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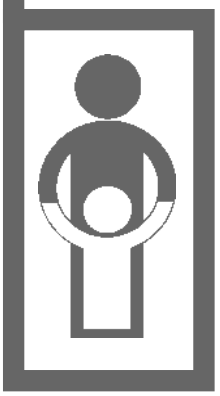

DEPARTMENT OF VACCINES AND BIOLOGICALS

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Glossary

AIDS	acquired immunodeficiency syndrome
ALV	Asian leukosis virus
ARI	acute respiratory infection
BCG	Bacille Calmette-Guèrin (vaccine)
CBER	Center for Biologics Evaluation and Research
CDS	WHO Communicable Diseases cluster
CRD	Communicable Diseases Research & Development (including TDR)
cGMP	current good manufacturing practices
CMI	cell-mediated immunity/immune (response)
CSA	chondroitin sulfate A
CT-B	cholera toxin B-subunit
CTL	cytotoxic C
DDC	double dimer construction
DHF	dengue haemorrhagic fever
EAV-0	endogneous avian retrovirus
Env	one of three major HIV genes
ELISA	enzyme-linked immunosorbent assay
EPI	Expanding Immunization (formerly Expanded Programme of Immunization)
ETEC	enterotoxic *Escherichia coli*
FECD	first episode of central demyelisation
Gag	one of three major HIV genes
GMP	good manufacturing practice
GPI	glycosyl phophotidylinositol
GST	glutathion-S-transferase
Hib	*Haemophilus influenzae* type B
HLA	human leucocyte antigen
HTP	Health Technology and Pharmaceuticals

HIV	human immunodeficiency virus
HPV	human papillomavirus
IMCI	Integrated Management of Childhood Illness
IND	investigational new drug
IVR	inter-cluster Vaccine Research Initiative
LT-B	heat-labile enterotoxin B subunit
MAP	multiple antigen peptide system
MAPREC	multiple analysis by polerase chain reaction amplification and restriction enzyme
MHC	major histocompatibility complex
MS	multiple sclerosis
MSF	Médecins Sans Frontières
MSP	merozoite surface protein
NAT	nucleic acid amplification test
NIAID	(US) National Institute of Allergy and Infectious Diseases
NV-C	Norwalk virus capsid
PCR	polymerase chain reaction
PERT	product-enhanced reverse transcriptase
Pol	one of three major HIV genes
RESA	ring-infected erythrocyte surface antigen
RNSP	Réseau National de Santé Publique
RSV	respiratory syncytial virus
RT	reverse transcriptase
SI	syncytium-inducing
SV40	simian virus 40
TB	tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNESCO	United Nations Educational, Scientific and Cultural Organization
V&B	Department of Vaccines and Biologicals, WHO
VAAE	vaccine-associated adverse events
WC/BS	whole cell/B subunit
WC/(r)BS	whole cell recombinant B subunit

Opening address by the Director-General of WHO

Dr Gro-Harlem Brundtland

Ladies and gentlemen

I should like to add my welcome to those you have already received on the occasion of this WHO Vaccine Research Overview meeting here in Montreux. I am especially pleased that the meeting has been organized in collaboration with UNAIDS. As one of the co-sponsors of UNAIDS, WHO is committed to find solutions to the ever growing HIV/AIDS pandemic.

This meeting is important. The expectations for future achievements feed on the successes of the past. Vaccines have proven the most effective tool in our fight against infectious diseases in the 20th century. Thanks to vaccinations, the world is now free from smallpox and we are within reach of ridding it of polio. The list of smaller but still important successes is long.

This said, the list of challenges ahead of us is longer. We need to intensify our work towards finding vaccines for HIV/AIDS and malaria. We must find a better protection against tuberculosis. Vaccination technology must be made easier and cheaper to use.

Success may be within reach. The molecular biological revolution, now coupled with real progress in identifying novel adjuvants, means that for the first time in two to three decades, vaccine research is moving forward with purpose and renewed vigour.

WHO's role in this area of research is clear: leadership through advocacy, coordination and leverage. As an indication of WHO's commitment to this fundamental area of activity, we spent nearly US$10 million on our vaccine programmes in 1998 and will spend a similar sum this year.

Over the next two days, you will hear the details of our work, along with news of complementary work by other agencies.

When we started the process of change at headquarters last year, we saw the need to pull together our vaccine research into a single WHO-wide programme of work. This would allow better focus on our disease priorities, such as diarrhoeal diseases, malaria, measles, respiratory infections and tuberculosis. It would create synergies in application of the new technologies, cost-cutting and opportunities for concerted resource mobilization. These savings more than justify the investment of time and energy we have put into this over the last six months.

Then there is the crucial area of HIV vaccines. I am pleased that this meeting has been organized in collaboration with UNAIDS. WHO is now joining forces with

UNAIDS to establish a common vaccine development programme, taking advantage of the work that WHO has already done in the field of vaccine development in general and the progress that UNAIDS has already accomplished with regard to HIV vaccine.

There are no quick fixes when you want to combine maximum change with a minimum of disruption of people and work. But we believe that we now have a new structure that will represent a great improvement over the past. We have named it the Inter-cluster Vaccine Research Initiative, or IVR.

IVR will allow us to do more, and it will make us a better partner in our collaboration with all of you. IVR capitalizes on the fact that in today's WHO, cluster and department boundaries are mainly for administrative and management convenience. Science can and must be able to cross such boundaries.

Instead of organizing activities along lines of departments, we have put in place a system where they are organized by type of research activity – exploratory, pre-regulatory and post-regulatory. From now on there will be a single work plan for everybody involved, a single report on progress and a single and focussed resource mobilization strategy.

My confidence in the success of this new structure is threefold:

- First, and most importantly, all staff involved in vaccine research have recognized the need for such an initiative.
- Second, IVR has the commitment of four of my key line managers in the areas most concerned, namely the Executive Directors of the Communicable Diseases (CDS) and Health Technology and Pharmaceuticals (HTP) clusters, Dr David Heymann and Dr Michael Scholtz, and the Directors of the Communicable Diseases Research and Development (CRD) and Vaccines and Biologicals (V&B) departments, Dr Carlos Morel and Dr Bjorn Melgaard. Such commitment is crucial, since matrix management systems like the one we now have put in place only work well if line managers allow it.
- Last, but equally important, WHO will recruit a key functional manager, the IVR Coordinator, to make it happen.

A large part of the success of the Initiative will depend on the skills of this IVR Coordinator. He or she will face a tough set of tasks, but they will be balanced by an opportunity to make a real difference.

The filling of this important position will take time and careful deliberation. In the meantime, Dr Win Gutteridge of our Communicable Diseases Research and Development department has agreed to take on the task of Acting Coordinator, aided by Dr Teresa Aguado and Dr Howard Engers.

IVR will make a difference to our vaccine research effort. It gives me great pleasure both to commend it to you and to launch it on its way.

Thank you and I wish you success in this inaugural meeting.

Executive summary

The inaugural meeting of the WHO Intercluster Vaccine Research Initiative (IVR), held on 16-18 June in Montreux, Switzerland, marked the remodelling of WHO's and UNAIDS' scattered vaccine research and development (R&D) activities into one shared entity. The meeting was convened to seek guidance on how to use most effectively WHO's resources in this area, under the auspices of the above-mentioned WHO-wide initiative. For a better understanding of how WHO intends to handle vaccine R&D in the future, the following paragraphs summarize the essential features of the IVR:

R&D Portfolio: Two WHO Clusters, CDS and HTP, and UNAIDS are currently involved in vaccine research and development. CDS/CRD (including the Special Programme for Research and Training in Tropical Diseases – TDR) is supporting work directed towards the development of vaccines for the following parasitic diseases: malaria (*Plasmodium falciparum*), schistosomiasis (*Schistosoma japonicum*) and leishmaniasis (visceral and mucocutaneous). The primary objective is regulatory approval of efficacious vaccines. If resources become available, CDS is considering enlargement of its current disease research portfolio to include TB and dengue. HTP/V&B is promoting the development and field evaluation of vaccines for major bacterial and viral diseases: pneumococcal diseases; diarrhoea caused by *Shigella sp*, enterotoxic *Escherichia coli* (ETEC), cholera, tuberculosis, meningococcal meningitis, rotavirus, dengue, measles, respiratory syncytial virus, Japanese encephalitis and human papillomavirus (HPV). Special attention is also given to generic issues in vaccinology (e.g. mucosal and early life immunization, use of DNA/live vectors and needle-free vaccination procedures). The main objective is to accelerate the development of priority vaccines, together with industry and other partners, until a stage when a formal recommendation can be made on their use. UNAIDS' strategy for HIV vaccine development is based on five components: (a) advocacy and policy dialogue, (b) guidance and co-ordination, (c) promotion of development of appropriate vaccines, (d) facilitation of trials through capacity building and (e) exploring options for future availability of effective vaccines.

Structure: It has been agreed to establish a single WHO research initiative for the discovery and development of vaccines and related vaccination strategies for priority infectious diseases, including parasitic diseases, through the formation of a CDS/HTP inter-cluster vaccine research (IVR) initiative. Such an activity will seek to avoid duplication of effort around activities of common interest and provide opportunities for the identification of joint projects which deserve a high priority and require additional

resources. This initiative will closely collaborate with UNAIDS on vaccine R&D matters. The administrative umbrella for this collaboration has yet to be decided. All of WHO's and UNAIDS' vaccine research projects have been grouped according to the following structure:

- exploratory: promoting and, where necessary, financing discovery research aimed at the discovery of candidate vaccines for agreed priority communicable diseases (especially malaria, *Shigella* dysentery, TB), and at new vaccination approaches (e.g., mucosal immunization, neonatal infancy immunization, needle-free immunization devices);
- pre-regulatory: promoting, co-ordinating and, where necessary, financing of research aimed at the preclinical and clinical studies necessary to achieve regulatory approval for candidate vaccines;
- post-regulatory: evaluation of new vaccine safety, immunogenicity and efficacy within the context of epidemiological conditions encountered in targeted developing countries; development and assessment of new vaccination strategies.

Management: A unified matrix management structure for IVR has been developed, whereby line management will remain within the current cluster structure, but functional management will be organized in an inter-cluster fashion, based on type of above activity. This will open up opportunities for synergy between the various ongoing scientific and technical activities. Also, it will allow a more streamlined management of operational activities, including reduction in the number of steering/advisory committees and thus be more cost-effective. The programme will be integrated, highly interactive and better focused on current communicable disease priorities. The key new appointment will be the "IVR Project Leader", charged with actioning the system, maintaining the overview, ensuring that interfaces mesh, trouble-shooting, collating plans and reports and mobilizing resources. Programme review will be on an inter-cluster basis, most likely involving an annual overview, scientific and technical review and monthly/bimonthly R&D committee meetings for pre and post-regulatory activities. Line management – mainly personnel and financial matters – will remain within the individual clusters and will be firmly connected with the functional management through a small group of senior managers who will meet frequently.

Topics covered during the meeting included the spectrum of activities that currently form part of WHO's and UNAIDS' vaccine R&D portfolio, grouped by the above-mentioned categories: exploratory, pre-regulatory and post-regulatory studies/ research on vaccination strategies. The meeting was opened by a session giving an overview of the state of the art in the development of vaccines against HIV and malaria, the two conditions that carry the highest burden of infectious disease caused by a single agent. The closing session dealt with the complexity of vaccine safety and the public perception thereof.

During the presentations and subsequent discussions held during the meeting, the following concepts and lessons emerged regarding the key roles for WHO in vaccine R&D.

Overall

The overall objective is the enhanced development of vaccines needed in the developing world. This consists of two (parallel) efforts:

- involvement in the development of vaccines against pathogens of major public health importance; and
- helping in the process of making those already developed available, and facilitating their use.

Normative function

WHO can exert a normative role in the areas of:

- vaccine specifications/design;
- strain categorization/typing;
- guidelines for vaccine evaluation;
- standard reagent/strain panels and evaluation/standardization of assays;
- agreement on manufacturing process; and
- diagnostic tests.

The "neutral broker"

WHO can provide a neutral meeting ground and mediation between:

- academic/academic;
- academic/industry;
- industry/industry; and
- country/country.

The "biased broker"

WHO can advocate the interests and needs of developing countries by:

- promoting/catalyzing the development of vaccines, simpler and/or more appropriate for use in developing countries;
- providing access to capacity building; and
- acting as ethical/safety "guardian" for countries without well-developed regulatory authorities.

Commissioning research

Circumstances under which WHO should directly fund research, not unlike a "classical" research sponsor, include an array of activities, among which key areas are:

- development of orphan vaccines (e.g. leishmaniasis);
- development of new technologies to simplify and improve immunization;
- studies addressing modified vaccine regimes, e.g. pneumococcal vaccines, decreased dose for *Haemophilus influenzae* type B (Hib);
- research on epidemiological patterns, on both the geographic distribution of the pathogen (strain surveillance networks) and the magnitude of the host burden of disease (for diseases targeted by new or improved vaccines); and
- assay development.

Expediting clinical research

WHO can accelerate clinical trials through:

- identification/development of trial sites;
- establishment of laboratory networks; and
- vaccine trial issues: design, ethical issues and trial oversight.

Settling controversies

WHO should coordinate studies to:

- address consumer fears regarding the safety of vaccines; and
- assess the risk of adverse events and evaluate risk-benefit relation.

Resources are therefore needed for convening meetings, for supporting collaborating centres, external consultants and advisers and for funding of all needed commissioned research. The different WHO/UNAIDS vaccine programmes have been forging partnerships with stakeholders in the vaccine development continuum. These are a most valuable resource and represent one of the best opportunities to interact and achieve common goals. They include, among others: academic scientists, the vaccine industry, technical agencies dealing with vaccines (e.g. regulatory agencies), donor agencies, developing country authorities and the public health community, in general.

1. Opening session

Dr Michael Scholtz, on behalf of the two co-sponsoring WHO clusters and UNAIDS, welcomed the participants to Montreux, emphasizing the importance that WHO and UNAIDS attach to the sharing of experience and knowledge with this illustrious assembly and the advice and wisdom that would emerge from this meeting. He reminded the audience that, beyond questions of a purely technical nature, research was also needed to address the burning problem of how to prevent degradation of the public acceptance of vaccines and immunization.

The Chairperson, Sir Gustav Nossal, used his welcome to put this meeting, focusing mainly on vaccine research and development issues, into the context of the global vaccine and immunization effort. In particular he elaborated on the planned "Global Alliance for Vaccines and Immunization", a strong body that will comprise such major institutional stakeholders in this area as WHO, UNICEF, the World Bank, the vaccine industry, bilateral aid donors and non-governmental organizations. Amongst the latter, Sir Gustav gave particular mention to the "Bill and Melinda Gates Children's Vaccine Programme" as an important new partner in bringing a new generation of highly effective vaccines to all children in the world.

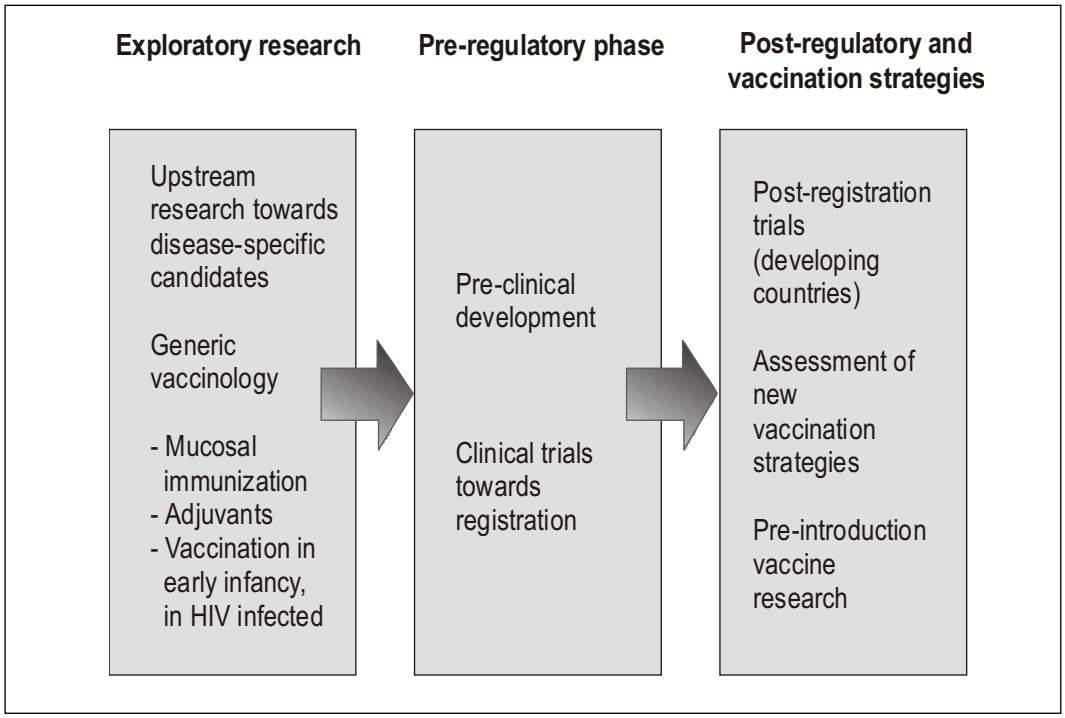
Dr Win Gutteridge gave the following insights into the philosophy behind the creation of IVR, its current status and the role this meeting would play in its inception.

IVR has been conceived as an instrument to consolidate WHO's and UNAIDS' various vaccine research and development programmes into a single, highly interactive and more cost-effective initiative. At the same time, the establishment of cross-cluster administrative, management and review systems will avoid counter-productive movement of people and resources.

The integration of all vaccine-related R&D activities within WHO and UNAIDS allows the development of a focus that is compatible with the disease priorities of these two organizations. Translation of the overall WHO/UNAIDS disease focus into IVR vaccine R&D priorities is currently in process. As a first step in this direction, current activities have been classified into three components of manageable size on the basis of their stage in the R&D process: exploratory, pre-regulatory and post-regulatory (see the figure below). For each of these programme areas, a functional management system will be put in place to matrix with the existing line management. A description of the post for a joint CDS/HTP-funded "IVR Coordinator" position has been agreed upon and will be advertised shortly.

The IVR Coordinator's role will be to "action" the system, ensure that the interfaces mesh, collate plans/reports and mobilize resources. For the interim, a coordination group has been established: Dr Gutteridge is acting as IVR coordinator with the assistance of Drs Aguado and Engers.

Proposed framework for vaccine research in WHO



A comprehensive review system for IVR is in place or under active development, involving both internal and external expert panels. Priorities will be set annually and there will also be an overall scientific and technical review on the same basis. As a trouble-shooting measure interim administrative reviews of IVR will be performed at a monthly meeting of the IVR coordinator with department heads and team leaders from all involved areas. Also on a monthly basis, vaccine R&D committees will be convened for scientific and technical review.

The Montreux meeting was organized along the three aforementioned stages in vaccine research: exploratory, pre-regulatory and post-regulatory research/ vaccination strategies. Furthermore, an entire session dealt with research issues related to the public acceptance of vaccination. In the final session, outcomes of the meeting and the implications for WHO's vaccine research strategy and priorities were reviewed. The objectives of the meeting were twofold:

- to share information on the range of vaccine research activities in WHO and UNAIDS and to put this in the context of research efforts internationally in this area;
- to give the broader vaccine R&D community an opportunity to make constructive criticism on the area covered by IVR, and, in particular, to consider whether or not there is a proper focus within the field of priority diseases on areas where the two international organizations can make a difference.

The aim of the conference organizers was: (a) to share their excitement at the pace of current vaccine research both within and outside WHO and the opportunities and challenges this presents, (b) to obtain endorsement of the plans to establish a single, WHO-wide vaccine research initiative (IVR), and (c) to hear words of encouragement regarding the proposed matrix management system, intended to allow maximum inter-cluster activity without unnecessarily moving people or resources.

2. Learning from the past and forging the future

2.1. Is there a future for AIDS vaccine? – *P. Johnston*

A global effort has resulted in a number of HIV candidate vaccines in the pipeline, at different stages of development. Out of these, more than 25 different HIV candidate vaccines have been tested since 1987 in Phase I/II trials, involving over 3000 HIV-negative volunteers, mostly in the United States and Europe, but also in some developing countries.

The first Phase III trials of an HIV candidate vaccine were initiated in June 1998 in the United States and in March 1999 in Thailand, using a recombinant gp120 candidate vaccine. The US trial will enrol a total of 5000 HIV-negative volunteers representing mostly men-who-have-sex-with-men, using a bivalent BB gp120 product. The Thailand trial will involve 2500 intravenous drug users and uses a bivalent (clade B/clade E) candidate vaccine. Both bivalent vaccines contain gp120 proteins derived from both R5 and X4 strains. Efficacy data from these two trials is expected to be available toward the end of 2001.

The next vaccine concept that may be evaluated in efficacy trials, under the sponsorship of the National Institute of Allergy and Infectious Diseases (NIAID), is likely to be a recombinant canarypox vector expressing multiple HIV genes, which may be evaluated in combination with an envelope protein boost (e.g. "prime-boost"). Unlike gp120 alone, which does not induce detectable cytotoxic T lymphocytes (CTL) in human volunteers, the canarypox plus envelope combination induces both antibodies and CTL in a majority of recipients. Vector optimization studies and envelope combination studies are now underway so that an efficacy trial could begin in the next two years.

In addition, a canarypox vector expressing clade E envelope boosted by various clade E envelope proteins is being considered for evaluation by Thailand, in collaboration with the United States Department of Defense. Clade C canarypox vectors are earlier in development. A series of trials to determine if a canarypox vector can help prevent mother–infant transmission is also under discussion.

The first phase I trial of a candidate vaccine in Africa, also under the sponsorship of NIAID, began in Uganda early in 1999. This trial, which will evaluate canarypox expressing multiple clade B genes, will help answer several critical questions. In addition to safety, the trial will evaluate the level of CTL induced in Ugandan volunteers and the breadth of cross-reactivity of those CTL, particularly against indigenous strains of HIV.

Other candidate vaccines are in earlier stages of clinical development and are unlikely to reach the stage of efficacy trial, alone or in combination, before the

year 2002. In phase I trials are: HGP-30w, a peptide vaccine tested in the United States and Europe; DNA vaccines expressing *env/rev* or *gag/pol* tested in the United States; vaccinia vector expressing *gag/pol/env*, tested in the United States; an attenuated salmonella vector expressing *env* tested in the United States; and canarypox, administered by mucosal routes in the United States.

Many interesting candidate vaccines are in preclinical development, including a recombinant bacillus Calmette-Guèrin (BCG) expressing a portion of *env*; a DNA-plus modified Ankara strain of vaccinia combination designed for possible testing in the United Kingdom and Kenya; Venezuelan equine encephalitis replicons for possible testing in the United States and South Africa; pseudovirions to be tested in the United States; and *gag* particles to be tested in the United States.

2.2. Malaria vaccines in the pipeline – *W. R. Ballou*

There can be little doubt that the global impact of a safe and effective vaccine against malaria would be very significant, especially if a major reduction in morbidity and mortality among children in sub-Saharan Africa were to be a consequence of a widespread programme of immunization. A number of observations, some of them quite old, indicate that such a vaccine may indeed be feasible, including:

- increase with age of clinical immunity to malaria, as a result of repeated infections;
- protection against infectious challenge after immunization with attenuated sporozoites; and
- mosquitos refractory to infection by ingestion of blood meals from immune hosts.

With these observations, there have been repeated waves of optimism about the prospects for a vaccine, largely driven by the availability of promising new technologies. In practice, real progress has been very slow.

Discoveries over the past decade have revealed some of the sophisticated mechanisms by which *Plasmodium falciparum* has established itself as such an elegantly-adapted parasite. Among these are numerous examples of allelic polymorphism in antigens that are subject to immune pressure or antigens that are able to morph into completely new serotypes as a consequence of sophisticated genetic rearrangement. Still other antigens closely mimic host sequences so as to be rendered essentially invisible to the immune system. To further complicate matters, recent studies have revealed that most, if not all, infections in holoendemic regions involve multiple distinct strains that circulate simultaneously between the vector and the human host.

An effective vaccine may ultimately need to include multiple targets from different stages of the life cycle. By inhibiting the development of liver stage schizonts, fewer asexual stage parasites are released. Even partially effective sporozoite vaccine might reduce malaria morbidity by decreasing the rate of multiple infections. Blocking the growth of blood stage parasites should lead directly to a reduction in clinical disease. A quantum leap has been made recently in the area of pre-erythrocytic stage vaccines. Through *in vivo* models, the circumsporozoite

protein has been identified as a target of sporozoite-neutralizing antibodies as well as effector T lymphocytes that kill infected liver cells. Based on data emerging from several laboratories, a strategy was developed to include both antibody and T-cell targets in the vaccine, to enhance the underlying immunogenicity of the construct by expressing it as so-called RTS,S particles as a fusion protein with HBsAg, and to further drive the immune response towards a TH1 phenotype through the use of potent adjuvants. RTS,S particles formulated in SBAS2 adjuvant induced very high antibody titers and TH1-like cell-mediated immune (CMI) responses in humans and, more importantly, were shown to protect a significant proportion of subjects from a homologous experimental sporozoite challenge. To date, more than 40 volunteers have been protected, with efficacy ranging from 40% to 86% depending on dose and immunization schedule used.

Another strategy that has undergone considerable progress has been the development of an asexual stage vaccine based upon the C terminal processing fragments of MSP-1. This antigen is expressed as a large surface-associated complex on the merozoite and undergoes proteolytic cleavage during the invasion process. Protection appears to correlate with the presence of antibodies that inhibit the final processing step in which a 42M fragment is cleaved into 33 and 19M products. Small amounts of clinical grade material have been produced and a Phase I trial initiated in Australia. Phase II trials in Papua New Guinea are anticipated in the next year or so. There are several other promising candidates under development as recombinant protein vaccines, including RAP-1, SERA, EBA-17 5, and MSP4/5, each of which has a unique set of technical and conceptual obstacles to overcome.

While both RTS,S and MSP-1 deal only with a single malaria antigen, conceptually two or more recombinant proteins could be formulated together to broaden the immune response and enhance vaccine efficacy. Several combination strategies are in clinical trials, including a combination MSP-1, MSP-2 and RESA vaccine under development in Australia. The use of synthetic peptides to create novel immunogens containing putative protective epitopes from several malaria antigens has also undergone rather extensive clinical evaluation in the form of SK66. Finally, a five-gene DNA vaccine mixture (MUST-DO 5.1), designed to target the sporozoite and developing liver-stage parasite, is expected to undergo clinical trials later this year in the United States.

While still at much earlier stages of development, several other strategies deserve to be watched closely. The first involves PfEMP-1, a large variant antigen that induces specific immunity characteristic of endemic populations. Here, the technical challenge will be to determine whether a limited number of consensus motifs can be identified that could cover a majority of parasite strains. If this is possible, then a method of economically delivering these antigens in an immunogenic form – e.g. a safe and inexpensive attenuated live vector – must be identified. Such an approach may allow regional or periodic reformulation to cover emergent variants, analogous to the approach used for influenza. Much of the morbidity of malaria appears to be a consequence of pathologic immune-activation caused by the release of parasite-derived glycosyl phophotidylinositol (GPI). Antibodies against this non-protein molecule are acquired over time and appear to be potent blockers of the release of inflammatory cytokines by the interaction of GPI and its receptors. A major bottleneck for a vaccine based on GPI is the ability to synthesize the glycoprotein on a practical scale. Finally, there

have been very exciting new developments concerning the molecular pathophysiology of severe malaria in pregnant women. Chondroitin sulfate A (CSA) expressed in the placenta has been found to be a receptor for a parasite ligand found on the surface of infected red cells. Identification and characterization of the CSA ligand are proceeding and could theoretically lead to a vaccine that could protect this particularly vulnerable population.

A major technical hurdle to malaria vaccine development is not scientific but of logistic nature – inadequate process development for large-scale production of clinical trial material. Service-oriented product development is not attractive to publication-oriented scientists, and with an orphan vaccine industry rarely becomes interested at such an early stage in the development process. In the case of malaria, this has led to testing of suboptimal vaccines and ultimately makes interpretation of poor immunogenicity and adverse reactions very difficult. Therefore, a far greater emphasis on process development is needed and industrial know-how must be tapped. This is one of the major items that will be addressed by the Gates Foundation, which is making a major investment in malaria vaccine development.

3. Exploratory vaccine research

3.1. Away from pneumococcal conjugate vaccines? – *D. E. Briles*

To be considered for use in the developing world, a vaccine must be both effective and affordable. In the case of pneumococci, preliminary evidence has demonstrated that a multivalent capsule-conjugate vaccine is highly immunogenic in children and can prevent bacteremia. However, with present technology there is not an inexpensive means of producing a multivalent polysaccharide protein conjugate vaccine for widespread use in the developing world.

An alternative strategy exists, which may be able to provide affordable and effective pneumococcal vaccines. This approach would rely largely, if not exclusively, on the use of protection-eliciting pneumococcal proteins. Several proteins are known which have been able to elicit protection against pneumococcal infection and colonization. Protection against invasive disease in animals has been elicited by the proteins PspA and pneumolysin; and PspC has recently been shown to elicit protection against sepsis by eliciting antibodies cross-reactive with PspA. Protection against carriage has been elicited by PsaA, PspA and PspC. Each of these proteins can be produced in recombinant form and should be able to be used to make inexpensive vaccines.

It is anticipated that a successful vaccination programme would elicit protection against carriage as well as invasive disease. By protecting against carriage it should be possible to prevent transmission, much as has been observed for the *Haemophilus influenzae* group B vaccine. By preventing transmission of pneumococci it should be possible to prevent disease even in immunodeficient individuals or individuals who have not yet been immunized.

Pneumococci are highly diverse, and it has been possible to devise selected animal models using selected strains of pneumococci where any one of these proteins can be shown to elicit better protection than the others. At present the broadest protection against invasive disease appears to be elicited by PspA and the broadest protection against carriage appears to be elicited by PsaA (although the carriage data are still very limited). Moreover, data from a number of experiments now indicate that mixtures of these proteins are more protection-eliciting than any of the proteins used by themselves. Therefore, it is anticipated that mixtures may afford broader protection than vaccines containing a single protein. For invasive disease, present data would favour a mixture of PspA and pneumolysin. Experiments relating to carriage are much less extensive, but the ideal mixture will probably contain PsaA mixed with either PspC or PspA.

PspA is the only pneumococcal protein to reach human trials. PspA is a highly cross-reactive surface protein present on virtually all pneumococci. Previous studies

with PspA have shown that antibodies raised in mice, rabbits or monkeys can protect mice from otherwise fatal infection with mouse-virulent human isolates of *Streptococcus pneumoniae*. It has also been observed that in spite of its cross-reactivity, PspA exhibits significant structural variability and has been classified into three families. The PspA family was determined for several hundred pneumococci from around the world. Over 95% of the strains examined carried family 1 or family 2 PspAs. Humans immunized intramuscularly with a single family 1 PspA produce antibodies that are highly protective against test infections in mice with capsular type 4 and 6 pneumococci expressing both family 1 and family 2 PspA. These findings provide strong encouragement for the continued development of PspA as a human vaccine.

3.2. Do we need vaccines against all HIV subtypes? – *S. Osmanov*

HIV is one of the most variable biological entities known today. No two viral isolates recovered from patients are identical. Nucleotide sequences of HIV from Africa and North America can differ by close to 40%. What is truly astonishing is the fact that despite those enormous differences HIV manages to maintain its biological characteristics with regard to tropism, route of transmission and pathogenic potential. Genetic analysis has allowed classification of different HIV-1 strains into three groups, M, N and O. Within the main (M) group, multiple subtypes have been documented, designated subtypes A-J. It is important to analyse the correlation of these subtypes with distinct functional, e.g., immunologic features, to determine whether each of these subtypes requires a distinct vaccine/ vaccine component:

- HIV is characterized by pronounced biological variability and can be classified in different biological phenotypes based on:
  - *In vitro* growth characteristics: slow/low vs rapid/high;
  - Use of secondary receptors: CCR5 vs CXCR4;
  - Cytopathic effects: syncytium-inducing (SI) vs non-syncytium-inducing (NSI);
  - Preferential cell tropism: T-cell vs macrophage tropism; and
  - Propagation in different T-cell systems: primary vs laboratory strains.

  This biological variation has been mapped to point mutations in functional sites of the viral envelope, but it is not associated with genetic subtypes.
- The outcome of HIV infection and rates of disease progression can vary significantly between different individuals, which can be attributed to various factors determining virus–host interactions. On the viral side, the latter include the potential to induce syncytia (SI/NSI), the use of secondary receptors (CCR5/CXCR4) and attenuation. Host factors comprise deletions in secondary receptors (Δ32/CCR5), human leucocyte antigen genotype, persistence of HIV-specific CTL, neutralizing antibodies, etc. However, it has not been possible to confirm any clear association of HIV-1 genetic subtypes with the natural history of HIV infection.
- There is no direct correlation between genetic subtypes and antigenic serotypes, nor do genetic subtypes represent classical neutralization serotypes.

- There is growing evidence of extensive intersubtype cross-reactivity of cell-mediated immune responses in humans, including:
  - CTLs in individuals infected with subtype B virus can kill target cells primed with non-B targets (*gag, pol, nef*);
  - CTLs in individuals infected with non-B virus are cross-reactive against subtype B primed targets (*gag, pol, nef*);
  - CTL derived from vaccinees receiving subtype B specific immunogens can kill the target cells infected with viruses of multiple non-B subtypes;
  - Cross-subtype ADCC activity against *env* proteins can be readily demonstrated in individuals infected with subtype E or B strains.

Taken together, none of the above parameters shows clear-cut correlates with genetic subtypes. If protective immune responses are mainly based on CTL, this supports the rationale that candidate vaccines may not need to be developed for each subtype. If, however, humoral immune responses are needed for protection, then a subtype-specific vaccine/vaccine component may be needed. In any case, only vaccine efficacy trials will be able to provide a conclusive answer to the question whether future vaccines must contain distinct components to cover for all HIV genetic subtypes.

3.3. Edible vaccines – *M. Levine*

Research on edible vaccines was initiated as a direct response to a call of the Children's Vaccine Initiative for cost-effective and easy-to-deliver new vaccines for the developing world. Once developed, those vaccines may fulfil most of the criteria for a new vaccine suitable for developing countries, such as:

- oral delivery,
- easy storage/distribution, and
- (presumably) low production cost.

For proof of principal, initial research has focused on established plant genetic systems, such as *Agrobacterium*-mediated transformation of tobacco, potato and tomato plants. A number of vaccine antigens have been cloned into these plants, including rabies virus G protein, Norwalk virus capsid (NV-C) protein, *E. coli* heat-labile enterotoxin B subunit (LT-B) and cholera toxin B subunit (CT-B). In all of these systems it was encouraging to observe that the plant-derived antigens spontaneously adopt natural conformation and assemble into oligomers or virus-like particles, respectively. More importantly, feeding experiments produced serum and mucosal immune responses, and in the case of LT-B and CT-B studies immunized experimental animals were protected against challenge with the corresponding intact toxins.

However, none of the above plants are ideal as an edible vaccine delivery system. Therefore, efforts now focus on the use of bananas as plant vector. Bananas offer a number of attractive features such as a minimal requirement for processing, ease of production and the fact that it is native to many developing countries. Now that efficient banana transformation techniques have been developed, the main limitation of the banana system comes to bear during the development phase,

namely a long time lapse between plant transformation and the possibility of evaluating the transgenic fruit (two years and more – as compared to weeks or months when using tobacco or potato).

A number of biotechnology companies are focusing on this approach, and two clinical trials have been completed. The results of a phase I trial demonstrated that ingestion of potato containing LT-B was safe and induced both systemic and mucosal immune responses in healthy volunteers. The second phase I trial using NV-C protein also showed a rise in specific IgA antibody-secreting cells in 19 out of 20 volunteers, with best responses after the second dose. It is assumed that the Norwalk capsid protein system may also provide new leads for the production of a transgenic rotavirus vaccine.

An important question of a more general nature is still open, namely, can edible vaccines replace injection vaccination technology? Trials using hepatitis B surface antigen expressed in potato are already planned to address this issue. At least of equal importance is the question of "formulation" of those vaccines produced in edible plants: whether to use raw, processed (e.g. banana chips) or extracted vaccine. The answer to this problem will most likely require input from regulatory agencies and will (to no small degree) depend on the choice of the plant vector and the ability to standardize vaccine content and other quantitative as well as qualitative parameters.

3.4. Peptide vaccines – *R. Amador*

The long-term aim of research at the Institute of Immunology in Bogotá is the development of multi-unit synthetic vaccines designed to protect against multiple microorganisms that present a significant health problem throughout the world.

Synthetic peptide fragments are able to induce antibodies, and during the past 15 years the Immunology Institute has developed and improved chemical peptide synthesis to generate the SPf66 malaria vaccine as a paradigm for synthetic peptide vaccines. We are now in the era of increased understanding of the potential impact of SK66, including its improvements, the testing of new adjuvants, the development of novel production techniques, the testing of special risk groups, and the flourishing of new vaccine candidates. Our increased knowledge of the molecular structure of pathogens and, in particular, of the structure and conformation of their antigens and the way in which the immune system responds to them, now provides us with new and rational approaches to vaccine development.

Current synthetic vaccine research is confronted with new challenges, such as solubility, production efficiency, low cost and health considerations. New developments in chemical synthesis let us approach these issues with better results. These techniques allow for the prediction and selection of epitopes, and the improvement of mimicry with selected peptides derived from intermediary peptides generated by catalysis during the loading process of the MHC molecule – key events in the generation of a cellular immune response against a foreign pathogen. Modern analytical methods with increased quantitative resolution have improved vaccine characterization. In addition, a range of immunological techniques like immunogenicity, antigenicity, specificity and biological lot-by-lot potency are used to evaluate the antigenic and biological properties of the vaccine peptides.

New synthetic systems have become popular since the 1980s, such as the direct synthesis of a Multiple Antigen Peptide system (MAP). Today "Dendrimer" chemistry is now accessible to obtain molecules with molecular weights higher than 5000 Da. Our research group has developed a method using unprotected peptides as dimer building blocks linked by disulfide bridges, which is an important step in protein folding and other biological activity. This method involves a Double Dimer Construction (DDC) system using standard F-moc solid phase peptide chemistry. Its advantage is the ease of the synthesis of macromolecules containing multiple antigens, requiring only one purification step to achieve copious amounts of peptides of high purity.

While these peptides have been shown to be good immunogens with different deposit-based adjuvants, they are species-specific. The ideal adjuvant would have the efficacy of Freund's complete adjuvant but without its various side-effects. Antigen delivery has now become as important as antigen selection.

As are most current human vaccines, SPf66 has been formulated in combination with mineral gels like aluminium hydroxide. The efficacy of this formulation in reducing first-attack clinical malaria incidence is 23%, with a 95% confidence-interval ranging from 12% to 32%, and 38% for the total number of clinical episodes (95% confidence-interval ranging from 29% to 47%). To improve upon the immunogenicity of SPf66 vaccine, we developed new formulations that incorporate the potent saponin adjuvant QS-21 immunostimulator.

QS-21 formulated vaccines were evaluated for safety and immunogenicity in healthy young subjects. The vaccines induced a 45 to 272-fold increase in anti-SPf66 IgG titers over alum-based vaccines after the second and third doses. The anti-SPf66 antibodies reacted against asexual blood stage parasites in some subjects and recognized mainly a 195-0 parasite epitope in immunoblots. Antibodies generated by the new formulations have a longer immunogenicity duration compared to those evoked by alum formulations. These observations demonstrate that the use of a potent adjuvant can enhance the immunogenicity of peptide vaccines. As with other adjuvants being developed, however, they could be constrained by side effects or high costs.

3.5. DNA-based vaccines for infectious diseases; where is the field? – *S. L. Hoffman*

The first published reports of murine studies indicating that administration of "naked" DNA leads to protein expression in muscle, antibodies against the encoded protein, protection against a virus (influenza), and protection against a parasite (malaria), came out nine, seven, six and five years ago, respectively. Enthusiasm for DNA immunization (also known as nucleic acid and genetic immunization) focused on:

- the ease of construction and production of DNA vaccines;
- the potential for enhanced immunogenicity of $CD8^+$ T-cell responses and of production of conformationally appropriate B-cell immunogens; and
- the potential safety of DNA as compared with live recombinant infectious agent delivery systems, since there is no potential for reversion to virulence.

From the outset of interest in DNA immunization there have been several major safety concerns regarding the technology. These included:

- induction of anti-DNA antibodies that would lead to auto-immune/ connective tissue disease;
- integration of the plasmid DNA into the host chromosomes causing insertional mutagenesis which would lead to carcinogenesis;
- integration of the DNA into the chromosomes of host germ-line cells and passage of the DNA to the offspring; and
- induction of host tolerance to the protein encoded by the DNA.

During the past five years there has been an explosion of interest in DNA vaccines, with hundreds, if not thousands, of publications on use of DNA vaccines in mice, rats, rabbits, ferrets, cows, non-human primates and other animals. Preclinical safety studies in animals did not provide any data supporting the safety considerations outlined above. Based on these safety data, as well as immunogenicity and protective efficacy data in animals, a number of Phase I clinical trials were initiated during the past few years. The first reports on the safety, tolerability and immunogenicity of DNA vaccines in HIV-infected individuals and normal, healthy volunteers were published in 1998, and numerous other studies have been completed or are now in progress. These Phase I studies clearly demonstrate that in the short term DNA immunization is safe and well tolerated and that DNA immunization can lead to the induction of antibodies and $CD4^+$ and $CD8^+$ T-cell responses in humans. However, most data on DNA vaccines indicate that immune responses elicited by DNA vaccines can be focused and improved and the quantity of DNA required for effective immunization reduced by:

- altering the route and method of administration of the DNA;
- altering the antigen-encoding portion of the DNA plasmid;
- altering the backbone of the DNA plasmid;
- altering the vehicle of delivery of the DNA;
- delivering the DNA with plasmids-encoding cytokines and co-stimulatory molecules; and
- delivering the DNA with adjuvants.

Furthermore, there is now a rapidly developing body of data indicating that priming with DNA vaccines and boosting with recombinant poxvirus vaccines or with recombinant protein vaccines dramatically improves the protective $CD8^+$ T-cell and antibody responses, respectively, as compared to multiple doses of DNA, poxvirus, or recombinant proteins in adjuvant alone. Unpublished work has now also shown that a number of other strategies, including a nucleic acid vaccine-based strategy, may also be effective in boosting DNA-primed immune responses.

3.6. Is there a future for DNA vaccines? – *M. Liu*

Dr Liu's presentation focused on how DNA technologies have resulted in potential new vaccines for infectious diseases and cancer. In alluding to the disappointment that had accompanied the release of some of the first clinical trial data, she reminded that this technology was only in its early childhood and that obituaries may have been drafted a bit prematurely.

Unlike killed-virus vaccines, DNA vaccines induce not only antibodies but also cellular immune responses. While live viruses (including attenuated or weakened versions used in some vaccines or vector systems such as vaccinia) can also induce these cellular responses, they may be able to cause disease, and hence DNA vaccines may be safer than live viruses for diseases such as HIV. They may also be easier to manufacture and may be stable at room temperature. Both these traits would greatly facilitate development and distribution of vaccines to developing countries.

A host of technological advances addressing the weaknesses of first DNA vaccines are in the starting blocks, that is, in preclinical development or already in transition into clinical evaluation. These techniques include:

- DNA prime/protein boost technology;
- formulation of DNA on particles;
- *in vivo* electroporation;
- improved plasmids; and
- improved adjuvant technology, e.g. using CpG motifs, cytokines, "carrier" DNA.

Another interesting approach uses a viral particle known as a replicon, which although incapable of replicating can result in production of protein from a heterologous gene coding for an antigen. These replicons are very potent for inducing immune responses and may be useful for gene therapy as well. Of particular interest for vaccination purposes is the fact that these replicon-containing particles have a tropism for professional antigen-presenting cells and thus target expression of the vaccine antigens to where their presence induces immune responses most efficiently.

3.7. WHO-industry collaboration in upstream research: is it realistic? – *R. Rappuoli*

Collaboration between WHO and industry may occur at three levels, depending on the vaccine target and the priority of the project for the private sector:

- Programmes that have high market value in the USA and Europe. These programmes are usually high priority for industry and collaboration with WHO is minimal or absent.
- Programmes that have high market value in developed countries but are also important for developing countries. These programmes are usually also driven by industry. WHO can provide resources for field trials and expand the vaccine target population in developing countries.

- Programmes which are of great interest for WHO but have no market value in developed countries. In this case, WHO can try to facilitate the beginning of the programmes by providing infrastructure for clinical trials and proof of concept of vaccine feasibility. Decreasing the risk of investment for the private sector may encourage investment.

In addition, WHO and industry should collaborate towards a new image of "vaccines", which should not be seen as "low price", "cheap" products with little value, but instead as "high tech", "very valuable" products, which are expensive to develop and manufacture. The expensive products can be donated to those who cannot afford them.

In conclusion, WHO can provide infrastructure, competence, sites for clinical trials, and on some occasions proof of concept. A major limitation of WHO is the low budget available for some programmes, which may seriously diminish WHO's impact.

4. Pre-regulatory research

4.1. When should WHO be involved in pre-regulatory research? – *E. Griffiths*

Ensuring the consistent safety and quality of a vaccine has long been recognized as an essential element in a successful immunization programme. Thus a prerequisite to the routine clinical use of any new vaccine will be the development of appropriate laboratory methods to characterize the vaccine with respect to its component antigens, safety, immunogenicity and potency.

It is expected that vaccines will be produced under good manufacturing practice (GMP). Although important, GMP is a process and does not in itself guarantee safe and effective vaccines unless the control procedures carried out are appropriate. Likewise, lot release by National Regulatory Authorities is of little help unless the quality control procedures used by the manufacturers and national control laboratories are relevant. Defining appropriate quality control procedures as well as providing international standards and reference materials for assuring the comparability and reliability of data globally are thus key elements in developing safe and effective vaccines.

Special considerations apply to the control of vaccines and other biologicals (not applicable to chemical drugs). The basic problem is the inherent variability of biological source materials and production processes, and vaccines are often highly complex in molecular terms. Assuring the safety and quality of vaccines cannot be satisfactorily carried out by end-product specifications alone but relies heavily on tests on starting materials, tests carried out during production and on intermediate materials, as well as tests on the final product.

- The characterization, standardization and control of vaccine properties during development and clinical testing are therefore major issues. A well-defined candidate offers by far the best chance of success. If in a phase III clinical study a preparation is shown to be adequately protective and safe, the vaccine must subsequently be produced to the same specifications as the successful preparation. In the case of inadequately defined materials, it is never certain whether differences in protection or toxicity of different lots are due to unintentional variation in the vaccine preparations used, suboptimal vaccination schedules, poorly designed trials or differences in target populations.
- Vaccines are now being developed with a much better understanding of pathogenic mechanisms and immunology, and often using novel biotechnologies. Powerful purification procedures are available as well as a range of physico-chemical techniques for characterizing products.

Nevertheless, problems of ensuring consistent safety and efficacy of the product remain and new challenges arise with novel biotechnologies such as DNA vaccines.

- It is expected that by the phase III stage of development a comprehensive analysis will have been made, characterizing the product and establishing its specifications. Differences between lots are noted and used for setting limits for routine production and criteria for rejection of harvests and production lots. A more limited series of tests are selected for routine lot control. However, this selection is not made without difficulty and the question always arises as to whether the parameters selected are able to distinguish clinically ineffective or unsafe lots.
- Regulatory research thus includes the development and validation of appropriate, reliable, robust procedures for antigen characterization, for toxicity testing and for establishing, where possible, correlates of protection such as immunogenicity or biological potency. New approaches to address both new and old problems also need to be evaluated and validated. Examples of current areas of interest include: progress made in improving the safety and consistency of oral polio vaccine using the MAPREC assay for molecular consistency and transgenic mice susceptible to polio virus for neurovirulence testing; the exploration of new approaches to the difficult problem of potency testing of acellular pertussis vaccine either alone or in combination vaccines; the standardization of serological assays for evaluating immune responses to pneumococcal conjugate vaccine; and the ongoing issues related to the safety of cell substrates used for the production of vaccines and safety issues associated with DNA vaccines.
- WHO plays a major role in pre-regulatory vaccine development by providing a framework for: (a) international collaboration and coordination of work important to the quality and safety of vaccines; and (b) developing international consensus on appropriate standardization and control procedures, including the provision of international standards and reference materials and guidance documents. This work, carried out in collaboration with WHO International Laboratories and Collaborating Centres for Biological Standardization and the Expert Committee on Biological Standardization, plays a pivotal role in the transfer of vaccines from the laboratory to the clinic, in facilitating the international acceptance and use of new vaccines, and in underpinning their continued deployment in immunization programmes.

4.2. Dengue – *B. Innis*

There are two generations of vaccine candidates under development. The first generation consists of live attenuated vaccines that have a number of theoretical advantages but many practical problems. This type of vaccine exists in two competing versions, each of which has been administered to volunteers. The second-generation live vaccine is a product of infectious clone technology. Feasibility of such vaccines has not been established yet, but clinical trials of a tetravalent vaccine are planned for the year 2000. Prime-boost vaccination models, using inactivated DNA vaccine followed by live vaccine, are currently considered as the best alternative.

The main focus of this paper will be on how WHO can best contribute to development and utilization of a vaccine to reduce the public health impact of dengue. Currently, WHO monitors dengue disease status and is a proponent for disease control. Epidemic and case management guidelines are formulated and, when requested, WHO furnishes on-site consultation. In the area of vaccine R&D, WHO has been providing seed funds for vaccine discovery – three vaccine candidates arose from this programme. In the following section single aspects of the vaccine development process are screened for the need for WHO input.

Criteria for selecting vaccine candidates for downstream development: This area comprises evaluation of protection in primate models, numerous aspects of the product development and manufacturing process, as well as the whole complex of intellectual property rights. Although WHO may, upon request, be able to provide assistance in all these areas, a clear role is difficult to establish.

Tetravalent combination: Some formulations of tetravalent live vaccine produce interference. There is no evidence for synergy apparent yet and thus the selection of the best formulation is empirical. Again, there is no evident need for WHO input.

Risk of serious adverse events (AE): There is the possibility that vaccination could increase the risk for dengue haemorrhagic fever (DHF). This makes it mandatory for sponsors to present evidence of low risk for marketing approval and for clinical trial sites to provide evidence that their health care system can successfully manage DHF. WHO can help identify suitable study sites and also independently evaluate the risk/benefit equation.

Manufacturing process: WHO can facilitate international agreement on product specifications. In particular, questions regarding cellular substrates (none are used for other parental live vaccines!) and purification requirements need to be addressed urgently.

User profile: Age may influence vaccine effect. With infants being likely to carry interfering maternal antibodies and live vaccine being reactogenic in some adults, ages two through six may be the ideal target group, at least for live vaccines. WHO could facilitate early paediatric studies. While those trials should be deferred until there is evidence of vaccine benefit, they should be performed early enough to avoid discarding useful products.

Early development endpoint: An unequivocal immune correlate of protection remains to be defined. In primate studies, animals vaccinated with some non-replicating candidates made potent N antibody but had no protection against viremia when challenged. Some live vaccine recipients have N antibody to <4 DEN types but CMI to all. Furthermore, quantitation of N antibodies is not standardized. In this area, WHO could develop international standard reagents and promote consensus on tests for correlates of protection.

Test of efficacy: Low annual case rates for any dengue type (>0.5%) and the fact that type may not occur with a high rate for a two to three year period render field evaluation of vaccine efficacy difficult. Controlled challenge studies to supplant some efficacy testing may be considered. WHO can promote consensus interpretation of challenge data and assist sponsors to identify appropriate trial sites.

National programme integration: Interactions with other live vaccines are currently unknown (vaccines against Japanese encephalitis, yellow fever vaccine, measles, mumps, rubella and – although of less concern – rotavirus and poliovirus). With regard to recommendations for use in high risk groups as against universal, WHO can define where vaccination will be beneficial and support trials and/or formulate a strategy for concurrent vaccination.

In summary, WHO can provide a lot of practical assistance in the dengue vaccine development process by helping to address the above issues. In all these areas, some form of partnership with a vaccine sponsor/industrial partner will be indispensable.

4.3. Current status of first-generation and second-generation vaccines against Leishmaniasis – *D. L. Sacks*

The overall objective of the TDR/WHO leishmaniasis vaccine programme has been to develop vaccine(s) for the prevention of all forms of leishmaniasis. Two approaches are being pursued: (a) The first-generation vaccines composed of killed parasite with or without BCG (used as adjuvant) represent materials which can be used presently for clinical trial; and (b) recombinant molecules or genetically engineered organisms which will require extensive preclinical development. The rationale for using a killed whole-cell vaccine in clinical trials includes:

- ease of preparation of the product;
- efficacy of killed vaccines when used with certain adjuvants in animal model; and
- demonstrated safety and immunogenicity of crude killed antigens in humans when used in immunotherapeutic trials and in early immunoprophylactic trials.

The safety of single and multi-dose injections of heat-killed *Leishmania (L.) major* antigen (ALM), produced under current good manufacturing practices (cGMP), plus BCG has been clearly demonstrated in clinical trials in Iran. A recently completed Phase III trial of a single injection of ALM plus BCG revealed significant protection against anthroponotic cutaneous leishmaniasis in the second year of follow-up. Multiple injections of this vaccine are currently being evaluated in Phase III trials in Iran. A field trial of a similar killed vaccine against New World cutaneous leishmaniasis has recently been completed in Ecuador; in a 12 month follow-up, the incidence of cutaneous leishmaniasis was reduced by 73%. Additional field trials of cGMP-produced ALM with or without BCG as adjuvant are planned or are currently near completion in Brazil, Columbia, Ecuador and Venezuela.

Preclinical testing of killed whole-cell Leishmania antigen using alternative adjuvants, including alum and recombinant human IL-12, have been completed in monkey models of cutaneous and visceral disease. Powerful protection was obtained when a single dose of ALM was administered with alum and BCG, or with alum and IL-12. Phase I trials of each of these vaccines are planned for the near future.

Second-generation vaccines involving genetically engineered, live attenuated promastigotes have demonstrated partial protection in mouse models of cutaneous disease. Subunit, recombinant vaccines involving as many as 10 different antigens have each shown partial protection in the mouse. In each case, adjuvants were required for vaccine efficacy. Most recently, DNA vaccines encoding leishmania antigens have produced partial protection in the mouse. Importantly, the DNA vaccines could be administered sub-cutaneously without adjuvant, and at least in one case the immunity appeared to be far more durable than that elicited by the corresponding recombinant protein.

4.4. Vaccine strategies against schistosomiasis – from concepts to clinical trials – *A. Capron*

At the end of the 20th century schistosomiasis still represented a major public health problem in many developing countries. As the second major parasitic disease in the world after malaria, schistosomiasis affects 200 million people, with 800 million exposed to the risk of infection. In spite of undeniable chemotherapeutic progress there is a considerable spreading of endemy, in particular in West Africa. It is now clearly established that mass treatment of infected populations does not affect reinfection and that within a period of six to eight months following chemotherapy the prevalence has returned to its initial level. Moreover, recent observations tend to indicate the possible emergence of drug-resistant strains of schistosomes.

Vaccine strategies do therefore represent an essential component of the control of these major parasitic diseases. Vaccination can be either targeted towards the prevention of infection or the reduction of parasite fecundity, schistosome eggs being responsible for both pathology and transmission of infection. Strategies of immuno-intervention during ongoing infections can also be considered. In this chronic infection, where the deposition of millions of eggs in mucosae and tissues (in particular liver) is the essential source of pathology and disease, the concept of an anti-pathology and anti-transmission vaccine targeted on parasite fecundity and egg viability appears therefore entirely relevant.

Research developed in our laboratory for over 20 years has led in a first phase to the identification in animal models and in man of an effector mechanism of protective immunity against infection or reinfection. The essential role played by IgE antibodies, which we had originally demonstrated *in vitro* and *in vivo* in animal models, has now been entirely confirmed in human populations through many epidemiological studies performed in Brazil, Egypt, Gambia, Kenya and Zimbabwe. The identification and the molecular cloning in our laboratory of a target antigen of the effector response have allowed numerous approaches regarding its vaccine potential to develop in the last 10 years. Vaccination experiments were performed in various experimental models (rodents, primates and cattle) with a recombinant version of this molecule, the enzyme Glutathion-S-transferase (Sm28GST). These experiments led not only to a demonstration of the partial protective effect of the molecule (reduction of 40–80% of the worm burden) but also to evidence of a very significant inhibitory effect on female worm fecundity and egg viability. It has been further demonstrated that the inhibition of fecundity was associated with the inhibition of enzymatic activity of GST represented in N terminal and C terminal regions of the molecule.

Research undertaken to identify immune mechanisms induced by vaccination and involved in inhibition of parasite fecundity led in animal models and in man to the original demonstration of the role played by lgA antibodies.

These observations have led during the last two years to a double strategy:

1) The extension to various animal models and to several schistosome species of the relevance of this vaccine target.

   The molecular cloning in our laboratory of the genes encoding GST from the schistosome species *S. haematobium*, *S. bovis*, and *S. japonicum* has allowed the confirmation both in primates, by homologous or heterologous immunization, and in cattle of the very significant anti-parasite fecundity or ant-egg viability effect reaching 75–85% in primates and 94% in young calves.

2) The development, on the basis of the potential role of IgA antibodies, of novel vaccine strategies by mucosal routes.

All these studies have confirmed, in a large array of animal models, the vaccine potential of Sm28GST, Sh28GST and Sb28G5T by significantly inhibiting parasite fecundity and egg viability.

The decision was made, as a first approach to human vaccination, to use *S. haematobium* 28GST (Sh28GST) for the following reasons:

- Resistance to *S. haematobium* is strongly associated with immune-mediated inhibition of fecundity;
- Methods of quantitative evaluation of eggs through filtration procedures are reliable and easier to handle than stool examination;
- Urinary schistosomiasis provides a unique opportunity to follow by non-invasive methods; and
- The existence of a demonstrated synergy between immune response to GST and Praziquantel treatment provides a unique opportunity to evaluate, under strict ethical conditions, the efficacy of the vaccine in association with chemotherapy in comparison with chemotherapy alone.

Promising preclinical trials performed in rodents, primates and cattle encouraged us to start Phase I clinical trials in September 1998. Sm28GST has been produced under GMP conditions by our industrial partner (Pharos Eurogentec) and named Bilhvax. Phase Ia trials have been performed in Lille at the Center for Clinical Investigation and have concerned 24 healthy volunteers (Caucasian men). The main objective of this study was the evaluation of the safety of Sh28GST and as a secondary objective the evaluation of immunogenicity. Consistent with toxicity studies performed in rats, rabbits and dogs, where no systemic toxicity was observed and no cross-reactivity with rat and human GST detected, no adverse reactions were observed in human volunteers and no cross-reactivity with the human GST(Pi) was detected, in spite of a high-titred specific Ab response and the production of neutralizing antibodies.

Phase Ib has now started at St Louis du Senegal in two groups of 12 children in order to evaluate the safety of Bilhvax in non-infected children from an endemic area. Phase Ic will follow shortly in order to evaluate safety in already infected

adults. Phase II trials were to be initiated in December 1999 both in Niger and in Senegal in order to evaluate safety and immunogenicity of Bilhvax in the context of association with chemotherapy.

4.5. WHO and new tuberculosis vaccine – *D. Young*

With an estimated one third of the world's population infected with *Mycobacterium (M.) tuberculosis*, enhanced susceptibility to clinical disease in the wake of the HIV pandemic, and emergence of multidrug-resistant strains, the best prospects for global control of TB lie in combining available treatment regimens with improved diagnosis and effective vaccination. The current BCG vaccine provides protection against childhood forms of TB but insufficient protection against the predominant pulmonary disease in adults. Recent advances in biomedical research of importance for vaccine development include:

- determination of the genome sequence of *M. tuberculosis*;
- identification of deleted genes in BCG substrains;
- development of tools for genetic manipulation of mycobacteria; and
- demonstration of protection by DNA vaccination in animal models.

Together with general progress in understanding of cell-mediated immune mechanisms, these advances underpin renewed efforts towards vaccine development.

Vaccine candidates: Two general approaches are being taken to generate new vaccine candidates, based on (a) live attenuated mycobacteria, and (b) subunit vaccines. Novel attenuated vaccine candidates include strains of *M. tuberculosis* debilitated by removal of genes required for virulence and modified BCG strains engineered to express additional antigens or immunomodulators. Subunit vaccines are based on a combination of recombinant proteins with appropriate adjuvants, DNA immunization, or delivery of selected genes by other vaccine vectors. In addition, non-protein components of mycobacteria have been shown to elicit responses of particular T-cell subsets and are also under consideration as vaccine candidates. It is not clear at present which type of candidate will be optimally effective, and emphasis is placed on comparative analysis of the ability of different candidates to protect against virulent challenge in animal models (mouse, guinea pig and, subsequently, primates).

Clinical trials: While efficacy in experimental models provides some guidance in selection of candidates for clinical trials, it is unlikely that any model will accurately reflect vaccine performance in man. There is a pressing need to identify assays that could be used as "correlates of protection" suitable for preliminary immunogenicity trials in man. For subsequent efficacy trials, two general approaches are being discussed. The first approach would be to test the ability of new candidates to substitute for BCG. This would involve immunization of individuals prior to their first exposure to *M. tuberculosis*, and trial populations might include infants and unexposed adults. Problems associated with this approach include consideration of ethical problems of withholding BCG vaccination and the time-frame required for accumulating a significant number

of cases of adult disease. The second approach would involve vaccination designed to augment immunity already induced by BCG vaccination or *M. tuberculosis* infection. This approach, which could focus on trials in high-risk young adult cohorts, has logistic attractions in terms of trial design but would require a candidate able to act as a "post-exposure" vaccine.

Role of WHO: In considering the role of WHO in TB vaccine development, it is probably appropriate to reflect on the critical advantage of WHO as an "honest broker", together with its critical limitations as a funding organization. The costs of developing and marketing a new tuberculosis vaccine are unlikely to be met by public funds but will be borne by a pharmaceutical company if there is a realistic expectation of their recovery from sales of the vaccine. The market for an effective tuberculosis vaccine is undoubtedly immense, though predominantly focused on the less prosperous amongst the world's population, but the development costs and chances of success remain highly speculative. It is this gap that has to be filled if the opportunities for tuberculosis vaccine research are to be translated into a genuine benefit to global health. Steps that WHO can take to promote this include:

- advocacy of the relevant research efforts underlying vaccine development; provision of a neutral forum for discussions between academic and industrial researchers;
- fostering of interactions between vaccine researchers and health care providers in high-incidence countries with the greatest need for the vaccine;
- formulation of international standards for preclinical evaluation of vaccines;
- promotion of discussion of regulatory issues associated with TB vaccines;
- development of strategies for assessing vaccine efficacy in clinical trials; and
- promotion of economic/political changes designed to encourage vaccine development.

Conclusions: In summary, progress in fundamental biomedical research has opened a window of opportunity for TB vaccine development. Many intellectual and practical problems remain to be faced in developing a rational strategy for exploiting these opportunities. WHO can make a major contribution in this area by providing a global forum for discussions: (a) between academic and industrial researchers, (b) between vaccine developers and regulatory authorities, and (c) between representatives of high-tech low-incidence countries that have strong vaccine development programmes and representatives of low-income high-incidence countries that have expertise in how best to make use of a vaccine.

4.6. First or second generation typhoid vaccines – *T. Pangestu*

First-generation typhoid vaccines include the killed whole-cell vaccine, the Vi polysaccharide vaccine and the live oral Ty21a preparation. Due to several problems associated with these vaccines, there has been a concerted effort to develop second-generation vaccines, which includes Vi-protein conjugates and improved versions of live oral vaccines developed by recombinant DNA technology.

The decision to recommend the use of first-generation or second-generation typhoid vaccines should be based on several important criteria:

- available information on efficacy and safety following extensive trials, especially in developing countries;
- duration of protection;
- ease of delivery (e.g. number of doses, route of administration);
- presence of a memory response upon revaccination;
- immunogenicity in children;
- stability;
- cost of vaccine; and
- ease of technology transfer to developing countries.

Based on currently available information and experience, WHO should focus primarily on implementing the more widespread usage of first-generation rather than second-generation vaccines. However, the further development and evaluation of second-generation vaccines should be pursued vigorously to enhance the available armamentarium to prevent typhoid fever.

4.7. Preparing AIDS vaccine trials – *J. Esparza*

Despite all international efforts, HIV continues to spread, at a rate of 16 000 new infections every day. In 1998 alone, some 2.5 million people died of AIDS, which now is the leading cause of death in Africa, and the fourth cause of death worldwide. As with other infectious diseases, the control of the HIV/AIDS pandemic may ultimately hinge on the development of a successful preventive vaccine. HIV vaccine development, however, confronts multiple challenges – not just scientific, but also logistic and ethical, which are discussed below.

Before field trials of HIV vaccines can be conducted in developing countries, several critical issues must be addressed:

Site development: Since 1991, WHO and UNAIDS have helped scientists and national authorities in the establishment of field sites for HIV vaccine trials. This effort has resulted in a comprehensive development of three sites in Brazil, Thailand and Uganda. It is important to mention that these sites are in countries that have developed national plans for the development and evaluation of HIV vaccines. Capacity strengthening has been provided to the trial sites in the form of research infrastructure and training. In preparation for efficacy trials, various vaccine-related studies, in particular phase I/II clinical studies, have been successfully implemented at all sites. Success of the above strategy is evidenced by the fact that a phase III study was to be initiated in Thailand in 1999.

HIV variability: The significance of HIV variability for vaccine protection or the immunologic correlates of protection is not yet known. Therefore, genetic and antigenic characterization of HIV in the trial populations is being done in preparation for efficacy trials. This will help ensure that the most appropriate vaccines are selected and will make it possible to evaluate subtype-specific vaccine

efficacy during the trial. A WHO/UNAIDS Network for HIV Isolation and Characterization has been established to monitor HIV genetic and antigenic variability worldwide. Primary laboratories in all vaccine evaluation sites and back-up laboratories in the United States and Europe collaborate to ensure better understanding of the significance of HIV variability, interact with vaccine manufacturers to disseminate relevant results and provide viral strains and other vaccine-related reagents.

Repeat Phase I/II trials: In order to assess the safety and immunogenicity of HIV vaccines in developing country populations with different endemic diseases and immunologic responses, it is becoming necessary to repeat phase I/II trials locally before initiating a large-scale phase III trial. UNAIDS is working with vaccine manufacturers, national authorities, local scientists and other institutions to develop the capacity to conduct these trials with appropriate vaccines.

Ethical and socio-behavioural issues: All HIV vaccine trials must be conducted according to the highest ethical standards, and systems must be in place to ensure the protection of human rights. In the cultural context of many developing countries, however, concepts and procedures such as randomization, blinding, placebo, informed consent and risk/benefit may be largely unknown. To ensure truly informed consent, methods are being developed to communicate these concepts effectively to potential trial participants. To ensure community support, the population at large must be informed as well. In addition, vaccine-related social and behavioural research is needed to determine ethical and logistically feasible incentives for recruiting trial volunteers and ensuring their cooperation in long-term follow-up. Finally, new methods that are applicable to developing country populations are being developed to assess and monitor risk behaviour.

Conclusion: A global effort has resulted in a number of HIV candidate vaccines in the "pipeline" at different stages of development. Phase I/II trials have shown that many of these candidate vaccines are safe and immunogenic, and ongoing and future Phase III trials will provide information on their efficacy in protecting against HIV infection or AIDS. Active and full participation of developing countries in the worldwide effort of HIV vaccine development and evaluation will not only ensure an expeditious progress towards globally effective vaccines but will also help to provide future access to effective vaccines by populations who are in need of such a vaccine. This will certainly require significant investment and capacity building in developing countries. UNAIDS and WHO are collaborating with multiple partners in government, academic and research institutions and the vaccine industry, in both industrialized and developing countries, to meet that challenge.

4.8. Pre-regulatory and regulatory research for the development and evaluation of new and improved methods for vaccine standardization and control – *G. Schild*

Research and development activities relevant to the standardization and control of vaccines make a critically important contribution to public health. This is particularly true when, as now, an increasing number of vaccine quality and safety issues are arising and require urgent investigation. It is essential that the

methods in routine use for vaccine evaluation reflect the best available science and technology and are updated in line with scientific progress. Long-term, high-quality research is often needed to provide the scientific basis for a new approach. For instance, the work to elucidate the molecular basis for virulence of the Sabin type-3 poliovaccine required some 15 years of intensive international collaborative research for completion and provided the essential basis for the important practical developments discussed below. Currently the limited availability of resources for regulatory research and international collaborative studies needed to evaluate and introduce new methods is a seriously limiting factor.

Examples of new approaches to the laboratory evaluation of viral and bacterial vaccines include progress on safety and consistency testing of Sabin polio vaccines using molecular analysis (MAPREC) and neurovirulence tests in transgenic mice expressing the human poliovirus receptor. These methods are currently the subject of intensive international collaborative studies to validate them and to evaluate the reproducibility of results between laboratories. They have good potential for complementing or replacing the existing standard WHO neurovirulence test, initially for type-3 vaccines and ultimately for type 1 and 2 vaccines.

Nucleic acid amplification tests (NAT) have been put to good effect in examining vaccines or their substrates for the presence of unwanted adventitious agents. Work on testing polio vaccine for SV40 will be described. Other recent examples of the use of modern molecular techniques for the investigation of vaccine safety issues include the use of NAT to study the hypothesis that measles vaccine may be a contributory factor in Crohn's disease (our studies failed to find evidence of this); in relation to the significance of low-level expression of RT activity in chick-cell derived measles vaccines, no evidence of an infectious retrovirus was detected by sensitive PERT assays.

Concerning bacterial vaccines, testing for biologically active clostridial neurotoxins (e.g. tetanus and botulinum) in animals is a laborious and variable procedure. Specific endopeptidase assays using synthetic peptide substrates show considerable promise with regard to replacing *in vivo* assays for these toxins. Capsular polysaccharide antigens, e.g. in Hib vaccines, are being characterized by nuclear magnetic resonance spectroscopy, and the methods are robust and are being taken into routine use. This is the first routine application of advanced physico-chemical analysis for the standardization and control of a vaccine and others will follow, particularly in respect of the new generation of conjugate meningococcal and pneumococcal vaccines. For acellular pertussis vaccine a new murine challenge test for examining vaccine potency is giving promising results. Good progress is being made in the standardization of the antigenic content of these vaccines in respect of each component using antigen-specific single-radical-diffusion methods and enzyme-linked immunosorbent assay (ELISA) techniques. Immunological correlates of vaccine-induced immunity indicate an important role for cell-mediated responses. Physicochemical methods such as CD spectroscopy are being used successfully for monitoring the detoxification of components of cellular pertussis vaccine.

For many vaccines the use of appropriate WHO International Standards or Reference preparations is essential for quality control potency and safety testing. The preparation and evaluation of these requires intensive international collaboration and must be underpinned by specialized research and development work. Provision of suitable reference materials must go hand in hand with vaccine

development and the introduction of new vaccines. Providing the framework for international collaboration and coordination of the work of WHO International Laboratories and Collaborating Centres is a major aspect of the normative functions of WHO Health Technology and Pharmaceuticals Division.

4.9. Preregulatory research at the Center for Biologics Evaluation and Research – *K. Zoon*

There are many important reasons for the regulatory agencies such as the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration to conduct research, especially as they relate to vaccines. First, our research facilitates the approval of safe and effective products. Second, it supports decisions to withdraw products that are found to be unsafe. Third, our research anticipates public health needs and supports informed decision-making in the prevention of and response to public health crises. Fourth, it encourages the industry-wide adoption of new technologies. Fifth, it facilitates the development of industry-wide standards and methods. Finally, it contributes to improvements of existing products and the development of new products.

CBER research has contributed to the development of safe and effective vaccines, including rubella vaccine, *H. influenzae* vaccine and diphtheria, tetanus and acellular pertussis vaccine. A number of current research studies regarding new vaccines are underway at CBER. These projects include broad classes of new vaccine approaches such as DNA vaccines, vaccines from novel substrates, e.g. tumour cell, and live attenuated AIDS vaccines. There are also a number of very specific vaccine research projects being conducted at CBER which include hepatitis C, dengue virus, tuberculosis and leishmaniasis vaccines. In addition, new methods for lot release testing of vaccines are also underway, e.g. use of the MAPREC test, a molecular assay to detect and quantify mutations in live viral vaccines and other improved neurovirulence assays for viral vaccines. This research is critical to our review of vaccines at the pre-IND (investigational new drug), IND and pre-licensing stages of the regulation of biological products. It facilitates product development, and it often leads to the development of vaccine standards and methods. Finally, our research addresses many quality and safety issues both pre- and post-licensing of vaccine products.

5. Post-regulatory studies and research on vaccination strategies

5.1. Use of oral cholera vaccine in refugee and displaced populations – *C. Paquet*

Cholera is one of the major health risks during complex emergencies and large population displacements. The most dramatic epidemic affecting refugees happened in Zaire (now Democratic Republic of Congo) in July 1994. 700 000 people from neighbouring Rwanda sought refuge in and around the town of Goma. The first cases of cholera were reported a week after the arrival of the refugees. Within three weeks 35 000 presumed cases of cholera were treated in special centres, and it is estimated that a similar number of cases occurred that did not seek care. An estimated 23 800 cholera deaths occurred during that epidemic – most of these people never received treatment.

A controversy on the vaccination against cholera during emergencies followed the Goma outbreak, which prompted WHO to organize a meeting on the potential role of new oral cholera vaccines in such situations. Following this meeting, two studies were commissioned by the Global Programme for Vaccines and Immunization/WHO and carried out by Epicentre in collaboration with several scientific partners:

- A cost-effectiveness evaluation of the different strategies for controlling an outbreak of cholera in a refugee population, allowing comparison of strategies with and without vaccination. A mathematical model was constructed using the data that Médecins Sans Frontières (MSF) had collected over a 10 year period in the Mozambican refugee camps of Malawi.
- A study for documenting the feasibility of a mass cholera vaccine campaign in a large refugee population. This study used killed whole-cell B-subunit (WC/BS) vaccine that has a field-demonstrated effectiveness of 85% for six months in adults.

These two studies have confirmed that refugee populations could benefit from new cholera vaccines. Both the mathematical model and the feasibility study indicated that a reactive strategy that involves launching a mass vaccination campaign once the cholera outbreak has already started is likely to have only a limited impact. Similarly, the studies suggested that during the acute phase of complex emergencies, priority should be given to basic relief activities, including provision of food, clean water, shelter and basic medical care, and that cholera vaccination could not be recommended in this situation.

Pre-emptive mass vaccination against cholera is feasible and could be useful among refugees and displaced populations established in high-risk areas, once the basic

needs are covered. However, before recommending strategies based on pre-emptive vaccination of populations at risk, issues related to vaccine cost and availability must be addressed. The price of WC/BS has been set for the traveller's market but not yet now for large-scale use in developing countries. Furthermore, there is no stockpile of WC/rBS readily available to quickly cover the needs of any large preventive operation. Regulatory issues related to the implementation of such a stockpile have also to be worked out. For all these reasons, more work is needed to get a cholera vaccine, easy to use and effective, that would be affordable for large-scale use. In this regard, it is interesting to mention that a two-dose killed oral cholera vaccine, produced at low cost, is now being field tested in Viet Nam. If this bivalent (01 + 0139) vaccine proves to be effective, its use in refugee situations could be considered.

5.2. Vaccines against rotavirus infections: efficacy and potential role within vaccination programmes – *B. Ivanoff*

WHO estimates that, globally, diarrhoeal diseases and typhoid fever account for 2.4–2.9 million deaths each year, principally among children less than 5 years of age. Rotavirus alone causes a mortality of about 600 000–700 000 worldwide. The age group most affected by this viral infection ranges between 6 and 24 months in the USA and Europe and between 6 and 18 months in developing countries.

Improvements in sanitation, in particular provision of sewerage and drinking water, generally contribute to the decrease in the incidence of diarrhoeal diseases of bacterial origin. Unfortunately, the same does not apply to rotavirus infections as evidenced by a comparable percentage of rotavirus infection in hospitalized infants in China, Europe, Indonesia and the USA. Therefore, there is a real need for effective control of rotaviral disease, and vaccination represents an interesting approach towards that goal.

The challenge comprises development of a vaccine, the composition of which reflects the antigens present in rotavirus strains found in the field. In the majority of cases the same serotypes are present in most countries, e.g. G1 serotype: 60%. However, in certain developing countries like Bangladesh, Brazil, or India strains can be found that show different antigenic profiles; the latter will have to be taken into account in the composition of future vaccines.

The two most advanced candidate vaccines are administered orally in three doses at one-month intervals. These are two reassortant vaccines – hybrids containing genes of human and animal origin. The first, which has already been licensed in the USA, is a tetravalent vaccine (RRV-TV) the animal strain of which is of simian origin; the second is based on a strain of bovine origin. Both vaccines contain the principal serotypes P(8)G1, P(8)G3, P(8)G4 and P(4)G2. However, the present formulation is not final and other important serotypes could be included, i.e. those playing a major role in developing countries.

Safety, immunogenicity and protective efficacy have been evaluated in the Finland, South America and the USA. The first studies performed in South America using the concentration effective in countries of the north (10^4 pfu) have shown that the viral concentration had to be increased by one log in order to obtain an immune response sufficient to induce good protection. The latest trials with this concentration have shown that these vaccines confer excellent protection

(85–100%) against severe rotaviral diarrhoea – the main cause of mortality – and an efficacy of about 50% against all rotaviral diarrhoea. The duration of protection conferred by the vaccine lasts up to two years. The fact that protection decreases during the second year following vaccination is not a major obstacle given the fact that the age of highest risk ranges from 6 to 24 months. For the USA, it has been estimated that vaccination could be considered both efficacious and cost-effective if the number of hospitalizations due to severe rotavirus diarrhoea could be decreased by about 30%.

Another interesting approach is a human-based candidate vaccine called 89-12. This is a monovalent vaccine (one paediatric attenuated strain). Given orally in two doses, one month apart, it provided good protection in infants enrolled in a clinical phase II trial.

As discussed above the vaccine must be administered before the age of six months. The most favourable period would therefore coincide with the Expanding Immunization (EPI) vaccinations scheduled at 6, 10 and 14 weeks of age. However, in order to recommend inclusion of this vaccine into developing country EPI, a certain amount of data is still needed. These data requirements have been defined and recommendations have been made by WHO to accelerate this process. This concerns two main activities: strain surveillance and evaluation of the vaccine in areas where it has not yet been studied, like Asia and Africa.

Surveillance activities:

It has been recommended:

- that guidelines are developed for the surveillance of rotavirus infections for developing and industrialized countries; and
- that networks are set up for the surveillance of rotavirus strains and to standardize strain characterization techniques.

Further evaluation of the vaccine:

It has been requested:

- that immunogenicity studies be conducted in countries where the vaccine has been given at the lower dose (10^4 pfu) and in countries where it has never been evaluated;
- that studies be set up on protective efficacy and cost-effectiveness in Africa and Asia; and
- that the efficacy be evaluated of three-dose versus four-dose regimens, the first dose being given with BCG.

All of the above research has been performed or is being initiated. A vast study is therefore presently being conducted in 13 different sites on three continents (Africa, Asia and South America), to answer these questions. The results will be decisive in determining WHO's recommendation regarding the introduction of rotavirus vaccine into the EPI*.

* **Post-meeting footnote:** These studies (as well as the use of this vaccine in general) have been put on hold due to the occurrence of intussuception as a rare but severe side effect.

5.3. Hib and pneumococcal vaccine trials – *K. Mulholland*

This paper addresses the research issues involved in the development and introduction of new vaccines against *Haemophilus influenzae* type b, pneumococcus and rotavirus from the perspective of the generic questions raised by the Global Forum for Health Research.

1) What is the disease burden?
2) Why does the burden persist?
3) How good is the knowledge base?

Disease burden can be considered in terms of both morbidity and mortality. Childhood vaccination programmes are largely directed at prevention of mortality, which is consequently usually the focus of discussions of disease burden. For acute illnesses such as pneumonia and acute diarrhoea this is appropriate. For bacterial meningitis the mortality burden must be considered alongside the fact that in developing countries a substantial proportion of survivors suffer permanent disability.

Of the "new vaccines", Hib is the only one widely available. For most of the world, reasonable estimates of the incidence of Hib meningitis exist, based on population studies of proven disease. These usually range from 20 to 60 per 100 000 children under 5 years per year. There is very little direct evidence of the incidence of Hib pneumonia, although extrapolation from vaccine trials in Chile and the Gambia suggest that it is about five times more frequent than Hib meningitis in developing countries where pneumonia is common. In those countries it is believed to account for about 20% of episodes of severe pneumonia. Based on rough estimates of this sort it is reckoned that Hib accounts for 300 000–400 000 child deaths each year, most from pneumonia in infants in developing countries. Predictably most of these deaths occur in settings where basic medical care is not available.

The burden of Hib disease in Asia is a matter of considerable controversy. Several published studies indicate that the incidence of Hib disease is very low (<5 per 100 000 children under five per year). Whether this low rate is real or an artefact due to imperfect bacteriology is debatable. Reasons suggesting why it may be truly low range from overuse of antibiotics to lower inherent susceptibility among Asian races.

Substantially less is known about the burden of pneumococcal disease. There is no doubt that most of the burden lies with children in developing countries. The few studies of the population based burden of invasive pneumococcal disease in developing countries show rates ranging from 81 to 554 per 100 000 infants per year. These studies are restricted to blood or cerebrospinal fluid culture-positive cases and therefore probably miss the great majority of cases that are manifested as blood culture negative pneumonia. Estimates of the global burden of pneumococcal disease start with an estimate of the total number of deaths attributable to acute respiratory infection each year, which was derived from infant mortality rate data. Then the proportion of those deaths due to pneumococcus is estimated based on studies of the etiology of severe pneumonia. It is assumed that these hospital studies are a reliable guide to the cause of pneumonia deaths in the community. These rough calculations lead to an estimate of 1–2 million child deaths each year due to pneumococcus.

Figures for the global mortality attributable to rotavirus are derived from similar calculations. The proportion of severe diarrhoea due to rotavirus is estimated, based on studies of children taken to hospital with severe diarrhoea. This is then applied to estimates of the number of children in the world believed to die of acute diarrhoea yearly, to conclude that about 600 000 children die as a result of rotavirus diarrhoea every year.

Deaths from pneumococcal, Hib and rotavirus disease occur predominantly in communities without access to basic health services. For the first time vaccines are becoming available which in some respects offer an alternative to the provision of curative services. Effective use of these vaccines will require a careful analysis of available options and a detailed understanding of disease burden. If these vaccines are introduced in order to prevent hospital admissions and episodes of illness among children who already have adequate access to health services, the effect on mortality may be small. A sound understanding of the patterns of these diseases is required in order to integrate the introduction of new vaccines into a cohesive strategy for improving child survival. Such a strategy should include improvement in curative services through integrated management of childhood illness (IMCI), improvement in the delivery of existing EPI vaccines, prevention of protein-calorie malnutrition and micronutrient deficiencies, and improvement in environmental factors such as water, sanitation and indoor air quality. Understanding of the epidemiological patterns of acute respiratory infection and diarrhoeal diseases within a country is an essential first step in the development of an integrated solution that may or may not involve the introduction of new vaccines in the first instance.

4) How good are the research prospects?
5) What resources are being applied to the area?

The three vaccines considered in this paper are all directed against pathogens of considerable importance in developed countries as well as developing countries. Thus, while the commercial impetus for the development of pneumococcal and rotavirus vaccines has been the prevention of (usually minor) illness in infants in rich countries, the true market in humanitarian terms are the poorest children in the poorest countries who are actually dying from these diseases. Bridging the knowledge gap to meet the needs of the true market is the responsibility of international public sector organizations such as WHO. From that perspective, the research needs in this field can be broadly described in two areas:

- Epidemiology/disease burden studies; and
- Definition and evaluation of regimens appropriate for developing countries.

If approached correctly, research in this area is always going to be productive, as it is essentially descriptive, describing either disease epidemiology, vaccine immunogenicity or vaccine effectiveness/efficacy. The only studies that carry significant risk of failure are disease burden studies that rely on the culture of bacteria from blood or cerebrospinal fluid, such as some of the Hib disease-burden studies currently underway in Asia. These studies carry the risk of producing inconclusive results that are not accepted because of questions about the methodology.

5.4. How to design future TB vaccine trials – *P. Smith*

There is now the potential for producing a large number of TB vaccine candidates, some of which have already entered the phase of evaluation of clinical safety and immunogenicity. One of the most urgent questions to be addressed is how to choose the vaccines to be taken forward in future phase III efficacy trials. The lack of serogate markers of protective immunity is a serious impediment to vaccine development.

The design of phase III efficacy trials will depend largely on the type of vaccine to be evaluated. Ideally, a vaccine would protect against primary infection but would also protect those who had been previously infected and reduce the risk of subsequent disease through reinfection or re-activation of the existing infection. In those areas where BCG vaccine affords protection, it appears to affect only the risk of disease due to primary infection. Much of the TB that arises globally is due to reinfection or re-activation in adults and though it clearly poses substantial immunologically challenging obstacles, the development of vaccine against these forms of disease would be an enormous advance in controlling levels of infection in the community. However, regardless of the type of vaccine, preparation of phase III clinical evaluation must begin as early as possible and a number of considerations common to most types of new TB are listed in the following sections.

Requirements for study area/population

Because of the variable efficacy of BCG, study populations will be required in several different geographical areas. The characteristics of each of the study populations should include:

- longitudinal data on tuberculosis incidence;
- relatively high rates of tuberculosis;
- low levels of migration (plan for 10 years follow-up);
- known (low) efficacy of BCG (e.g. Chingleput/India, Karonga/Malawi);
- known HIV prevalence (trials in areas of both low and high prevalence of HIV are desirable); and
- well-developed infrastructure for conducting large trials.

Trial design – decisions to be made

Questions to be addressed include:

- Focus on adult or child population (adults are preferable as they are the main source of infection and incidence rates of TB are higher)?
- Inclusion of tuberculin positive?
- Inclusion of HIV^+?
- BCG or placebo control?
- Stopping rules and assessing long-term efficacy?
- Evaluation of surrogate measures of protection?

- House-to-house or central point recruitment?
- Individual or community randomization?
- Passive or active follow-up?
- When and if to re-vaccinate?
- Surveillance for other mycobacterial diseases?

Role of WHO

WHO can play the following role:

- It can be an important "neutral" meeting ground.
- It can promote methodological developments. Examples include:
  - case-control evaluations of BCG;
  - multi-centre evaluation of reagents; and
  - standardization of products and methods.
- It can facilitate multi-location studies. Examples include:
  - case-control studies of BCG; and
  - trials of leprosy vaccines.
- It can act as ethical/safety guardian for countries without well-developed regulatory authorities.

Immediate steps

The following steps should immediately be taken:

- Make an inventory of sites/populations with potential to conduct Phase III trial – assess available data.
- Identify capacity development needs and actions required to build these.
- Develop the capacity to conduct Phase I & II studies at selected sites.
- Draft outline protocols for the conduct of Phase III trials by expert groups.
- Maintain close liaison with vaccine developers to anticipate/guide the nature of final products.
- Support selected population-based studies of epidemiology (and control) of tuberculosis.

5.5. Product profile for malaria vaccine: user views – *K. Mendis*

Product profile considerations for a new vaccine include factors such as likely impact, duration of immunity and cost-effectiveness when compared to existing interventions. In the case of malaria, with its two major types of pathogens as well as an epidemiology that varies geographically, a single product may not be what is needed.

Four groups of potential users of anti-*Plasmodium (P.) falciparum* malaria vaccine can be identified. The first three groups comprise individuals living in (a) areas of intense endemic transmission, i.e. sub-Saharan Africa, (b) areas of low to moderate intensities of endemic transmission, e.g. the Americas and Asia, and (c) areas prone to epidemics. The fourth group comprises travellers and non-immune migrant workers, and has distinct needs. Finally, *P. vivax* malaria will obviously require species-specific type(s) of vaccine. In the following the individual malaria vaccine needs of each group will be highlighted.

P. falciparum malaria in areas of intense transmission in sub-Saharan Africa is characterised by extremely high inoculation rates with disease and death predominantly occurring in young children. A vaccine should therefore reduce clinical attacks/mortality by 30% or more in African children under five years old, have a duration of immunity of three years and allow no rebound. This may be achieved by an asexual-stage vaccine that reduces blood parasite densities, e.g. even a moderately effective, "leaky" pre-erythrocytic vaccine.

Clinical attacks of *P. falciparum* malaria in areas of moderate transmission in Asia and the Americas affect adults and children alike. However, the risk of death is largely averted by vast use of anti-malarial drugs – which in turn may create a new problem, namely multidrug-resistant malaria. Such an epidemiological situation calls for a product profile that encompasses reduction of incidence of infection by at least 50% in all age groups and duration of immunity of at least three years. Both a transmission-blocking (anti-gamete) vaccine and a highly effective pre-erythrocytic stage vaccine may be able to fulfil this purpose.

In epidemic, *P. falciparum* malaria is distinguished by an extremely high transmission rate over a short period of time in a highly susceptible population. The challenge here consists in a reduction of the incidence of infection by at least 50% in all age groups. Duration of immunity of one year should be sufficient. Transmission-blocking vaccines as well as a highly effective pre-erythrocytic stage vaccine may represent adequate strategies to tackle the problem of epidemic malaria.

Finally, traveller/non-immune migrant workers as a previously unexposed target group are particularly vulnerable to *P. falciparum* disease. Here the challenge is clearly to avert extremely high case fatality by preventing the infection. This requires a vaccine that provides at least 90% protection over a short period of time – a few months to a year. The only vaccine that can afford such a product profile is a very potent pre-erythrocytic stage vaccine.

High morbidity, but not so much mortality, is the hallmark of *P. vivax* malaria, which constitutes an enormous socio-economic burden for developing nations (days of work/school lost!). The challenge consists in a reduction of the incidence of infection by at least 50% and relatively long lasting immunity – at least three

years. *P. vivax*-specific transmission blocking and pre-erythrocytic vaccines may be the way to go.

In summary, a moderately effective pre-erythrocytic vaccine may be able to alleviate a major part of the *P. falciparum* disease burden, namely that in children from sub-Saharan Africa. More effective and more sophisticated tools, however, may be required for other types of epidemiological malaria situations. The latter should include fully effective pre-erythrocytic vaccines to protect the individual and to reduce infectivity. Transmission-blocking (anti-gamete vaccines) will not protect the individual, but when used in combination with other vaccines, will prevent spread in the community and the escape of vaccine-resistant mutants.

6. Public acceptance of vaccination: research issues

6.1. SV40, polio vaccines, and cancer: research progress versus public perceptions – *J. S. Butel*

Simian virus 40 (SV40) was introduced to millions of people from 1955 through early 1963 as an unknown contaminant of polio vaccines. A polyomavirus of rhesus macaque origin, SV40 had been present in monkey kidney cultures used to prepare vaccines and had escaped detection. After its discovery in 1960, SV40 was eliminated from polio vaccines. SV40 is recognized as a potent tumour virus with broad tissue tropism that induces tumours in rodents and transforms cells from many species in tissue culture. It has been an important laboratory model for basic studies of molecular processes in eucaryotic cells, for mechanistic studies of cellular transformation and neoplasia, and for development of tools used in molecular biology and genetics.

SV40 can replicate in certain types of monkey and human cells. Infections in monkeys are normally benign, but may become pathogenic in immunocompromised animals. SV40 DNA has been identified in normal human tissues, and viral neutralizing antibodies have been detected in individuals not exposed to potentially contaminated polio vaccines. Reports are accumulating on detection of SV40 DNA in human tumours, especially mesotheliomas, brain tumours, and osteosarcomas. DNA sequence analyses ruled out the possibility that the viral DNA detected in tumours was due to laboratory contamination of samples or that the virus was misidentified. Additional studies are necessary to prove that SV40 is the etiologic cause of certain human cancers.

Dr J.A. Lednicky and I recently published an article that reviewed the status of the field. Ensuing media reports focused on the possible connection between polio vaccines and human cancer development. There was obvious public interest in whether people who received contaminated polio vaccines were at higher risk of getting cancer and whether polio vaccines today were safe. I conclude that the public has concerns about possible delayed side effects from vaccines and great interest in related health reports.

6.2. SV40, polio vaccines and similar safety concerns – *E. Griffiths*

The detection of SV40 sequences in certain human tumour tissues revived interest in polio vaccine as a possible source of human infection with SV40. Infection of primary monkey kidney cultures with SV40 in the 1950s led to the contamination of some early batches of polio vaccine. Once the problem was recognized, WHO and vaccine manufacturers introduced measures to exclude SV40 from production cultures. These included a quarantine period for monkeys and the testing of all

single harvests for extraneous agents in SV40-susceptible cell lines. This was the state of the art when introduced in the 1960s. A requirement to use only kidney cells from monkeys that were negative for SV40 antibodies was also introduced.

All polio vaccines on the market are shown to be free of live SV40 by the above procedures. Since new molecular tests are now available it was considered prudent to determine whether the current state-of-the-art polymerase chain reaction (PCR) tests supported these findings. Work was undertaken at the WHO International Laboratory for Biological Standards, the National Institute for Biological Standards and Control, Potters Bar, and the WHO Collaborating Centre for Biological Standardization, Center for Biologics Evaluation and Research, Bethesda, to test current polio vaccine seeds and harvests, as well as historical samples, for SV40 by means of PCR. The results of these studies were very reassuring and suggest that tests for SV40 given in WHO Requirements have effectively excluded SV40 from polio vaccines for over 30 years. Although SV40 sequences were detected in one sample of seed made in 1962, no SV40 infectivity was detected. This was reassuring, but it was considered sensible to recommend that SV40 sequences should be absent from seed viruses. The WHO Expert Committee on Biological Standardization at its meeting in October 1998 adopted the recommendation that seed viruses for the production of polio vaccine should be shown to be free of SV40 sequences, thus giving an additional level of security.

This testing programme has now been extended to include seed and vaccine lots requested by WHO from vaccine manufacturers globally. The study is in progress.

Concerns similar to those raised in connection with SV40 and polio vaccine have arisen over the discovery of extremely low levels of reverse transcriptase activity in virus vaccines produced in chicken cells, including measles, mumps and yellow fever vaccines. This was made possible by the use of a recently developed highly sensitive technique called product-enhanced reverse transcriptase (PERT) which allows detection of the presence of reverse transcriptase activity undetected by conventional assays. Working closely with its Collaborating Centres for Biological Standardization, other laboratories and vaccine manufacturers, WHO reviewed data and coordinated research aimed at clarifying the nature of this enzyme activity and in assessing the risk of infection in vaccinees from some unknown retrovirus. Extensive research showed no transmission of reverse transcriptase activity or productive infection and that the detected enzyme activity was associated with particles identified as incomplete endogenous retroviruses of avian origin (ALV and EAV-0). These and other data were reviewed at WHO consultations and by the Expert Committee on Biological Standardization, which concluded that the risk of vaccine-preventable disease was real and quantifiable but that the risk posed by chicken-cell derived particles was theoretical and remote. It was recommended that the vaccines should continue to be used taking account of existing WHO recommendations for their production and control. Further studies are underway to resolve such outstanding theoretical concerns as pseudotype formation with the vaccine virus.

In response to these issues and their global importance, WHO is to establish a task force to coordinate continued collaborative regulatory research relevant to the characterization, quality control and safety assessment of all cell substrates intended for use in vaccine production.

6.3. Hepatitis B vaccine and multiple sclerosis: basis and impact of the French controversy – *D. Lévy-Bruhl*

In 1994, France added hepatitis B to the infant vaccination schedule and launched a vaccination campaign in schools, targeting preadolescents in the first year of secondary school, aged 11 to 12 years. These campaigns were to be discontinued after 10 years, when the first cohort of children vaccinated during the first two years of life reached secondary school age. In France, vaccination of preadolescents was highly successful, with coverage reaching 75.0–79.4% during the first three years of the schools-based campaign. However, vaccination extended far beyond the recommended target groups, as more than 75 million doses of vaccine had been sold in late 1997, of which more than 80% were sold after 1994. More than a third of the French population has now been vaccinated. Coverage of the age group 16–20 (too old to have been covered by the schools-based campaign) had reached 80% by late 1997. In contrast, vaccination of infants was less well accepted, only reaching about 30%.

Notifications of neurological disorders resembling exacerbations of multiple sclerosis (MS) after hepatitis B vaccination led to a national pharmaco-vigilance survey being launched in 1994. As part of this survey, three case-control studies were started among adults in 1994. All data available in late 1998 can be summarized as follows:

- The above epidemiological studies neither confirm nor disprove a small increase in risk in adults.
- There is a need to consider the consequences of a possible association between Hepatitis B vaccination and first episode of central demyelinization (FECD).
- The maximal risk of FECD attributable to hepatitis B vaccination by age group is nil for infants, less than 0.3/100 000 in vaccinated pre-adolescents and less than 1 in vaccinated adults.

Although none of the statistical tests was significant at the 5% α threshold, given the consistency among the results of the different studies, the French Minister of Health asked the Réseau National de Santé Publique to conduct a risk–benefit analysis of hepatitis B vaccination. The analysis was designed to serve as a decision tool for possible revision of the vaccination strategy. The risk/benefit analysis consequently came to the conclusion that there was no reason to question the current infant vaccination strategy and that in pre-teenagers the long-term benefits far outweigh potential risks linked to vaccination. In adults, the risk of FECD, if it exists, appears negligible for high-risk individuals, and high-risk individuals/ situations had already been redefined in early 1998.

Following on the risk benefit analysis, the French Ministry of Health announced its new hepatitis B vaccination policy:

- maintenance of the three vaccination strategies (infants, pre-teenagers, adult high-risk groups); and
- change in operational modalities for pre-teenagers from school-based to individual vaccination in private practice.

The discrepancy between the conclusions drawn from the safety data analysis and the decision to move away from school-based campaigns created confusion in the media, in the public and also in the medical community. It can be assumed that this puzzlement has played an important role in the observed decrease in coverage of hepatitis B vaccination, as evidenced by a slump in vaccine sales. Fortunately, however, the negative impact, although spreading to hepatitis A vaccine, did not extend to other vaccines, e.g. those for childhood immunizations.

6.4. Immunologic evaluation of vaccines – *B. J. Ward*

The short history of vaccine development is one of extraordinary achievements. This history is also littered with modest disasters, near misses and lucky guesses. By objective measures, vaccines compare favourably with other pharmaceuticals. However, several characteristics of vaccines and vaccine use tend to stiffen resistance to vaccination.

- Most vaccines are given repeatedly to children.
- Almost all vaccines are given for prevention.
- All vaccines are inherently immunogenic.
- There is a widely held view that some infectious diseases are "natural".
- Many governments mandate the use of vaccines.

The spectrum of adverse events linked to vaccines is broad and growing. The strength of these associations ranges from definite to "creative". There is no question that vaccines may rarely harm individuals and that some of the harm is immunologically mediated. However, the search for tools to predict vaccine-associated adverse events (VAAEs), immunologically-mediated or otherwise, has proved to be enormously frustrating. To date, we know almost nothing about the pathogenesis of VAAEs. It is impossible to discuss all of the plausible immunologic consequences of vaccination since the discipline is moving so rapidly. New tools in immunology and genetics may eventually provide answers but these answers will not come quickly. Furthermore, several of the infectious agents are likely to be "gone" before we have complete answers (e.g. polio, measles). The principal points chosen for discussion are:

- Vaccines can have profound effects for months to years. This is not surprising since immune responses can be long-lived after vaccination.
- Early (or initial) antigen exposures can have prolonged consequences.
- There are few studies of the long-term consequences of vaccination (no control group!).
- Vaccine-induced immune responses may be "good" (or bad) in unanticipated ways.
- Resources (both public and private) need to be committed to the discovery and evaluation of VAAEs commensurate with the number and complexity of vaccines in use, if vaccination programmes hope to maintain public support over the long term.

6.5. The link between hepatitis B vaccination and demyelinating disease – evidence versus public perception – *M. De Wilde*

Dr de Wilde complemented Dr Levy-Bruhl's paper with a presentation summarizing the results of a number of studies regarding the link between hepatitis B vaccination and the occurrence of demyelinating disease. This presentation included the above French studies plus three studies done in the United States. One of the latter was a retrospective cohort study (134 698 people, of whom 27 229 were vaccinated; and a control of 107 469 people non-vaccinated), using the research database from six US health care plans, showing no evidence of a causal relationship between initial or recurrent attacks of CNS demyelinating disease and hepatitis B vaccination.

Results of all these studies taken together suggest that:

- the incidence of MS is no higher amongst the vaccinated population than the non-vaccinated population;
- the age distribution patterns for coincidence observations and general population are similar;
- the age distribution of reported cases of MS in hepatitis B vaccinated people is independent of the age distribution of vaccination;
- the onset of symptoms after vaccination shows no set pattern;
- there is no epidemiological evidence of an association between MS and an exposure to HBs antigen; and
- there are no experimental data to suggest that HBs antigen is involved in pathogenesis of demyelinating disorders.

Annex A: Agenda

Overview of Vaccine Research in WHO and UNAIDS, Montreux, 16-18 June 1999, Eurotel-Riviera

Wednesday 16 June

17.00–17.45	**1. Opening session**	
	Opening remarks	M. Scholtz
	Objectives of the meeting and Expected outcomes	C. Morel J. Esparza W. Gutteridge
	Introduction by the meeting Chairman	G. Nossal
	2. Learning from the past and forging the future	
17.45–18.10	**2.1** Is there a future for AIDS vaccines?	P. Johnston
18.10–18.30	Discussion	
18.30–18.50	**2.2** Malaria vaccines in the pipeline	R. Ballou
18.50–19.10	Discussion	

Thursday 17 June

	3. Exploratory vaccine research	
	Co-chairperson: Margaret Liu	
	3.1 WHO and UNAIDS involvement in upstream research: some failures and achievements:	
08.30–08.45	**3.1.1** Away from pneumococcal conjugates?	D. Briles
08.45–09.00	Discussion	
09.00–09.15	**3.1.2** Do we need vaccines against all HIV sub-types?	S. Osmanov
09.15–09.30	Discussion	
09.30–10.00	*Coffee break*	
10.00–10.15	**3.1.3** Update on edible vaccines	M. Levine
10.15–10.30	Discussion	
10.30–10.45	**3.1.4** Peptide vaccines: revisited	R. Amador
10.45–11.00	Discussion	

11.00–11.15	**3.1.5** Successes and failures with DNA vaccines	S. Hoffman
121.15–11.30	Discussion	
	Views from industry	
11.30–11.45	**3.1.6** Is there a future for DNA vaccines?	M. Liu
11.45–12.00	Discussion	
12.00–12.30	**3.1.7** WHO-Industry collaboration in upstream research: is it realistic?	R. Rappuoli
12.30–12.45	Discussion	
12.45–14.15	*Lunch*	
	4. Pre-regulatory research	
	Co-chairperson: Kamini Mendis	
14.15–14.35	**4.1** When should WHO be involved in pre-regulatory research?	E. Griffiths
	4.2 Should WHO focus on first or second-generation vaccines?	
14.35–14.50	Dengue	B. Innis
14.50–15.05	Discussion	
15.05–15.20	Leishmania	D. Sacks
15.20–15.35	Discussion	
15.35–15.50	Schistosomiasis	A. Capron
15.50–16.05	Discussion	
16.05–16.30	*Tea*	
16.30–16.45	Tuberculosis	D. Young
16.45–17.00	Discussion	
17.00–17.15	Typhoid fever	T. Pangestu
17.15–17.30	Discussion	
17.30–17.45	Preparing AIDS trials	J. Esparza
17.45–18.00	Discussion	
18.00–18.30	Views from regulatory agencies and industry	G. Schild

Friday, 18 June

	5. Post-regulatory studies and research on vaccination strategies	
	Co-chairperson: Claire Broome	
08.30–08.45	**5.1** Should cholera vaccines be used in refugee camps ?	C. Paquet
08.45–09.00	Discussion	
09.00–09.15	**5.2** Assessing the geographic distribution of rotavirus serotypes: networks	B. Ivanoff
09.15–09.45	Discussion	
09.45–10.00	**5.3** Hib and pneumococcal vaccine trials	K. Mulholland
10.00–10.15	Discussion	
10.15–10.45	*Coffee*	
10.45–11.00	**5.4** How to design future TB vaccine trials?	P. Smith
11.00–11.15	Discussion	
11.15–11.30	**5.5** Product profile for malaria vaccines: users views	K. Mendis
11.30–11.45	Discussion	
12.00–13.30	*Lunch*	
	6. Public acceptance of vaccination: research issues	
	Co-chairperson: Claire-Anne Siegrist	
13.30–13.45	**6.1** SV40, polio vaccines and human cancer	J. Butel
	6.2 SV40, polio vaccines and similar and safety concerns	E. Griffiths
13.45–14.00	Discussion	
14.00–14.15	**6.3** HBV and multiple sclerosis: basis and impact of the French controversy	D. Levy-Bruhl
14.15–14.30	Discussion	
14.30–14.45	**6.4** Immunological assessment of the risks of vaccination	B. Ward
14.45–15.00	Discussion	
15.00–15.20	Views from industry	M. De Wilde A. Shaw
15.20–15.45	*Tea*	
15.45–17.15	Outcomes of the meeting and implications for prioritization of vaccine research activities at WHO	B. Melgaard D. Heymann G. Nossal
17.15	Closure of the meeting	

Annex B: List of participants

Overview of Vaccine Research in WHO and UNAIDS, Montreux, 16–18 June 1999, Eurotel-Riviera

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* **Post meeting footnote**: Since the meeting, Dr Pangestu has taken up the post of Director, Research Policy and Cooperation, Evidence and Information for Policy (WHO).

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