB vaccine candidate, Aeras 402/ Crucell Ad35, is based on an adenovirus 35 vector expressing three Mtb antigens (85A, 85B, and TB 10.4 antigens). The vaccine is in phase IIa testing in adults as well as in HIV infected infants.

One of the most advanced protein subunit vaccines, the GSK M72 fusion protein, has been in several clinical trials to-date including a phase II trial. A similar fusion protein approach has been developed by the Statens Serum Institute, which developed two vaccine candidates that are in early clinical evaluation, H1 (Hybrid 1), which expresses a 85B-ESAT6 fusion protein, and HyVac-4/Aeras 404, which expresses a 85B-TB 10.4 fusion protein. The H1 candidate vaccine is now in Phase IIa trials in adolescents, whereas the HyVac-4 vaccine just entered Phase I trials.

Finally, two killed mycobacterial preparations are currently being tested as treatment adjuncts (RUTI) or as BCG booster vaccines to prevent TB in HIV-positive individuals (*M. vaccae*). A phase III trial of the latter in Tanzania has shown, after 5 doses of vaccine, a significant difference in the “definite TB” endpoint.

A shortage of suitable sites for clinical efficacy trials represents a serious obstacle to TB vaccine development. An annual incidence rate of 1% in infants and 0.5% in adolescents is considered a minimum requirement in order to keep trials manageable and affordable. Only some high burden countries in South-East-West Africa as well as few Asian countries show this type of TB epidemiology. With the current incidence figures, an efficacy trial will require at least 20 000 infants or 30 000 adolescents. Since no single site will have this type of enrolment capacity, multi-centered trial designs will be necessary. The difficult diagnosis of TB represents another challenge for TB vaccine clinical trials, in particular in infants and children. As a consequence, it will be impossible to perform TB efficacy trials in areas with high infant and under-five mortality. Another complication stems from the diagnostic problem: it may not be possible to break down clinical endpoints in TB vs. no TB but rather into several sub-categories (definite/ confirmed vs. probable vs. possible etc). Therefore, adaptive clinical trial designs may have to be implemented even in experienced sites in order to counter these types of uncertainty.

In the *Discussion*, Dr Hawkridge explained that: 1) homologous BCG boosting does not work, as was shown recently in a trial on 100 000 school children in Brazil; 2) BCG alone is a better vaccine against leprosy than against TB, which would be one more reason to keep BCG (or a derivative thereof) as part of a future new TB vaccination schedule; 3) current thinking suggests that a new TB vaccine should provide at least 60% efficacy, in the case of an infant vaccine, protect for at least 3 years, and in that of adolescent or adults vaccines, probably longer; and 4) the induction of polyfunctional T cells is assumed to be advantageous in resistance against TB, but this assumption still is surrounded with a lot of uncertainty.

6. Keynote Address: Polio eradication- Overview of current status, December 2009

Moderator: Samba Sow

Speaker: Peter Ndumbe, University of Buea, Buea, Cameroon

From 1 January to 17 November, 2009, 1387 poliomyelitis cases were reported from 23 countries, not a major difference from the 1473 cases from 16 countries reported for the same period in 2008. The great majority (78%) of these cases occurred in four 'polio-endemic' countries, Afghanistan, India, Nigeria, and Pakistan, in which indigenous wild type poliovirus (WPV) transmission never was interrupted, in spite of great efforts to reach vulnerable populations. The small decline in cases from 2008 to 2009 was primarily due to a significant drop in the number of cases from Nigeria, where substantial progress was made in engaging dialogue with political and traditional leaders, resulting in considerable improvement in reaching children during mass vaccination campaigns and a rapid decline in transmission of all poliovirus types. In India, Afghanistan, and Nigeria, the size of polio-infected geographical areas has been reduced.

However, at the same time, nearly 20% of the global polio cases were reported from 19 previously polio-free countries which were re-infected. Angola, Chad, and Southern Sudan have shown sustained WPV transmission for over 12 months and must now be considered as having re-established endemic transmission.

The timeliness of response to WPV importations was markedly improved in 2009, and 70% of all importation events in the last 12 months were resolved (i.e. did not result in continued transmission). It is hoped that the recently developed bivalent oral polio vaccine (bOPV) will be introduced in the polio eradication programme before the end of the year.

As confirmed by a recent independent evaluation of major barriers to Interrupting WPV transmission, the main remaining obstacles include a) the difficulty to sustain the programme momentum in view of the very high technical and financial cost of vaccination activities required to eliminate poliovirus transmission in countries where the disease is still endemic; b) the limited access to communities in key endemic and re-infected areas affected by conflict, c) the persistence of transmission in a handful of re-infected countries which now pose a major threat as a source of continued international spread of the virus, and d) the need to rapidly engage political and health leaders from re-infected countries to respond quickly and effectively to WPV importations.

Both the Independent Evaluation Team and the Advisory Committee on Polio Eradication (ACPE) recently concluded that, were these issues to be addressed, polio eradication could be achieved. Recent efforts in endemic countries must be continued and intensified to sustain the current momentum and ensure that polio eradication is completed.

Progress will depend on rapid improvements in several key areas: a) the rapid introduction of bOPV into programme vaccination, b) assuring high level political commitment to polio eradication from both ‘endemic’ countries and countries with re-established transmission (Angola and Chad) or at risk of re-established transmission (Southern Sudan and Democratic Republic of Congo), c) the full implementation of existing ACPE recommendations in response to outbreaks in re-infected countries, d) rapidly improving the independent monitoring of cases in all re-infected countries, e) the development of plans for strengthening routine immunization in endemic countries and countries at persistent high risk of importation, and f) the development of a new Programme of Work for global polio eradication for the period 2010-2012, building-up on the findings of the Independent Evaluation.

7. Satellite Workshop on Correlates of protection relevant to the African context

Chair: Paul Fine

Rapporteurs: Uli Fruth and Ana Maria Henao-Restrepo

7.1 Objectives of the workshop (*Paul Fine*)

The definition of correlates of protection has important implications for basic research, vaccine licensure and vaccine monitoring. There however are inconsistencies in terminology and lack of agreement about methods used to define them. The objectives of the workshop were therefore to consider the terminology in current use; to review existing methods/ approaches for the evaluation of correlates of protection; and to review evidence regarding correlates for selected vaccines. The overall challenge is to fit the evidence on immune responses and on protection together.

The desirable outcomes of the workshop include an outline of appropriate methods for the identification/confirmation of correlates/surrogates; the identification of critical knowledge gaps and methods to fill them; and a new impetus towards the development of a research agenda.

7.2 Correlates of vaccine-induced immunity for licensed vaccines: An overview (*Stanley Plotkin*)

‘Correlates of protection’ is a term often used in relation to vaccine licensure. The use of correlates permits the licensure of a vaccine without demonstration of field efficacy when such studies are not feasible or available. Correlates of protection are also used to guide vaccine development and to evaluate licensed vaccines. A major objective of vaccine research is to identify a vaccine-induced immune response or a surrogate serologic test that will predict protection against infection or disease. Such responses are mainly used to predict the vaccine’s protective effect in a new setting, in which vaccine efficacy has not been directly measured. In an ideal world, vaccine efficacy should correlate with measurable immune responses. However, for some vaccines, the correlation is weak. For other vaccines, the correlation is often uncertain and no true correlates are available but only (useful) surrogate markers of protective responses.

The immune system is redundant, and the different types of immune responses to vaccines act in a synergistical manner. Thus, cellular immunity, which allows the killing or suppression of intracellular pathogens, may also synergize with antibody responses. Immune memory is always a critical correlate, with effector memory playing a major role for short incubation diseases, and central memory for long incubation diseases.

One of the challenges is that we are faced with an inconsistent use of the terminology. In general, it is accepted that a correlate of protection constitutes a statistical association between an immunological parameter and protection, whereas a surrogate marker includes in addition a strong element of biological plausibility, indicating that the immune function measured is directly related to protection. In the context of vaccine regulation, broad guidelines exist to define when a correlate or surrogate is an acceptable evidence to support the licensure of a vaccine.

A correlate of protection is the immune function that protects as shown by statistical correlation. Correlates are the measurable signs that a person (or other potential host) is immune, in the sense that she is protected against becoming infected and/or developing disease. Correlates of protection represent a predictable relationship, based on a statistical probability, which says that if one thing happens, a related something else will follow. Correlates of protection after vaccination are sometimes absolute (when a certain level of response almost always guarantees protection) but most often are relative (protection is achieved above a certain threshold of response, but breakthroughs can occur even at these supposedly ‘protective’ levels).

The term “cocorrelates” is used to refer to situations where antibodies on mucosal surfaces may also play a role in protecting against pathogens which exert their pathogenicity on these surfaces or which must colonize the mucosa before invading the body in a systemic fashion. Cell-mediated immunity may also be a cocorrelate, but usually cellular immune responses protect against disease once infection has taken place, rather than inducing protection against infection. In situations where the true correlates of protection are unknown or difficult to measure, surrogate tests (usually antibody measurements) may be adequate predictors of the protection elicited by the vaccine.

7.3 Correlates for bacterial polysaccharide vaccines: responses, immune memory and assays (*David Goldblatt*)

Antibody responses to the capsular polysaccharides of encapsulated bacteria are critical for protection against clinical disease. Vaccines designed to protect against *Haemophilus influenzae* type b (Hib), Meningococcus or Pneumococcus are based on purified capsular polysaccharides or on polysaccharides which are conjugated to protein carriers. While the polysaccharide itself provides short protection against some infection syndromes in individuals older than 2 years of age, the conjugated version provides robust, long lasting protection of even young infants against a variety of clinical syndromes.

Approaches to developing correlates of protection have understandably focused on the relationship between antibody levels to the capsular polysaccharide and either clinical protection measured during vaccine trials or vaccine effectiveness measured following the introduction of the vaccine into a routine immunization program. While historical data from Hib polysaccharide vaccine trials were simply extrapolated to Hib conjugate vaccines to provide correlates of protection, the approach with meningococcal and pneumococcal vaccines has been more sophisticated. The correlate of protection for meningococcal C (MenC) vaccines was originally developed in the context of polysaccharide vaccines measuring functional antibody responses by a serum bactericidal assay (SBA); but it was re-evaluated in the context of Men C conjugate vaccines used in infants, children and adolescents.

In contrast, correlates of protection for pneumococcal vaccines have been derived from antibody levels measured by a binding ELISA test and have focused on concentrations measured after the initial, primary dose of vaccine during infant immunization, ignoring the responses that follow booster immunization. This approach has raised a number of issues, which include the use of post-primary responses to derive a correlate when a booster dose of vaccine is later administered, the relative merits of binding antibodies versus functional antibodies and the relationship between correlates of protection against invasive pneumococcal disease and against other disease syndromes.

7.4 Study designs to evaluate substitute endpoints: An epidemiological perspective (*Peter Ndumbe*)

The use of surrogate endpoints implies the availability of laboratory markers of immunity that can reliably predict clinical protection. They constitute biomarkers in infected participants for the temporally distal disease endpoint of interest. In practice, the strength of the evidence for surrogacy depends upon (1) the biological plausibility of the relationship; (2) the demonstration in epidemiological studies of the prognostic value of the surrogate marker for the clinical outcome; and (3) evidence from clinical trials that modification of the surrogate response corresponds to modification of the clinical outcome. There are methodological issues with the use and interpretation of substitute end points in various epidemiological study designs.

In observational studies, there is a need to consider that the vaccine might already have been given some time earlier (maybe years), before the assessment, and that differences between vaccinated and unvaccinated individuals (in terms of levels of the immune marker) may be due to factors other than vaccination (e.g. different levels of exposure to the pathogen being studied). Because of the lack of randomization in this type of study, the establishment of causal inferences can be hampered (e.g. differences in nutritional status between vaccinated and unvaccinated individuals). Moreover, the immune marker needs to be measured before individuals develop the outcome of interest. Lastly, imprecision in the measurement of the immune marker and lack of association could occur if the wrong type of antibody is measured.

During ecological studies, associations are assessed using different population groups and not at the individual level. To investigate the mechanism underlying differences in the efficacy of BCG vaccines against pulmonary tuberculosis in various populations, randomised controlled studies were set up to measure vaccine-induced immune responsiveness to mycobacterial antigens in various populations. Results suggested that production of IFN by CD4⁺ T cells is necessary to prevent disease after exposure but it apparently is not an adequate correlate of BCG vaccine-induced protection.

In case control studies, the aim is to compare potential substitute endpoints between subjects who develop the clinical outcome and those who do not. This is done in a context where blood samples are collected and stored prior to the outcome of interest. Subjects were for example followed for several months after pertussis (PT) vaccination to document the occurrence of whooping cough, after which the median PT IgG concentration in those who developed severe disease and in those who did not develop the disease were compared, which allowed one to establish that there was a highly significant correlation between the level of vaccine-induced serum PT IgG and protection against pertussis.

In cohort studies, subjects are classified by vaccination status and followed up to measure their immune response; or they are classified by their immune status and followed up until the occurrence of the clinical endpoint. Studies to evaluate various strains of measles vaccine included classification of subjects according to their antibody titers. Seropositivity and seroconversion were defined using predefined prevaccination unprotective levels (e.g. < 200 milliunits/ml) and postvaccination seropositive values, or as an increase in a prevaccination seropositive value after vaccination. In natural history studies, investigators follow up those individuals who develop infections and recover, in order to analyse the components of their immune system after recovery. It is not known how humoral and cell-mediated immune responses induced after varicella vaccination differ from those obtained after natural infection. Previously infected (postchickenpox) and vaccinated subjects were tested for their varicella zoster virus (VZV)-specific antibody levels and for their lymphocyte stimulation responses to VZV antigen. Few weeks after a first exposure, the magnitude of the response was determined by both ELISA and IFT. Antibody responses to VZV were better in naturally infected than in vaccinated subjects. IFT was described as a more sensitive technique for antibody detection in vaccinated subjects.

Immunogenicity studies are designed to assess the proportion of subjects who show high antibody levels in the vaccine group as compared with the placebo group. Studies to determine the immunogenicity of a pneumococcal conjugate vaccine (PCV) included estimating proportions of infants with antibody concentrations above 0.2, 0.35 or 1.0 µg/ml. The geometric mean concentrations (GMCs) of anti-pneumococcal polysaccharide antibodies were compared among children that received various doses of PCV and those in the placebo group. The estimated overall protective antibody level for all vaccine serotypes, based on the vaccine efficacy against vaccine-type invasive pneumococcal disease (IPD) was estimated and the data were used to conclude that PCV was immunogenic in the study population.

Randomized Clinical Trials constitute the gold standard method to assess both the association between vaccination and immune markers, and the association between markers and clinical endpoints. Neonatal rotavirus candidate vaccines were tested in double-blind, placebo-controlled dose escalation trials. Differences in clinical adverse events or laboratory toxicity were observed between vaccine and placebo recipients. Four-fold increases in rotavirus immunoglobulin A titer were documented after each dose of vaccine; the differences between these groups and placebo recipients were statistically evaluated. The results were used to conclude that three administrations of vaccine doses were safe and, resulted in a robust immune response.

Substitute endpoints represent a significant research tool as they allow for the earlier identification of beneficial effects of new candidate vaccines on a given population and permit a more efficient evaluation of new vaccines. The absence of apparent immune correlates can pose a significant obstacle to vaccine research and development.

7.5 A regulatory perspective: Issues of correlates versus surrogates of protection and implications for licensure and recommendation (Norman W. Baylor)

Endpoints used to evaluate clinical efficacy in randomized controlled trials can range from disease incidence to a well-established correlate of protection. While the terms ‘correlate of protection’ and ‘surrogate’ are often used interchangeably, they represent two distinct regulatory concepts. A correlate represents a frequent, but not unambiguous, marker of the protective immune response. A surrogate is considered a consistent and reliable indicator of protection. For example, in the case of influenza, although a high HAI antibody level correlates with protection, it cannot be considered as a surrogate of protection. A correlate of protection is generally a laboratory parameter shown to be *associated with* protection against clinical disease, while a surrogate endpoint is a laboratory or physical sign that is used in clinical trials as a *substitute* for a clinically meaningful endpoint. Further, the terms are not mutually inclusive: a biomarker identified to correlate with protection does not always equate a valid surrogate endpoint.

An immunological correlate of protection is most useful if clear qualitative and quantitative relationships can be determined, e.g., a certain type and level of antibody correlate with protection. For some vaccines, there is ample evidence that a certain level of a defined antibody response correlates with protection, e.g. Hepatitis B vaccine and anti-HBs antibody levels. Attainment of such antibody levels in a significant proportion of the target population following immunization may be the basis for licensure in the absence of additional efficacy studies.

7.6 The use of serological correlates of protection for the introduction of meningococcal serogroup C conjugate vaccines in the United Kingdom of Great Britain and Northern Ireland (Nick Andrews)

Meningococcal C conjugate vaccines (MCC) were licensed on the basis of serological correlates of protection without efficacy data in the field. This was the first vaccine to be licensed without efficacy data and this was only possible because a correlate of protection was available. Without such a correlate licensure would have been too expensive: a clinical trial to demonstrate efficacy for such a rare disease would have required in excess of 250 000 children.

The original correlate of protection for meningococcal C vaccine was a serum bactericidal antibody assay using human complement (hSBA): titers $\geq 1:4$ were shown to predict protection in military recruits (Goldschneider 1969). A similar assay using rabbit complement (rSBA) was used for licensure, but comparisons with hSBA showed that a higher cut-off was required. Vaccinees with rSBA titers $\geq 1:128$ all had a hSBA titer $\geq 1:4$, but those with rSBA titers of 1:8 to 1:64 were not always $\geq 1:4$ by hSBA. Therefore an additional requirement of a four-fold rise in titer pre to post vaccination was required for licensure.

Post licensure, the correlate of protection using rSBA titer was evaluated by comparing predicted vaccine effectiveness and observed vaccine effectiveness (Andrews 2003). Predicted effectiveness is calculated based on the distribution of antibody titers post vaccination in clinical trials, whereas observed effectiveness is calculated using the screening method (Farrington 1995) where data on the vaccination status of confirmed cases is compared to population vaccine coverage. Comparisons were made using titers at various time points after vaccination and also using effectiveness estimates by time since vaccination. The results showed that the correlates of protection were valid and helped demonstrate that a cut-off titer of 1:8 by rSBA was a reasonable correlate, whereas a cut-off of 1:128 would have underestimated observed effectiveness.

7.7 The use of serological correlates to evaluate immune responses to meningococcal A conjugate vaccine and predict vaccine effectiveness (*Simonetta Viviani*)

Group A *Neisseria meningitidis* is the predominant cause of epidemic meningitis in sub-Saharan Africa. The Meningitis Vaccine Project (MVP), a partnership between the World Health Organization and PATH, was created in 2001 through core funding from the Bill & Melinda Gates Foundation with the goal of eliminating meningococcal epidemics in sub-Saharan Africa through the development and use of a conjugate meningococcal vaccine. The meningococcal A conjugate vaccine (MenAfriVac) was developed and manufactured by Serum Institute of India Ltd, based on group A *N meningitidis* capsular polysaccharide conjugated to tetanus toxoid as a protein carrier.

MenAfriVac is licensed in India and prequalified by WHO and will be used as a single dose during mass vaccination campaigns to eliminate epidemic meningitis in the Africa meningitis belt countries. The target population will consist of children, adolescents, and adults 1 to 29 years of age. Licensed polysaccharide vaccines were consistently used as a comparator throughout the clinical development as they are recommended by WHO for use in reactive mass vaccination campaigns during meningitis epidemics in high endemicity African countries. Standardized serum bactericidal antibody assay (SBA) and group A-specific IgG ELISA were used to evaluate the immune response to MenAfriVac in clinical trials. A 4-fold increase in SBA titer was used as primary end point criterion of a successful immune response. Other SBA and IgG ELISA secondary end points, some of which considered as putative serological correlates of protection, were also tested in clinical trials in Africa and India. Despite the high baseline SBA titres found in the African population aged 2-29 years (> 70% with SBA titer $\geq 1:128$) those vaccinated with MenAfriVac vaccine showed a significantly higher immuneresponse than those vaccinated with PsACWY vaccine both in terms of proportion of subjects with 4-fold increase in SBA titer and of GMTs. Similar results were observed in 12-23 months old children. Whether the established serological correlates of protection (SBA titer $\geq 1:8$ and $\geq 1:128$) against group C *N meningitidis* disease will also be confirmed as correlates of protection for group A *N meningitidis* disease sub-Saharan Africa, can only be assessed once MenAfriVac is introduced at large scale in the African meningitis belt countries.

7.8 Combining humoral and cellular immune read-outs: Defining correlates of protection for malaria vaccines (RTS,S) (*Philippe Bejon*)

Correlates of naturally acquired immunity against *Plasmodium falciparum* malaria are poorly defined but are thought to lie in IgG responses to blood-stage parasites. The most advanced malaria vaccine candidate, RTS,S/AS01, is in Phase III clinical trial evaluation. RTS,S is a recombinant fusion protein with a portion of the *P. falciparum* circumsporozoite (CS) protein covalently linked to HBsAg, the HBV surface glycoprotein. A clinical protection efficacy of 50% against infection was reported in a clinical challenge trial in adults in the United States of America, and a 30%-50% efficacy against infection and clinical disease was observed in adult and paediatric field trials in several distinct epidemiological settings in Africa.

Analyses of association between immunogenicity and efficacy in the RTS,S/AS01 efficacy trials to date support a critical role for IgGs against the CS repeat sequence in the protection seen against infection, whether in adults in the United States of America or The Gambia, or in children under 5 years of age in Mozambique, Kenya or Tanzania. No absolute correlate of protection has however been identified which would allow prediction at the individual level. Both CD4⁺ IFN γ - secreting T cells as detected by ex vivo ELISpot and multifunctional CD4⁺ T cells measured by intracellular cytokine staining were also associated with protection against infection. Th1 cells therefore play a role in RTS,S-mediated protection, in addition to the contribution of IgGs. Preliminary analysis of the association between anti-CS IgGs and efficacy against clinical disease, as seen in a recent Phase II trial in Kenya and Tanzania, did not however reveal a clear-cut correlation.

Exploratory studies to shed some light on the fine specificity and protective mechanism of the IgG response to RTS,S are a high priority. Second generation malaria vaccines that are able to match the protective B cell response seen in RTS,S vaccinees, but improve on the cellular immunity aspect, might have a good chance of showing higher efficacy. A degree of partial efficacy of 20%-25% has been observed in clinical challenge trials of other malaria subunit vaccines, particularly prime-boost combinations of DNA-recombinant adenovirus vaccines or of adenovirus-poxvirus recombinant vaccines. Various antigens were included in these trials and preliminary data suggest that CD8⁺ T cells may have played a critical role in the protection observed.

7.9 Combining cellular immune read-outs: Defining correlates of protection for tuberculosis vaccines (*Shreemanta Parida and Stefan H. E. Kaufmann*)

Tuberculosis (TB), a leading killer of young adults worldwide, kills one person every 18 seconds. The recent increase of TB in the developing world has many causes including the HIV pandemic, emergence of multi-drug resistance, political or civil instabilities and poverty. One third of the world population harbors the causative organism *Mycobacterium tuberculosis* (*Mtb*) in a latent form (non-replicating persistent state) due to successful containment of the infection by an effective immune response, but these individuals are at risk of developing clinical disease upon HIV infection, ageing or any other condition affecting their immune system. The paucity of our knowledge of the distinct factors which determine protection versus susceptibility to TB has hindered progress to find an effective intervention.

The vast majority of all those infected by *Mtb* control the pathogen throughout their life without developing clinical signs of disease. Thus, the host immune system is able to control the pathogen efficaciously although it does not achieve sterile eradication of *Mtb*. There is a great deal to learn from this naturally induced host response to better understand the mechanisms that control infection and to exploit their value as potential indicators of protection. This would help define biomarker(s) of protection against TB and serve as guidelines for monitoring vaccine efficacy earlier than the clinical end-point of TB disease.

A consortium comprising of 15 partners, supported through the Grand Challenges in Global Health Program of the Bill and Melinda Gates Foundation has embarked upon an ambitious project to elucidate in the most endemic countries in Africa the differences in the immune response between individuals exposed to TB but protected from the disease and those who develop active disease under normal situations as well as in the context of HIV/AIDS. Objectives are to define biomarkers of protection and disease for clinical testing of novel TB vaccines, drugs and diagnostics. In addition, the outcomes will be helpful for the design of novel vaccine candidates. In the last four years, a cohesive team was established comprising multiple partners across geographic, cultural, social and working diversities. Six different prospective study cohorts in different age groups and contexts were established in seven field sites in Africa as well as in the United Kingdom of Great Britain and Northern Ireland that are being followed-up using state of the art techniques including immunological readouts, genome wide gene expression profiling and other platforms such as metabolomics and proteomics.

Microarray expression profiling studies of *Mtb* under different *in vitro* conditions mimicking the latency and reactivation in the host environment have led to identification of bacterial gene products which can serve as potential candidates for immunologic markers at different stages of infection. More than 80 of these antigens were produced by recombinant technology and purified to a high degree to be used for T cell studies in healthy infected individuals using IFN γ as readout as well as multicytokine assays using Luminex technology to profile the cytokine patterns. These tools have been refined to analyze the individuals who are protected against the disease versus those who succumb to the disease during the two year follow-up period. Further molecular assays to delineate specific T cell subsets such as effector memory and central memory T cells as well as epitope mapping are in place for a more detailed analysis at the end of the study.

7.10 Correlates of vaccine-induced protection: Methodological issues (Sara Thomas)

Although regulatory bodies have drawn up definitions for ‘correlates’ and ‘surrogates’ of protection for the purpose of licensure, the terms are not used consistently in the literature. Several different study designs have been used to evaluate immunological substitute endpoints of vaccine-induced protection; these have different strengths and limitations, affecting the quality of evidence for identifying and evaluating particular endpoints. A range of statistical methods have been developed to evaluate these endpoints, but many epidemiologists are unfamiliar with the details of these methods. Immunological substitute endpoints can be relative rather than absolute, and further information is needed on how they can be affected by factors such as the challenge dose, the mechanism of action of the vaccine, or the immune system of the host.

The mere demonstration that a vaccine induces a specific immune response is not proof that the vaccine is protective. Similarly, the fact that an immune response is statistically associated with the risk of the clinical endpoint does not mean that it is responsible for the protection, or that it can predict the protective effect of the vaccine. Further criteria are therefore needed.

Two questions are implied when assessing an immune marker as a substitute endpoint for clinical protection to estimate vaccine efficacy:

- (i) Is the immune marker a valid and reliable substitute for vaccine-induced clinical protection in individuals? This is equivalent to assessing the marker's place in the succession of events leading from vaccination to clinical protection.
- (ii) If the immune marker is a valid substitute endpoint, what is the specific titer(s) of the marker that quantitatively predict(s) vaccine efficacy?

There is a large body of literature addressing statistical methods for validation of substitute endpoints in clinical trials. Most of these methods are found in the field of non-communicable diseases (e.g. cancer and cardiovascular research) which have a longer history of using substitute endpoints for more distal clinical endpoints.

A key development was reported by Prentice in 1989, who proposed a hypothesis-testing approach for the validation of substitute endpoints. Prentice defined a surrogate endpoint as “a response variable for which a test for the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint”. His four criteria used to validate a surrogate endpoint can be reformulated for vaccine trials as follows:

- 1) Protection against the clinical endpoint is significantly related to the vaccine
- 2) The substitute endpoint is significantly related to the vaccine
- 3) The substitute endpoint is significantly related to the clinical endpoint
- 4) The full effect of the vaccine on the clinical endpoint is explained by the substitute endpoint, which lies on the sole causal pathway

An individual-level regression model can be used to demonstrate that the relationship between the immune marker and the incidence of the clinical endpoint is the same in vaccinated and unvaccinated individuals, and that the protective effect of the vaccine is entirely explained in the model by the immune marker.

7.11 Concluding remarks (*Paul Fine*)

This workshop offered an overview of existing definitions and methods in the area and provided a framework to guide discussions between relevant experts. A better understanding of the relationship between vaccination, the immune response and clinical outcomes is of interest not only to regulatory authorities but also to microbiologists, immunologists, epidemiologists and statisticians. This is a controversial and complex topic, and many aspects need clarification.

‘Correlates of protection’ is a term frequently used in the context of vaccine regulation, which is equally relevant to vaccine research and to evaluation of the impact of vaccines already in use. Typically, correlates aim to fit immunogenicity as measured in laboratory assays with clinical protection. There is some inconsistent use of terminology, and while a *correlate* constitutes a statistical association between an immunological measure and protection, a *surrogate* includes in addition a strong element of biological plausibility, indicating that the immune function measured is directly related to protection. Some would even restrict the term to causal factors. Regulators apply pragmatic rules when data for clinical protection are needed, and when a correlate or surrogate is an acceptable evidence for product licensure.

Several different study designs have been used to evaluate immunological substitute endpoints of vaccine-induced protection, and these have different strengths and limitations. A widely used approach to relate an immune response to clinical protection is to plot antibody titers against percentage population that is above a certain titer as a reverse cumulative plotting. Using clinical trial data, this approach has been successfully used to define threshold antibody concentrations correlated with population protection. These studies have also shown that thresholds may vary from population to population, for reasons which are not fully understood.

Apart from clinical trial results, many other epidemiological approaches can be used to identify immune correlates. Particular consideration needs to be given to the definition of the clinical or other endpoint to be measured, as was discussed for malaria vaccines. A range of statistical methods has been developed to evaluate these endpoints, but many epidemiologists are unfamiliar with the details of these methods. Given the complexity of immune responses involved in protection, it would be useful to illustrate the processes in causal diagrams. An important theoretical consideration is the distinction between true threshold markers, reflecting absolute protection at the individual level, from those related to partial protection at the individual level.

In conclusion, there is an obvious need for a better coordinated action between immunologists, vaccine regulators, epidemiologists and statisticians to address the challenges in this important area of work. The outcomes of these discussions encourage the development of a broad research agenda on correlates of protection.

8. Satellite workshop on new vaccine technologies: what are they? and what do they bring?

Chair: Adrian Hill
Rapporteur: Patrice Dubois

8.1 Overview

Numerous new technologies are becoming available that can improve vaccine manufacture as well as enhance the induction of protective immune responses, or simplify vaccine administration. These are likely to facilitate the development of new vaccines over the next decade.

Technologies which can improve vaccine manufacture include technologies that make vaccine manufacture safer (for example using recombinant antigens or DNA vaccines) or faster (for example recombinant influenza antigens expressed in insect cells, filamentous fungi or plants, which can be produced faster than growing the virus in eggs), as well as those which lead to enhancement of production capacity (for example adding adjuvants to influenza vaccines to enable antigen dose reduction), or simplify purification and reduce costs (for example the use of affinity columns for antigen purification).

Adjuvants, viral vectors, and DNA vaccines may also permit the induction of protective cell-mediated immunity, opening up the possibility to produce vaccines against diseases against which previous vaccine attempts were unsuccessful. And technologies are also becoming available which can simplify the administration of vaccines, such as needle-free injection devices, aerosol inhalation, and dermal patches. By simplifying and making immunization safer, these technologies may improve the coverage and effectiveness of vaccination.

8.2 Plant-based production following transfection (*Vidadi Yushibov*)

The demand for recombinant biopharmaceutical proteins and industrial enzymes is expected to rise dramatically in the near future. However, the current capacity and cost of production of eukaryotic recombinant proteins limit their availability. Thus, it is important to evaluate new production systems and choose those that ensure a functional, yet cost-effective, product. An ideal system should be applicable to every protein, and also address environmental concerns (containment, risk of gene escape etc).

One eukaryotic production system which is simple to scale up, and potentially cheaper and quicker than classical eukaryotic tissue culture is plant-based expression. Numerous approaches to plant-based expression have been evaluated, as many suffer from limitations with regards to yield, biomass growth times, and environmental risks.

The platform selected and developed by the Fraunhofer center is based on the transient expression of genes in tobacco plants, using Agro-infiltration, i.e. the inoculation of *Agrobacteria* carrying the gene for the protein of interest into the leaf of tobacco plants. The vector targets recombinant protein expression to the endoplasmic reticulum (ER), thus avoiding complex glycosylation.

The advantages of the system include: rapid growth of biomass (~4 weeks) and transient expression: the plants are not genetically modified, there is no risk of gene escape and entry into food chain. Other advantages are high yield expression of the target and simplified harvest and protein extraction. The platform is applicable to a range of proteins including enzymes and monoclonal antibodies. It is particularly suited for influenza vaccines where the HA and NA glycoproteins can be expressed as VLPs: the time from identifying the HA/NA sequence to large scale production of influenza vaccine can be much faster than for classical production methods. Plant-derived influenza VLPs are currently in preclinical development.

8.3 Production of anti-HBsAg antibodies in *Nicotiana* plants (*Merardo Pujol*)

In spite of the great number of publications reporting the successful expression of recombinant proteins in plants, only a small number of projects have advanced to the stage of scaling-up of the production. Furthermore, regulatory approval for the large-scale production and use of recombinant plant-produced proteins has been granted to only a very small number of molecules. It is currently recognized that the consistent and feasible expression, extraction, and purification of recombinant proteins from plants following Good Manufacturing Practices (GMP) is a difficult and complex task with very few antecedents.

CIGB has developed a platform for the production of a recombinant murine monoclonal antibody specific for the hepatitis B surface antigen (HBsAg), expressed in stably transformed transgenic *Nicotiana* plants. This MAbs is produced in confined conditions following Good Agricultural and Good Manufacturing Practices. It can be used for the affinity purification of recombinant HBsAg produced in yeast, which is the active pharmaceutical ingredient of the Heberbiovac® HepB vaccine. The plant-derived monoclonal antibody has been fully characterized and compared with its mouse-derived counterpart, and the production process has been validated.

The large-scale use approval by the Cuban National Regulatory Agency for Medicines (CECMED) for this antibody produced in plants was granted in 2006. It remains one of the few examples of plant-derived recombinant proteins for pharmaceutical use which is currently approved and produced on an industrial scale.

8.4 Novel Influenza vaccine production systems (*Rick Bright*)

Influenza vaccine production is a rapidly evolving field with many innovative technologies in development. Current influenza vaccines are based primarily on the HA protein for the induction of neutralizing antibodies. This requires constant reformulation of the vaccine because of constant drift in viral surface antigens. Current vaccine production mostly relies on embryonated egg technology and is limited in its capacity to respond quickly and in large surge capacity to meet needs in the context of influenza pandemics. Thus, new, high performance technologies are needed to address unmet needs of pandemic situations.

New technologies for influenza vaccines should fulfil a number of criteria including safety, production capacity, speed of implementation, low cost and simplicity of manufacture that could permit local or regional production in low-resourced countries. Technologies such as live attenuated viruses, recombinant virus-like particles (VLP) and protein expression in plants are currently in development and offer good prospects for meeting the needs for rapid response to pandemics.

The live attenuated virus (LAIV) technology relies on the production of a ‘cold-adapted’ reassortant backbone influenza virus strain that expresses the desired HA and NA glycoproteins in native conformation and presentation. This vaccine is administered as a nasal spray, achieves good antigen sparing, broad immunity and is highly efficacious especially in naïve (children) populations. LAIVs can be produced in eggs or cell culture and can be produced rapidly in response to the emergence of a new influenza strain. However, correlates of protection remain unknown and there are some limitations to use in very young children and some high risk populations. Two LAIV vaccines are currently marketed for seasonal influenza. For pandemic influenza, the most advanced products have reached phase II clinical testing.

Virus-like particles that contain the HA, NA and M1 viral proteins resemble virions but are devoid of genetic material. They have potential to be produced very quickly and at high yields, elicit broad immune responses and technology transfer can be achieved easily. The most advanced and recent technologies include lentiviral vector-based production in mammalian cells, baculovirus-based expression in insect cells and production of VLPs in *Neurospora crassa*. These technologies are at an early stage of development and their scalability, safety issues such as removal of vectors or host cell components and the apparent need for adjuvants to enhance immunogenicity, remain to be addressed. While most VLP-based vaccines are still at an early development stage: the most advanced candidate, insect cell-produced VLPs, is currently in a large phase II clinical trial.

Plant-based expression systems rely on the use of agroinfiltration of *Nicotiana* plants (see above). This technology has potential to achieve rapid production (bulk material available within six weeks), can accommodate mixtures of vaccine components at very short notice and is highly scalable at low production costs. However, a number of issues such as regulatory hurdles, safety issues such as removal host plant components and apparently low immunogenicity without adjuvants still need to be addressed.

In summary, the landscape of new technologies to develop influenza vaccines is rich in variety and approaches to achieve effective, low-cost vaccines that will expand upon the limited speed and surge capacity seen with existing egg-based approaches. Continued effort and financial resources are critical to realizing potential from these modern technologies that could respond to a newly emerging threat from pandemic influenza.

8.5 Disposable vaccine manufacturing. Starting upstream with Wave *(Catarina Flyborg)*

Development and manufacture of vaccines are extremely challenging tasks, due to the broad variation in design and composition of different vaccines. Traditionally, many vaccines have been produced in eggs and purified using gradient centrifugation. Modern vaccine manufacturing is shifting to cell-based systems, where the efficiency of the cultivation and cell expansion conditions are key factors for final process yield.

Several innovations can greatly improve the yield of the final product, as well as the cost of the infrastructure and operations to produce the vaccine:

- 1) The use of microcarriers for tissue culture increases the surface area and yields for adherent cell lines. It also facilitates the separation of cells from secreted products and facilitates medium exchange.
- 2) The use of Wave reactors, which are essentially disposable, single-use sterile plastic bags placed on rocker tables to permit tissue culture growth, precludes the need for expensive installation and maintenance of classical stainless steel fermentors. These disposable reactors also permit faster change-over time. They are currently available in sizes ranging from 2 to 500 l, enabling scale-up from research to production.
- 3) The use of disposable downstream processing equipment, such as disposable single-use pre-packaged columns, pipes and equipment. These minimise the risk of contamination and speed up change-over, avoiding the need for cleaning and validation.

The use of disposables in manufacturing has demonstrated an impact on process economy and facility costs, as well as flexibility, all of which are of great importance when embarking into a vaccine production project. It was however pointed out that the use of disposable fermentors and disposable downstream material is likely to not be cost-effective over the long run in the case of sustained production, which tends to be the norm in the vaccine field, rather than campaign production.

8.6 DNA-based vaccines *(David Kaslow)*

The concept of DNA-based vaccines has now been on the scene for nearly 20 years. Despite the early promise that the technology (plasmids expressing the gene for the antigen) could be used for all vaccines, simplifying vaccine development and production, progress has been slow. Three DNA-based veterinary vaccines have been developed and are currently licensed (for horses, dogs, and fish), but in humans the immunogenicity of DNA vaccines is still a severe limitation.

The exact reasons for the lower immunogenicity of DNA vaccines in humans as compared to even large animals remain unexplained. The immunogenicity in humans can be increased by appropriate formulation, for example with cationic liposomes, where the exact nature of the lipid components also has a critical effect. However, the greatest challenge to getting DNA vaccines approved and introduced for human use is the choice of the disease target: using DNA vaccine to try not to do what can be achieved with protein-vaccines is the best approach.

DNA-based vaccines can be viewed as a disruptive technology that brings in an entirely new approach to vaccination. However, as with many other disruptive technologies in fields other than vaccines, new technologies initially compare badly with existing technologies for solving conventional problems. Introduction of such technologies is best done by identifying areas (disease targets) where existing technologies perform poorly. Even if the niche is small, successful introduction in such markets supports technological growth and may permit the disruptive technology to be more widely adapted.

8.7 Viral vectored vaccines and prime-boost approaches (*Adrian Hill*)

Viral vectors have been in development for over 20 years and are currently the leading technology for vaccine-mediated induction of T cell responses. Viral vector-based vaccines have a number of advantages including rapid generation, thermostability, low cost manufacturing as well as bypassing the need for protein purification. A number of candidates are currently in clinical development for anti-viral, mycobacterial or parasite vaccines, as well as cancer vaccines. DNA-MVA and Fowlpox-MVA prime-boost regimens have shown limited protective immunity in human malaria spore challenge models. New approaches using adenoviral vectors induce better CD8⁺ T cell responses in preclinical models. However, target populations have pre-existing human adenovirus immunity which may render the vaccine less effective. Chimpanzee adenoviruses such as AdCh63 have been selected for use in prime-boost vaccination approaches because they do not circulate at significant levels in the human population and induce protection against parasite challenge in the *P. berghei* model following a single administration. Furthermore, MVA boosting of AdCh responses leads to enhanced magnitude and polyfunctionality of CD8⁺ T cell responses.

Data from a phase IIa challenge trial using TRAP as an antigen, showed that protection against challenge could be achieved in volunteers vaccinated with AdCh63 followed by MVA. Protection correlated with CD8⁺ T cells expressing IFN γ . Furthermore, mean T cell responses still remained very high at 90 days after challenge. The use of a prime-boost regimen combining Adenovirus and MVA shows that it is possible to induce antibodies to blood stage malaria antigens in small animal models, non-human primates and human volunteers. Although further development of the prime-boost technology is needed and ongoing, major improvements have been achieved for this rapidly evolving technology.

8.8 VLP-based vaccines (*Gerardo Guillén*)

Existing vaccines are mainly limited to the microorganisms we know how to grow and produce in culture and/or to those whose killing is mediated by humoral response (antibody mediated). It has been more difficult to develop vaccines capable of inducing the functional cellular immune responses needed to prevent or cure chronic diseases. Several adjuvant formulations developed in the last twenty years can facilitate intracellular antigen processing and activate antigen-presenting cells, but adjuvant toxicity is often a limitation for new adjuvants to fulfil increasingly complex regulatory standards. With improving understanding of the immune system, however, together with successful achievements at the preclinical level, a great interest has appeared in the development of vaccines to treat chronic diseases including cancer, the so-called therapeutic vaccination. Several results suggest that specific enhancement of T-cell responses is possible in persistently infected patients, taking advantage of new strategies designed to improve cell-based immune responses and control or eventually clear the virus or tumor cells.

Preclinical and clinical results show that virus-like particles (VLPs) based on envelope, membrane or nucleocapsid microbial proteins induce a strong immune response upon nasal or systemic administration in mice, non human primates and humans and are able to stimulate mucosal as well as systemic immunity. In addition, the immune response obtained is biased in a Th1 sense. VLPs have also been able to enhance the humoral and cellular immune responses against several viral and cancer antigens as measured by LPA and IFN- ELISPOT assays. Studies in animals and humans with nasal and systemic formulations evidenced that it is possible to induce functional immune responses against HBV, HCV, dengue fever and also against prostate and cervical cancer.

8.9 Developing adjuvants for public use, a long and treacherous road (*Martin Friede*)

2009 was an exceptional year in the history of adjuvants: the FDA approved the Cervarix papillomavirus vaccine, which contains the adjuvant Monophosphoryl lipid A (MPL), and the EMA approved two pandemic influenza vaccines containing oil-in-water adjuvants. One of these emulsions was already in an influenza vaccine (FLUAD) that had been licensed for the elderly. Over 20 other novel adjuvants are in clinical development for vaccines against diseases ranging from malaria, TB and HIV to cancer and atherosclerosis.

The proprietary adjuvant in the Cervarix vaccine combines MPL with aluminium hydroxide (alum) and is referred to as AS04. This combination enhances the antibody titers and duration of response to the HPV antigens, and is also claimed to broaden the immune response to the vaccine. MPL is a non-toxic derivative of bacterial lipopolysaccharide, which acts as an adjuvant through stimulation of the innate immune response via interaction with toll-like receptor 4 (TLR-4). Several synthetic molecules which interact through the same receptor are also under development for use as adjuvants, including RC529, GLA, and E6020. These synthetic molecules may have some advantages over MPL in that they are pure, whereas MPL is a heterogenous mixture of molecules.

The oil-in-water adjuvants used in the licensed pandemic influenza vaccines are MF59 and AS03. Both are based on squalene (shark oil), and AS03 also contains tocopherol (vitamin E). These adjuvants permit significant antigen dose-sparing (7-10 fold), thus enabling many more doses of vaccine to be produced from existing manufacturing plants. They also induce a broadening of the immune response to the HA antigens, with cross-reactivity to drifted influenza virus strains, a significant advantage in the event of mismatch with the pandemic strain.

Although squalene-based emulsions have been shown to be safe in multiple clinical trials and have been administered to millions of persons, there is a public perception that squalene might be dangerous, which affected pandemic influenza vaccine uptake by the general population. The late 1990s Gulf-war Syndrome was blamed on the induction of antibodies to squalene by squalene-adjuvanted vaccines. Although it was later shown that antibodies to squalene are found in most people and the WHO GACVS concluded that the risk of inducing pathological antibodies was unfounded, websites claiming squalene and squalene-containing adjuvants to be dangerous are proliferating and becoming the major source of public information on squalene on the web.

Making new vaccines and getting them approved is difficult, but getting the public to accept vaccines containing a new adjuvant can be even more difficult.

9. Satellite Workshop on Herd Protection Effects of Vaccines

Chair: John Clemens
Rapporteur: Sunbeang Shin

9.1 Overview

A vaccine displays herd protection effects when its protective impact in a population far exceeds that expected from the proportion of the population vaccinated and the known protective efficacy of the vaccine. Herd protective effects of vaccines have been well documented during the past decades for several vaccines used in public health programs.

The herd effect of a vaccine can improve dramatically the benefits that can be expected from vaccination as it can enhance the protective effect for vaccinees and offer protection to non-vaccinees within the population. Consideration of vaccine herd effects has become increasingly important for rational decisions on new vaccine programs, particularly for vaccines that are expensive and/or if the direct protective effect of the vaccine is moderate in magnitude.

Such vaccine herd protection effects need to be incorporated into models of disease control by vaccination and estimations of vaccine cost-effectiveness, and newer approaches to the measurement of vaccine herd protection have been developed that can be employed even before vaccine licensure.

9.2 Concepts of herd protection and immunity (*Peter Smith*)

Herd immunity to an infectious agent has been defined in various ways, but the most useful definition is that the level of herd immunity is the proportion of a population who are immune to further infection, either through vaccination or because of prior infection. For infections that are transmitted from person-to-person, such as measles, rubella, or varicella, and for those for which humans are the unique reservoir, such as polio and malaria, the level of herd immunity directly impacts on the dynamics of infection transmission in a community and the proportion vaccinated affects the risk of infection among the unvaccinated. The impact that vaccine coverage has on herd immunity may be critical to take into account in disease elimination or eradication programs, as disease elimination does not require 100% immunity.

The “herd immunity threshold” (HIT), is the proportion of the population that must be immune, either through vaccination or due to natural infection, in order for herd protection to at a sufficiently high level that transmission of the infectious agent within the community can no longer be sustained. A simplified but useful way of thinking about the herd immunity threshold is with respect to its relation to the basic reproduction number (R_0). R_0 is the average number of persons an infected person will infect with an infectious agent in a completely susceptible population.

If the proportion of persons in a population immune to infection by the agent equals or exceeds the HIT value, transmission of the infection in the population will not be sustained. In the simplest model, assuming uniform mixing in the population, HIT is related to R_0 by the equation: $HIT = [1 - 1/R_0]$. If, for example, $R_0 = 5$ for an infectious agent, then $HIT = 0.8$, i.e. the proportion of persons immune in the population will have to be in excess of 80% for the transmission of the agent to cease. In real life the situation is more complicated because heterogeneous mixing in the population is the norm.

In individually randomized clinical trials, the herd effect of a vaccine may be impossible to measure and the protective efficacy determined may relate only to the individual protective effect of the vaccine, which may underestimate the beneficial effect of the vaccine when used in public health programmes. However, if communities are randomized to receive vaccine or placebo, the difference in incidence of the infection under study between the two kinds of community includes both individual and herd protective effects. Given the potential impact of herd immunity that can be associated with some vaccines, various trial design options have been devised to assess the level of herd protection during pre- or post-licensure phases. It is important to note, however, that herd immunity can have not only beneficial but also potentially deleterious effects: herd immunity can elevate the average age of infection, as has been shown for polio, rubella, measles and hepatitis A, and the shifted age distribution can result in more severe clinical outcomes or sequelae of the infection among those who are infected at older ages.

9.3 A case study of vaccine herd protection: the Hib vaccine *(Richard Adegbola)*

Haemophilus influenzae type b (Hib) is a leading cause of childhood bacterial meningitis worldwide, with a high case fatality rate and devastating lifelong disabilities among those who survive, especially in Asia and Africa. There are several types of licensed Hib vaccines, among which were conjugate vaccines, which proved to be effective in infants and were therefore introduced into routine EPI schedule in many countries.

After the Hib conjugate vaccine was introduced into the national immunization program in The Gambia, the incidence of Hib meningitis declined significantly among children under five years of age. Only a negligible number of Hib meningitis cases were still recorded from 1999 to 2002, as compared with an incidence of 50 to 70 cases per 100,000 person-years between 1990 and 1992, before the introduction of the vaccine. The herd protection effect of the Hib conjugate vaccine appeared to play a significant role in this dramatic decrease, vaccination offering protection to both vaccinated and unvaccinated infants and children.

Evidence for indirect protection provided by the Hib conjugate vaccine was provided by calculations showing that the actual number of children protected exceeded the number of children expected to be protected based on the vaccine coverage rate. The impact of the herd protection provided by routinely delivered Hib conjugate vaccines has been assessed and reconfirmed in various settings in many countries, including in children in Bangladesh.

9.4 Case studies of herd protection: pneumococcal vaccines (*Terhi Kilpi*)

Streptococcus pneumoniae (Pnc) causes a broad range of diseases in children under 5 years of age, from invasive meningitis and bacteremia to less invasive forms such as pneumonia, sinusitis or otitis media. Efforts have been made to develop improved pneumococcal vaccines based on the conjugation technology. Several conjugate vaccines already are or will soon become available for use in young infants, targeting different combinations of Pnc serotypes (PCV 7, 10, or 13).

Before conjugate vaccines were introduced, prevalence of nasopharyngeal Pnc carriage was high among young children both in developed and developing countries. In Finland, for example, the prevalence of Pnc carriage was found to vary from 9% in infants 2 months of age to 45% in young children 24 months of age. The Finnish cohort study was conducted from 1994 to 1997, before the introduction of any conjugate vaccine.

In randomized trials of the PCV7 vaccine in The Gambia and South Africa, the reduction of Pnc carriage rate was measured in both a vaccine group and a control group. Following three doses of PCV7, the vaccine group showed a lower carriage rate than the control group for the serotypes which are included in the vaccine formulation, but a higher rate for non-vaccine serotypes. When the analysis was done for the total reduction of carriage rate, regardless of serotypes, the overall rate of carriage remained higher in controls than vaccinees in the South African trial but was lower in the control group in the Gambian trial.

A potential herd effect of PCV7 in non-vaccinated individuals in terms of reduction of Pnc carriage was assessed in Southwestern American Indian communities in a cluster-randomized trial. The Pnc carriage rate of vaccine types among unvaccinated household members was higher in control communities than in vaccinated communities, suggestive of a herd protection effect of the vaccine. However, the rate of non-vaccine Pnc types among non-vaccinated household members was higher in the vaccinated communities than in the control communities. The overall prevalence of Pnc carriage, regardless of serotype, remained higher in the vaccinated communities, an indication that net serotype replacement had occurred.

The secular trend of invasive pneumococcal disease (IPD) was assessed comparing the incidence before and after introduction of PCV7 in the United States of America. In the pre-vaccination era, the incidence of IPD was much higher in children under 5 years of age than in the elderly population > 64 yrs of age. After routine vaccination of infants with PCV7 was implemented, the incidence of IPD dropped significantly in both age groups, albeit to a lesser degree in the elderly than in young children. The protective effect of the vaccine was therefore seen not only in the vaccinated young infants but also in the elderly who were not vaccinated.

Although serotype replacement was shown to occur and affect both the colonization rates and the incidence of IPD, there was a clear net protective benefit against all IPD due to the vaccination program. However, these data have not been confirmed in Europe, where no herd protection of non-vaccinated individuals by PCV7 could be demonstrated, and where serotype replacement was more marked than in the UNITED STATES OF AMERICA.

In brief, herd protection provided by PCV7 has been demonstrated in North America, but not in many other parts of the world so far. Ideally, vaccine herd protection should be assessed through more rigorous methodological approaches such as cluster-randomized controlled trials, considering the limitations of evaluating and interpreting the secular trends of disease rates pre- versus post-vaccination.

9.5 Epidemiological modeling of vaccine herd protection (*Nigel Gay*)

Mathematical models are increasingly used to evaluate the impact of vaccination programs on infectious disease incidence. Epidemiological models of infectious diseases are often built up based on the concepts of the basic reproduction number (R_0) and the effective reproduction number (R). R_0 is defined as the number of secondary infections produced by an infectious person in a totally susceptible population. R is similar to R_0 , but with the additional assumption that the population is partially immune. The value of R actually depends on the infectivity of the pathogen, the duration of infectiousness, host susceptibility and population characteristics such as demographics and social mixing patterns. To achieve the elimination of a disease, R needs to be below one. In a homogeneous population, R can be estimated from the simple equation: $R = R_0 \times x$, where x is the proportion of the population that is susceptible.

In the models with a heterogeneity assumption (dynamic models), however, R should be estimated with an age-specific compartmental structure, in which force of infection and transmission rates are to be estimated for each age stratum. Typically, models used for the prediction of benefits of vaccination programs for public health need to have an age-structure because most vaccines are meant for specific age groups while public health benefits (or costs) of vaccination may occur in other age groups.

Dynamic models can predict herd immunity and other indirect effects of vaccination programmes. For example, modeling can be useful in predicting the impact of Hib conjugate vaccine at lower coverage rates or using alternative vaccination schedules. The experience with the pneumococcal conjugate vaccine (PCV7) in the UNITED STATES OF AMERICA demonstrates that routine vaccination program can offer not only direct but also indirect protection to non-immunized individuals. In the United Kingdom of Great Britain and Northern Ireland, however, no indirect protection was demonstrated for PCV7, and the vaccination increased the carriage rate of non-vaccine Pnc types more significantly than it reduced carriage of vaccine-types.

Investigating the impact of conjugated pneumococcal vaccine programs with an epidemiological model has shown the following: 1) additional boosters or catch-up campaigns would lead to more rapid elimination of vaccine types; 2) results seem to be very sensitive to mixing, competition, and vaccine parameters; and 3) serotype replacement has been more obvious in the United Kingdom of Great Britain and Northern Ireland than in the US.

In brief, dynamic models can be used to design vaccine strategies, to investigate the impact of different immunization strategies, and to evaluate the economic impact of new vaccine program in different population settings. For certain vaccines, indirect effects of vaccination program may be sufficiently large to change policy decisions on vaccine introduction.

9.6 Incorporating herd protection into economic cost-benefit and cost-effectiveness models of cholera vaccine (*Marc Jeuland*)

Economic analyses are increasingly important tools of evaluating the benefits of new vaccination program. Both cost-effectiveness and cost-benefit analyses would provide more comprehensive information on the impact of vaccination program if one incorporates vaccine herd effects into the models.

As shown from the re-analysis of the cholera vaccine trial in Matlab, Bangladesh, the protection offered by oral killed cholera vaccine programs could be substantially greater if potential herd effects were considered. In that trial, the original analysis had shown an estimated 67% protective efficacy following three doses of cholera vaccines. Upon re-analysis, it was suggested that at least 80% of the population could be protected with a vaccine coverage at 40% and that cholera could be nearly completely controlled with 60% vaccine coverage.

Models were developed to calculate the cost-effectiveness of cholera vaccine programs in two different settings, Matlab in Bangladesh and Beira in Mozambique. The net public cost per DALY avoided was calculated under various assumptions of vaccination coverage and with or without herd protection, as well as with or without imposition of user-fee under the two scenarios of school- versus community-based vaccination strategies.

Several important insights were obtained from these analyses: 1) additional and different types of studies would be needed to evaluate the impact of various key parameters such as different target populations, population movement, and environmental factors, in the context of dynamic vaccination programs; 2) because the slope of increasing herd protection with increasing vaccine coverage was steeper at lower levels of coverage than at higher levels of coverage, the cost-effectiveness ratios were higher at lower than at higher levels of coverage. Therefore, one may consider a strategy of vaccinating those individuals with highest demands or targeting the most vulnerable groups; and 3) it is important to note that the cost effectiveness metrics may not provide straightforward advice for designing a vaccination program when herd effects exist.

9.7 Measuring herd protection: cluster randomized trials (*Ira Longini*)

Traditionally, herd protection is evaluated after a vaccine has been introduced in a population, precluding the possibility of providing data on herd effects to help decide of a vaccine introduction. New methodological developments now afford the possibility of evaluating herd protection during pre-licensure trials. One approach is the cluster-randomized trial, a design that allows evaluation of herd protection with minimal biases.

Cluster-randomized trials are based on the randomization of clusters at the group level instead of the individual level. Appropriate selection of clusters is very important because the choice of clusters determines the comparability of baseline characteristics among clusters.

Several considerations should be given in defining clusters to evaluate vaccine herd effects in a non-biased manner. Firstly, clusters must be selected so that transmission of infection does occur between individuals within clusters, but is minimal between clusters. Between-cluster transmission would attenuate measured estimates of vaccine herd effects. Secondly, there must be little migration of subjects between members of vaccinated and control clusters, as such migration would dilute the proportion of vaccinees in the vaccinated clusters, and enrich control clusters with vaccinees. Thirdly, multiple clusters are generally required for these trials, not only to safeguard against chance imbalances in baseline factors between vaccinated and control clusters, but also to allow for appropriate statistical inferences.

Another design issue is the sample size required for cluster randomized trials. Sample size must be appropriately inflated because of the intercorrelation of outcome events among members of a given cluster. Moreover, to account for such a design effect, special statistical methods must be used to analyze these trials.

Different from individually randomized trials designed to measure vaccine *efficacy*, cluster-randomized trials measure the *effectiveness* of vaccination. Within a cluster-randomized vaccine trial, comparison of attack rates of the target infection among non-vaccinated members of vaccinated clusters versus attack rates among individuals in control clusters gives an estimate of *indirect* vaccine protection. Comparison of rates among recipients of the vaccine versus recipients of the control agent gives an estimate of *direct* vaccine protection. Comparison of rates among all members of vaccinated clusters versus all members of control clusters gives an estimate of *overall* vaccine protection. Each of these estimates is based on concurrent, randomized comparisons, an important methodological strength that enhances the credibility of inferences made from trials designed in this fashion.

9.8 Measuring herd protection: individually randomized trials (*Mohammad Ali*)

Analysis of individually randomized trials by appropriately selected clusters created *post hoc* can also provide measurements of herd protection. In individually randomized trials, there may be differences in vaccine coverage in clusters of the target population due to chance variations in randomized assignments and to different rates of eligibility and participation. If suitable clusters can be identified and if there is sufficient variation in vaccine coverage between these clusters, vaccine herd effects can be assessed by evaluating the *correlation* of disease incidence with levels of vaccine coverage in these clusters. With this logic, an inverse relationship between the incidence of the target disease among non-vaccinees and the level of vaccination coverage in the cluster would indicate indirect protective effects. Similarly, an inverse relationship between the incidence of the target disease among vaccinees and the level of vaccine coverage of the cluster would reflect total vaccine protection.

It is important to note that the considerations for selection of clusters in such analyses are identical to those described above for cluster-randomized trials. As the level of vaccine coverage of clusters in individually randomized trials is affected by many non-random factors, such as choices to participate in the trial, the analyses are observational in nature, and care must be taken to adjust analyses to take into account possible factors that may bias the association between levels of vaccine coverage and disease rates.

This approach was recently used in a reanalysis of the 1985 trial of killed oral cholera vaccines in Bangladesh. This trial, which was placebo-controlled and individually randomized, found that the two vaccines under evaluation, a cholera toxin B subunit-killed whole cell vaccine and a very similar killed whole cell vaccine, conferred 53-63% protective efficacy against treated episodes of cholera during the first year of surveillance. Because the study population, totaling 89,596 persons, resided in 6,423 *baris*, linked groups of houses that had earlier been shown to correspond to the geographic unit of transmission of *Vibrio cholerae* 01, *baris* were selected as clusters for the analysis. The analysis found significant inverse relationships between vaccine coverage of *baris* and the incidence of cholera in recipients of both placebo and vaccine, reflecting indirect and total protection, respectively. In this approach, the non-random, non-blinded comparison of the clusters that were selected post hoc may have created a bias. A multi-variable model was therefore employed in the analysis to adjust for potential confounders. Also, the vaccine coverage of *baris* and the risk of dysentery, a syndrome that should not have been prevented by cholera vaccination, was evaluated. The result suggests no overall inverse relationship between the coverage of *baris* and the risk of dysentery implying the inverse relationships is not the reflection of a higher level of diarrhea in areas with lower levels of participation in the trial.

Published analyses of past trials of killed oral cholera vaccines, which did not evaluate their indirect effects, underestimated the potential public health impact of these vaccines. The study indicates that significant levels of indirect protection, in addition to direct protection, may be attained in public health programs that deploy these vaccines.

10. Session VII: Optimize immunization systems and technologies for tomorrow

Moderators: Abdrhamane Tounkara and Abraham Aseffa
Rapporteur: Michel Zaffran

To ensure that new vaccine products become readily available on the market, more attention needs to be dedicated to two areas usually taken for granted and therefore left to last minute rushed decisions: Product Characteristics and Supply systems in Countries

10.1 Designing vaccines for developing countries (*Michel Zaffran*)

In an ideal world, vaccine purchasers and end-users would send clear signals to vaccine developers about preferred product attributes and a dialogue would occur between the groups during research and development to sort through the inevitable trade-offs between added cost and a product feature or between one desirable attribute (e.g. liquid presentation) and another (e.g. stable formulation). Steps are being taken to work towards this ideal.

The Vaccine Presentation and Packaging Advisory Group (VPPAG) originated by the GAVI Alliance secretariat to address Pneumococcal and Rotavirus vaccines has now been reinstated under the auspices of WHO. VPPAG provides a unique forum for discussion between representatives of agencies and experts involved in public sector delivery of vaccines, and industry representatives from both the International Federation of Pharmaceutical Manufacturers' Association (IFPMA) and the Developing Country Vaccine Manufacturers' Network (DCVMN).

VPPAG has completed a draft generic preferred product profile (gPPP) for vaccines for developing countries. This consensus document between industry and the public sector can serve as a source for any entity involved in vaccine research for developing country markets. VPPAG also works to gather data and develop specific vaccine product profiles and can serve as a resource to vaccine developers on product presentation and packaging issues.

10.2 The supply systems in developing countries (*Modibo Dicko*)

In the past 10 years, the Expanded Program on Immunization has been very successful in most low and middle income countries (LMICs): vaccination coverage has increased while disease incidence decreased; and at the same time new vaccines and new delivery technologies have been successfully introduced on the market in national immunization programmes across LMICs.

However, to achieve this success, most attention was focused on processes within countries and little if any dialog was held with manufacturers. As a result, new vaccines showed characteristics that were adapted to industrial countries but extremely challenging for LMICs. Cold chain rules were simple and rigid: for instance vaccines were licensed for storage at 2 - 8 °C despite intrinsic heat stability. At the same time, several deficiencies were observed in the field throughout the countries: (a) vaccine supply chains were unnecessarily complex because tailored according to administrative structures instead of sound logistics requirements, (b) a mixture of distribution-based and collection-based systems existed and created conflicts at the border of the 2 systems; (c) problems with warehousing, distribution, stock control and wastage monitoring were enduring at central levels and were amplifying and rippling down the system though sub-national to peripheral level. In addition, supply chain expansion is no longer specific of immunization: an increasing number of interventions now expand services to a broader target group which needs to ensure reliable access to quality products.

We are today at a crossroad as the simplicity of the supply systems developed in the 80's has reached its limits. With increasing number of new vaccines planned for introduction in the coming years, storage and transport capacities as well as management information systems and operational practices must be dramatically improved in order to accommodate the increasing volumes of vaccines with diverging storage temperature requirements and high costs.

On-going efforts to address these challenges have resulted in the designing and launching of Project Optimize, a joint collaboration between the World Health Organization and the Program on Appropriate Technologies for Health (PATH). A collaboration was established by Optimize with the government of Senegal to study and demonstrate options to meet future challenges in the supply chain management for vaccines, drugs and other pharmaceutical health products. The Senegal project will first explore the integration of supply systems at central and provincial levels through the National Procurement Pharmacy. The purpose is to increase the synergies across the supply systems of the vaccine and other health intervention programs such as distribution of ARVs, reagents, ACTs, DOTs treatments and other pharmaceutical products.

A second area of focus will be to look at the Region of St Louis, Senegal and determine to what extent a “moving warehouse” concept for the distribution of vaccines and other pharmaceutical products, from the Provincial store to the local health facilities, can help ensure better stock management, avoid stock running-outs, overstocks and waste of resources through expired stocks.

A third area of activity will concern the use of solar energy to explore the possibility to eliminate the need for batteries and backup electricity generators through the provision of hybrid solar-grid electricity to the regional vaccine and drug cold store in Saint Louis and the installation of battery-free solar refrigerators in about 15 remote health centres.

All these efforts will be supported by the implementation of (a) a modernized and integrated supply chain management information system that will monitor in real time consumptions, storage temperatures, etc. and (b) an advocacy and communication campaign targeting all stakeholders involved in decision-making, implementation and utilization of the above-listed innovative systems.

Finally, a group of national experts from academia, research institutions and partner agencies will monitor project implementation and, based on results, prepare a plan for scaling up of successful interventions as well as a long-term vision for health supply systems.

11. Keynote Address: Etiology of diarrhoeal diseases in developing countries – The Global Enteric MultiCenter Study (GEMS)

Moderators: Alash'le Abimiku and Ted Bianco

Speaker: Mike Levine (CVD, University of Maryland School of Medicine, Baltimore, MD, UNITED STATES OF AMERICA)

Diarrhoeal diseases rank second in the list of most common causes of mortality among children under 60 months of age in developing countries, accounting for about 17% of deaths in this age group annually. Gastroenteritis may be classified as “simple” (watery diarrhea), “profuse, watery” (with ‘rice water’ stools and leading to a large risk of dehydration), “dysenteric” (with blood and mucus) or “persistent” (unabated for more than 2 weeks). Many different pathogens, whether viral, bacterial or protozoal, can be involved in this pathology. However, most data regarding actual diarrhoeal disease burden in developing countries and their precise etiology are outdated and badly need reactualization.

The Global Enteric Multi-Center Study (GEMS, also known as “Diarrhoeal Disease in Infants and Young Children in Developing Countries”) was launched by the Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, to measure, under the chairmanship of Dr Karen Kotloff, the burden, microbiologic causes and sequelae of diarrhoeal disease among young children in developing countries. Seven study sites were selected, four in sub-Saharan Africa (Basse, Gambia; Kisumu, Kenya; Bamako, Mali; Manhica, Mozambique) and three in South Asia (Mirzapur, Bangladesh; Kolkata, India; Karachi, Pakistan). Collectively, these include sites with moderate or high infant mortality rates, rural and urban settings, and high or low HIV and malaria prevalence.

In order to guide the development of preventive measures, each site will maintain continuous demographic surveillance of a defined population in which births, deaths, and migrations in and out of the community are monitored. Prior to initiating the study, each site performed a baseline Health Services Utilization and Attitudes Survey (HUAS) among 999 families having children less than 60 months of age to determine the attitudes and practices regarding diarrhoeal disease among caretakers for infants and young children. Ongoing HUAS information will be updated at least twice a year at each site through surveys nested within the demographic surveillance activities.

A case/control study has been undertaken to elucidate the etiologic agents associated with moderate and severe diarrhoea (MSD) among children 0-59 months of age by systematically enrolling each year for three consecutive years 220 cases with MSD from health care facilities and 220 matched community controls in each of three age strata: 0-11, 12-23, and 24-59 months. Participants will provide clinical and epidemiological data and a fecal sample for identification and antigenic characterization of the diarrhoeal pathogens possibly involved. Fortnightly, at each sentinel health center, the total health care visits of children under 60 months of age with MSD, the total number of children with diarrhoeal illness of any severity and the total number of health care seeking visits for any reason in that age group will be recorded. The incidence of diarrhoea by age and pathogen will then be calculated using census data and adjusted according to HUAS results.

A wide array of bacterial, viral and protozoal pathogens are sought in both cases and their matched controls without diarrhoea, using state-of-the-art molecular diagnostic methods, as well as immunoassays and classical microbiologic techniques (e.g., bacteriologic cultures). Serotypes of *Shigella* and antigenic types of fimbrial colonization factors of enterotoxigenic *Escherichia coli* (ETEC) are being characterized, as are the phenotype and/or genotype of other bacterial (Salmonella, Campylobacter, Vibrio, Aeromonas), viral (rotavirus, adenovirus, norovirus and sapovirus, astrovirus) and protozoal (Cryptosporidium, Entamoeba, Giardia) pathogens. These sensitive diagnostic techniques allow one to identify potential diarrhoeal pathogens in 75-90% of cases, depending on site and age group. Because of the high frequency of pathogen carriage in controls, however, rigorous statistical methods must be employed to calculate the fraction of cases associated with a pathogen that can be attributed to that pathogen. In this way, the relative burden of diarrhoea due to the various pathogens can be calculated at each site for each age group. A repository of well-characterized clinical specimens and isolates will be maintained so that they can be accessed in the future for research and technology development.

By adjusting for the proportion of all eligible MSD children enrolled at the sentinel health centers and using data from the HUAS to adjust for the proportion of all children under 60 months of age in the demographic surveillance population who seek care at the sentinel centers, pathogen-specific burdens will be calculated for each age group at each site. A single follow-up visit to households of cases and controls will be undertaken 60 days after enrollment to determine whether there are delayed deaths, nutritional consequences or other sequelae that follow the acute diarrhoeal episode and whether such outcomes are associated with particular pathogens. Preliminary analyses show that mortality is 8-fold higher in the cases than the controls (respective case fatality rates: 2.4% versus 0.3%). Notably, about two-thirds of the deaths occur more than one week after the child with diarrhoea is discharged from the health care facility and most of these deaths occur at home. Deaths among controls mostly occur between enrollment and the 60-day visit, corroborating that these are sites where mortality in children less than 60 months of age is relatively high.

Preliminary analyses have also revealed that several pathogens are strongly incriminated in association with death. The most prevalent pathogens in children in the African settings are Rotaviruses, followed by Shigellas, Cryptosporidium and ETEC, whereas in the Asian settings the most prevalent are Rotaviruses and Shigellas followed by Campylobacter, Vibrio, and Cryptosporidium. Nutritional consequences of acute diarrhoeal episodes have also been detected by comparing anthropometric data at baseline and at the 60-day visit between cases and matched controls.

What is special about GEMS is that, combined with the etiology data from the case/control study, water/sanitation/hygiene factors are being identified that enhance or diminish the transmission of specific pathogens. Detailed questionnaires and direct observations in households will be providing data on the sources of water for the household and methods of storage of water, means to dispose of human feces and hygienic practices. In this way, overall risk factors for the development of diarrhoea and protective factors will be identified. The public and private financial costs incurred by episodes of severe pediatric diarrhoea will also be assessed.

Enrollment into the GEMS will be completed in 2011 and a number of analyses of the full three-year data should be available by late 2011 or early 2012. The extraordinary statistical power and comprehensive microbiologic methods used in the GEMS should allow clear priorities to be set for enhancing the implementation of existing interventions and for developing new interventions to diminish the burden of moderate and severe diarrhoeal diseases among young children in developing countries.

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

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

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

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

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

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

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

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