2006 Report of the Steering Committee on Dengue and other Flavivirus Vaccines including Minutes of the Steering Committee Meeting

WHO, Geneva
15–17 May 2006

Immunization, Vaccines and Biologicals
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Abbreviations and acronyms

AE adverse events
AEFI adverse events following immunization
AFRIMS Armed Forces Research Institute of Medical Sciences
CBER Center for Biologics Evaluation and Research
CDC Centers for Disease Control and Prevention
cGMP current good manufacturing practices
CMI cell mediated immune response
DoD Department of Defense
DHF dengue haemorrhagic fever
DENV dengue virus
EC European Community
ECBS Expert Committee on Biological Standardization (WHO)
EPI Expanded Programme on Immunization
FDA Food and Drug Administration
GACVS Global Advisory Committee on Vaccine Safety (WHO)
GAVI Global Alliance for Vaccines and Immunization
GDP gross domestic product
GSK GlaxoSmihtKline
HIV human immunodeficiency virus
IND investigational new drug
IVR Initiative for Vaccine Research (WHO department)
JE Japanese encephalitis
MMR measles, mumps & rubella
Nab neutralizing antibody
NIAID National Institute of Allergic and Infectious Diseases
NRAs National Regulatory Authorities
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Abbreviation</th>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<td>PBMC</td>
<td>peripheral blood mononuclear cells</td>
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<td>PDVI</td>
<td>Pediatric Dengue Vaccine Initiative</td>
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<td>Pfu</td>
<td>plaque forming units</td>
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<td>PMS</td>
<td>post marketing surveillance</td>
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<td>PRNT</td>
<td>plaque reduction neutralization test</td>
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<td>QSS</td>
<td>quality safety and standards</td>
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<td>RT-PCR</td>
<td>reverse transcriptase polymerase chain reaction</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
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<tr>
<td>SC</td>
<td>Steering Committee (Dengue &amp; other Flavivirus Vaccines)</td>
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<tr>
<td>TBE</td>
<td>tick-borne encephalitis</td>
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<td>TDR</td>
<td>UNDP/World Bank/WHO Special Programme for Research &amp; Training in Tropical Diseases</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WNV</td>
<td>West Nile virus</td>
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<td>WRAIR</td>
<td>Walter Reed Army Institute for Research</td>
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<td>YF</td>
<td>yellow fever</td>
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Acknowledgements

Special thanks is given to the Chair of the meeting, Dr Allan Barrett, as well as to the rapporteur Dr Alan Rothman.
Preface

Introduction and General Objectives

The World Health Organization (WHO) Steering Committee (SC) on dengue and other flavivirus vaccines met for its annual meeting on 16-17 May 2006 at WHO Headquarters, Geneva, Switzerland. The meeting agenda was separated into scientific sessions on 16 May and the morning of 17 May, and a closed session for SC members on the afternoon of 17 May. The SC meeting followed a full day technical consultation on “Measuring Immunity to Dengue” cosponsored by the WHO Initiative for Vaccine Research (IVR) and the Pediatric Dengue Vaccine Initiative (PDVI). The outcomes of the consultation were presented and discussed at the SC meeting.

The SC meeting was opened by Dr Joachim Hombach (IVR), who introduced the SC chair, Dr Alan Barrett (University of Texas Medical Branch) and the rapporteur of the meeting, Dr David Vaughn (U.S. Military Infectious Diseases Research Program). Also, two new members of the SC were introduced: Dr Pedro Vasconcelos (Instituto Evandro Chagas, Belem, Brazil) and Dr Supamit Chunsuttiwat (Ministry of Public Health, Nonthaburi, Thailand). A full list of SC members and other meeting participants is provided in Appendix A. Meeting participants were informed of the new organigramme of the WHO department on immunization, vaccines and biologicals. Dr. Barrett briefly presented the minutes of the last SC meeting, also held in Geneva. Minutes of the meeting, as well as the agenda of the 2006 meeting were adopted by the participants.
Dr Hombach reviewed the major activities in the field of new flavivirus vaccines since the last meeting in April of 2005 and related them to the recommendations made to WHO at the 2005 SC meeting. The past year had proven to be particularly rich in activities, mainly supporting downstream efforts in relation to new JE vaccine introduction, as well as means to facilitate the evaluation and testing of dengue vaccines. More specifically, the key activities included:

- a Southeast Asia Region/Western Pacific Region/Program for Appropriate Technology for Health (PATH) bi-regional meeting on Japanese encephalitis immunization (JE);
- the publication of WHO JE surveillance standards as a field test version;
- a review on JE vaccine safety at the WHO Global advisory committee on safety of vaccines;
- a review of JE immunization at SAGE;
- the publication of the rationale for using correlates of protection for JE vaccine evaluation, and the endorsement of correlates of protection for induced by JE vaccines through the Expert Committee on Biological Standardization (ECBS);
- a technical consultation on correlates of protection for dengue vaccines;
- the annual meeting of the WHO task force on clinical trials of dengue vaccines;
- the funding of two new projects on developing live, attenuated dengue virus vaccines;
- an ECBS review of dengue reference reagents;
- new efforts on measuring dengue virus neutralization (in conjunction with PDVI); and the initiation of a review of clinical trial guidelines for dengue vaccines.
2. Dengue Vaccines – Measuring Immunity

2.1 Report from a workshop on Correlates of Protection for Dengue Vaccines

Dr A. Barrett gave a presentation on a workshop on correlates of protection induced by dengue vaccines, which was held 17-18 November 2005 at WHO Headquarters, and was supported by PDVI. The goal of the meeting was to identify potential primary and secondary correlates of protection. The Center for Biologics Evaluation and Research [CBER, US Food and Drug Administration (FDA)] definition of immune correlate of protection was used for the discussion, which reads “A predictor of vaccine efficacy based on a particular type and quantity of immune response associated with protection from disease or infection”. A draft meeting report was presented to the SC, and which will be published under separate cover. It was noted that any measurable level of neutralizing antibody (NtAb) has been correlated with protection for all licensed flavivirus vaccines [Yellow fever (YF), JE, and tick-borne encephalitis (TBE)]. The following evidence suggests that NtAb will also serve as a correlate of protection following dengue vaccination: 1) lifelong protection from repeat dengue disease with a single dengue virus (DENV) serotype is associated with long term detection of NtAb; 2) maternal dengue NtAb protects their infants from disease during the first months post-partum; 3) passive Ab transfer protects mice from challenge, and 4) NtAb elicited by dengue vaccination in monkeys correlates with protection from viremia. However, the tetravalent nature of dengue vaccines, the cross-reactive nature of elicited Ab, and the issue of antibody-dependent immune enhancement makes assessment of NtAb as a correlate of protection more complicated than for other licensed flavivirus vaccines. There is indirect evidence for the importance of cell mediated immunity (CMI) in protective immunity for dengue. It is important to better evaluate the roll of T cells in protective immunity as T cells seem to be associated both with protection and severe disease, as are cross-reactive NtAb. A comprehensive list of potential correlates was presented and the concept of multifactorial correlates was addressed. The following recommendations came out of the November meeting: (a) clinical trials of vaccine candidates, especially population-based studies and “proof of concept” trials should be systematically used to assemble a large quantity of immunological data on volunteers pre- and post-vaccination; (b) in addition to serological data, CMI should be assessed to establish databases on immunological profiles that will allow the assessment of protection, vaccine failure and severe disease; (c) in order to increase the comparability of data obtained from different studies, assays, and in particular the plaque reduction neutralization test (PRNT) should be harmonized, and specific action should be taken towards that goal; (d) prospective cohort studies should assemble information on susceptibility to and protection from natural disease; (e) antibody responses should be further characterized, including their specificity and kinetics; in that context, the human challenge model should receive further support and more studies should
be conducted. Finally, participants encouraged WHO to seek a dialogue with public health decision-makers and national control authorities in disease-endemic countries should be sought to clarify desirable target product profiles, and to start the discussion on criteria for licensing and post marketing surveillance. WHO should work in partnership with PDVI, vaccine developers and other stakeholders towards a better characterization of correlates of protection.

Discussion: Dr Frank Ennis (University of Massachusetts) felt that large Phase 3 or proof-of-concept Phase 2b trials may not be the best time for detailed analysis of new assays as potential correlates, though peripheral blood mononuclear cells (PBMC) should be collected from all volunteers at early time points to allow laboratory evaluation of rare events. The more suitable time for more intense sample collection, testing, and analysis may be smaller Phase 1 trials and experimental challenge studies. It was also felt that an oversight committee may be needed to comment on the use of limited specimens collected during field efficacy trials (sampling). It was pointed out that some vaccine developers had started to systematically measure immune responses to dengue vaccines, also with a view on screening for correlates. Overall, the recommendations were endorsed by meeting participants.

2.2 Report from the meeting of the WHO Task Force on Clinical Trials of Dengue Vaccines

Dr F. Ennis presented the minutes from the meeting of the WHO Task Force on Clinical Trials of Dengue Vaccines held in Washington, DC on 11 December 2005. The task force reviews new developments related to dengue vaccine development, with emphasis on candidates being in clinical evaluation. Several commercial and academic vaccine developers presented new findings, which are summarized in a report published under separate cover. The task force meeting concluded with a general discussion on common issues and obstacles to successful vaccine development, which triggered some recommendations for action. Among the key outcomes, Dr Ennis mentioned the following points. Overall, the task force meeting was considered a very successful venue for interaction among vaccine developers. Participants recommended the establishment of additional communication platforms including IVR, PDVI, Special Program for Research and Training in Tropical Diseases (TDR), and vaccine manufacturers. It was also suggested to give consideration to improve information sharing by means of continuing electronic commentaries (e.g. a password protected web portal to post neutralization test information and protocols). The validation of immunological assays and their harmonization in order to allow comparison of data between trials was considered a priority. Towards that goal, panels of sera should be established suitable for dengue neutralization test validation. To achieve harmonization, a guidance document on the dengue plaque reduction neutralization test (PRNT) should be produced. For the purpose of these planned activities, an ad hoc committee should be constituted with strong representation of vaccine developers. Also, the development of calibrated international reference reagents remains a priority and should be pursued together with the efforts on assay validation and method harmonization. While no formal collaboration on innovative assays, such as high throughput assays has been recommended, regular review of progress in this field should be conducted. Finally, there was a discussion of the prime boost vaccination strategies that was considered informative, but no specific recommendations could be made at that time. Progress in that area should be reviewed regularly.
Discussion: There were questions in relation to acceptable levels of viremia following live-attenuated vaccination and about the probability of recombination with naturally encountered DENV. Dr Ennis replied that decreased viremia in monkeys compared to parent strain DENV has been identified as a possible marker of attenuation for vaccine use in people. It was also noted that increased reactogenicity seen among volunteer recipients of the Vero cell-derived DENV-3 vaccine was associated with viremia titers of 3 to 5 log_{10}. Less than 3 log_{10} of viremia has been associated with a good reactogenicity profile. Viremias peak at 5 to 6 days post vaccination and the levels are considered too low to infect mosquito vectors. Recombination between vaccine virus and wildtype virus was considered unlikely, and a recent exchange on the topic in the scientific literature had corroborated this view.

2.3 Short Updates on Vaccine Development

Vaccine developers were given short slots to update on recent achievement on dengue vaccine development since the 2005 task force meeting.

Dr Jean Lang (SanofiPasteur) summarized clinical studies of the Acambis ChimeriVax-Dengue vaccine candidate. New formulations have been produced of 5 log_{10} plaque forming units (pfu) per virus strain, which are being given at 0 and 105 days, with a booster dose at 365 days. Age step-down pediatric trials down to the target age of 2-5 years in endemic countries (Mexico City and Manila) are under way.

Discussion: Trials started earlier this year and no severe adverse events have been reported to date in adults and adolescents. No prescreening for flavivirus Ab is being done though Ab-positive volunteers are expected to be rare in Mexico while representing approximately 20% of volunteers in the Philippines. Control vaccines will be YF in Mexico and typhoid in the Philippines. Primary vaccination is being given at 0 and 3 months as it was shown that 0 and 1 month was too close and that 0 and 6 months works well; 3 months represents a compromise in the attempt to decrease the vaccination interval. Blood will be collected every other day to assess viremia following vaccination. A third dose of vaccine may not be needed but will be assessed. The observation time after boost will be five years. Children age 2-5 are being targeted for vaccination. It is understood that vaccination for other flaviviruses and natural exposure to flaviviruses may complicate interpretation of results.

Dr Bruce Innis (GlaxoSmithKline - GSK) described status of the GSK live-attenuated tetravalent vaccine 9 years into the collaboration with Walter Reed Army Institute of Research (WRAIR). In December 2005, a new investigational new drug (IND) representing new vaccine seeds obtained through transfection of cells with viral RNA was submitted. A Phase 1 trial in adults began in April 2006 among 25 volunteers using the re-derived vaccine. There has been no severe adverse events though a mild drop in white blood cells and rash has been seen as is typical for the vaccine. Dosing is at 0 and 6 months and included mosquito feeding. Larger trials will start this year in the Americas and Asia.
Discussion: The vaccine viruses were reformulated as not all documentation from original formulation in the 1970s and 1980s is available so that the risk of transmissible spongiform encephalopathy cannot be fully ruled out. This was discussed with CBER who felt transfection was an acceptable approach to eliminate this risk and preclinical studies suggest that the quasispecies nature of the vaccine has been maintained. Vaccine dosing (serotype titers) remains proprietary.

Dr Steve Whitehead (US National Institute of Allergic and Infectious Diseases - NIAID) reported that all four monovalent candidate vaccines have been made according to cGMP. Phase 1 clinical trials for DENV-4, DENV-1, and DENV-2 have been completed. The Phase 1 trial for the DENV-3 vaccine (a DENV-4/3 chimera) will be completed this summer before proceeding with tetravalent vaccine clinical trials. Concurrently, second generation vaccines (point mutations to decrease ALT elevations) will begin. Dosing is at 0 and 4-6 months. Low level viremias (< 1 log pfu) are seen following vaccination.

Dr Beth Ann Coller (Hawaii Biotech Inc.) reported that GMP production of the recombinant DENV-1 component is underway with production of DENV-2, 3, 4, and NS1 to follow. The vaccine will be formulated with a new adjuvant. New monkey trials are underway at WRAIR. A pentavalent vaccine Phase 1 trial is anticipated to start in 2007.

Discussion: Vaccine will be produced without adjuvant, and adjuvant will be added at the time of injection to allow an assessment of vaccine:adjuvant ratios. Dengue virus vaccine components will be equal with one tenth the dose of NS1 to provide a balanced immune response. Antibodies elicited following vaccination persist for at least 5 months in monkeys prior to successful resistance to wild-type virus challenge (small drop in levels over that time). A new adjuvant is being used due to business considerations, including a merger with an Australian company that resulted in the acquisition of GPI100, a highly detoxified saponin-based adjuvant used in cancer vaccines. In current monkey studies, animals challenged with and protected from all four DENV serotypes. Nt Ab data are not yet available though boosts in NtAb following challenge are expected.

2.4 Validation Panels for Neutralizing Antibody Assays: Rationale, Plans, and Progress Report

Dr Harvey Artsob (Canada Public Health Laboratory) summarized a discussion on producing a validation panel for NtAb assays to be used by vaccine developers that took place the day before on 15 May 2006. The panel will be used as an assay validation panel for new and existing assay systems. The exercise could later on be expanded towards the provision of proficiency panels, and the establishment of an international reference reagent for dengue. That activity follows a request from vaccine developers and will be implemented jointly with PDVI. Dr Artsob has agreed to coordinate the initial phase of the exercise. Serum from monotypic (DENV-1, 2, 3, 4) and polyvalent (following a secondary or tertiary DENV infection) infections will be obtained and characterized along with negative control serum and non-DENV flavivirus serum for JE, YF, and West Nile virus (WNV). The non-DENV flavivirus portion of the panel may be developed after the DENV and negative control portion of the panel. While the precise composition of the panel will require some more consultation, it was proposed to generate some 20 sera, including half
from dengue vaccinees and half from naturally infected patients. Serum should be obtained in large volumes from a limited number of donors, probably through plasmaphoresis. Potential volunteers could be found at Johns Hopkins University for dengue, WRAIR for dengue and JE, and SanofiPasteur for YF, together with serum from patients with secondary DENV infections at the Dengue Branch, Center for Disease Control and Prevention (CDC) in San Juan, Puerto Rico and Mahidol University, Salaya Campus, Thailand. Serum will be quality controlled, aliquotted and stored frozen. Issues regarding the serum bank governance, access and shipment of samples need to be developed.

2.5 Guidance for Neutralizing Antibody Assays: Rationale, Plans, and Progress Report

Dr John Roehrig (US Centers for Disease Control, Ft. Collins) summarized a discussion of developing guidelines for NtAb assays held the day before on 15 May 2006. This activity is linked to the production of sera panels, and has also been recommended as an activity to increase comparability of results obtained from dengue neutralization assays. At the request of WHO, Dr Roehrig has called for a working group, that has been providing input into the production of guidelines since January 2006. The group included representatives from Hawaii Biotech, SanofiPasteur, Acambis, US CDC, US Department of Defense (DoD), US NIH, and Mahidol University, Thailand along with other consultants. The purpose of the document is to offer a standardized assay, to promote harmonization across assays, and to anticipate the development and use of new NtAb assays (microneutralization assays to accommodate large numbers of specimens requiring testing). Information on the current test protocols was gathered from ten laboratories and 19 test parameters were compared. The similarities and differences of the assays were reviewed. A draft outline of a guidance document was prepared and presented by Dr Denis Crevat (SanofiPasteur), which proposed to standardize a greater number of parameters. Based on the discussion at the meeting, Dr Roehrig will produce a second draft of the guidance over the next 2-3 months for consultation among the working group. Ultimately, the draft should go through a larger peer review and should be endorsed by the WHO Expert Committee on Biologicals Standardization (ECBS).
3. Clinical Evaluation of Dengue Vaccines

3.1 WHO Approaches in Relation to Guidance and Strengthening Regulatory Capacity

Dr David Wood (WHO/QSS) presented approaches and strategies to strengthen national regulatory capacities, as well as the role and function of WHO in relation to vaccine regulation. National Regulatory Authorities (NRAs) need to assure the quality of vaccines (quality, safety, efficacy). To comply with WHO-determined functions, they need to follow written regulatory documents such as those provided by the WHO, and exercise up to six critical regulatory functions [licensing, post marketing surveillance (PMS) for adverse events following immunization (AEFI), lot release testing, laboratory access, regulatory inspections, and authorization and monitoring of clinical trials]. Not all six of these functions are needed if vaccines are WHO prequalified and purchased from outside the country or if vaccines are provided by a United Nations (UN) agency such as United Nations Children’s Fund (UNICEF) or the Pan American Health Organization (PAHO). WHO prequalification provides UN purchasing agencies with independent advice on the quality, safety, and efficacy of vaccines for purchase. The WHO assesses NRA’s for compliance with critical functions. Many countries (200) have been evaluated with several, including the US, scheduled for review in 2006. New challenges include vaccine producers marketing directly to developing countries without first licensing in developed countries and the quality of clinical trials run in developing countries; these are currently a priority for WHO. A developing country vaccine regulators network has been established to promote assess capabilities in developing countries and encourage harmonization of standards between NRA’s. The forthcoming meeting (November 2006, Indonesia) was proposed for the discussion of evaluation and registration of new JE vaccines. The Global Advisory Committee on Vaccine Safety (GACVS) is a WHO initiative to monitor new vaccines from a safety perspective. Issues reviewed have included thiomersal, MMR and autism, and the safety of YF vaccines with findings published through the WHO Weekly Epidemiological Record and on the GACVS website at www.who.int/vaccine_safety/en/.

Discussion: The presentation was considered very useful, helping to put activities pursued by the SC into a wider perspective. It was stressed that WHO is not a regulatory agency, and prequalification of products are a required label for UN procurement, and are also required for GAVI financing. Prequalification is both a quality label but also assures that products are suitable for use population-based use in developing countries. If not prequalified, the product is not eligible for procurement, but no statement on the product’s quality is made. Besides the product qualification, the process of prequalification and the accompanying training is a major
contributor to the strengthening of NRA’s. It was also noted that prequalification is a time-limited label and it can be withdrawn for safety reasons. The work of the flavivirus vaccine SC supports the NRAs through the science base and the input into guidelines. NRAs are assessed by WHO audit teams that use checklists to assess compliance; this is used as a tool to strengthen NRAs if there are gaps. It was also mentioned that clinical trials are increasingly being conducted in countries without functional NRA, and hence there is no proper approval and/or oversight of the trials. WHO is trying to strengthen the capacity of NRA’s to assess trial protocols, and will encourage NRAs to assume its function as an oversight body. Ideally, trials should not be conducted in countries that cannot assume that function.

3.2 Public Health Expectations from Disease-Endemic Countries in relation to Dengue vaccines (Vietnam/Thailand)

Dr Tien Nguyen (Institut Pasteur, Ho Chi Minh City) opened this agenda item by discussing dengue in Vietnam and expectations for future vaccine testing and implementation. This public health perspective on dengue vaccines was requested to set the stage for the subsequent discussion on guidelines for dengue vaccines trials (item 4.3, see below). While the case fatality rate of dengue has decreased in Vietnam, dengue hemorrhagic fever (DHF) remains a leading cause of death in the south of Vietnam. Most (82%) of DHF cases are in the south and the mean age is increasing. It was speculated that this might be due to decreased disease incidence as a consequence of mosquito control efforts. Prospective dengue field trials are being conducted in An Giang and Bien Hoa provinces. Investigators are looking at infection and disease incidence, evaluating active and passive case finding approaches, and evaluating case definitions including the WHO grading classification. These are promising dengue vaccine test sites, and there is great interest to host dengue vaccine trials.

Discussion: There was some discussion in relation to case classification. Most suspected cases with significant bleeding are categorized as DHF with or without evidence of plasma leakage. Dr. Halstead pointed out that the key to classification, the gold standard, should be plasma leakage according to WHO criteria, certainly for scientific studies such as the study in An Giang.

Dr Chunsuttiwat reported that dengue remains a child killer in Thailand. As in Vietnam, the mean age is shifting to older children. The co-circulation of JE virus leads to challenges in the laboratory due to cross-reactive antibody and the presence of chikungunya complicates clinical diagnosis. Vector control has evolved but is still not successful due to an absence of proven methodologies and a lack of resources. Vector control will need to continue even if a vaccine is being introduced, in order to control chikungunya and to minimize the risk of YF introduction or DENV re-introduction from sylvatic cycles. Training in careful case management has lead to dramatic reduction in mortality. Thailand expects to participate in vaccine field trials as it expects to benefit from successful vaccines and it will help in capacity building. There are technical and ethical concerns about coming trials; the NRA will be involved in trials and importation of vaccine. Affordability and availability of vaccine will be important issues; multiple suppliers and local production will reduce risk. Thailand will continue to build capacity in anticipation of clinical trials.
Discussion: It was clarified that the NRA is a part of the Ministry of Public Health. The most expensive vaccines in the Thai Expanded Programme on Immunization (EPI) are JE, Hepatitis B, and MMR with costs of $1-2 per dose; dengue vaccine would need to be in this range. The Government pays for 95% of basic immunizations as a public health measure (EPI vaccines are also free in Vietnam). Dengue vaccine would best fit in early childhood as a part of the EPI with a booster dose in an older age group if needed. It was speculated if increased JE vaccination might account for the shift of dengue to older children. Vietnam and Thailand each have two field sites ready, or nearly ready, for dengue vaccine efficacy testing (An Giang and Bien Hoa in Vietnam and Kamphaeng Phet and Ratchaburi in Thailand). Some of these sites may also be useful as Phase 4 effectiveness sites.

3.3 Revisiting Guidelines on Clinical Evaluation of Dengue Vaccines

Dr Robert Edelman (University of Maryland) reported on progress to update draft guidelines for the clinical evaluation of dengue vaccines in dengue-endemic populations. A old version of that document was produced by TDR (http://www.who.int/tdr/publications/publications/dengueguidelines.htm). The need for an update of that document was identified by the WHO task force on dengue vaccines, and was considered imminent as several dengue vaccine candidates are now scheduled for population-based clinical trials. The scope of this document is to assist NRAs, but also vaccine developers, in planning and assessing dengue clinical trials in disease-endemic countries. For the purpose of the update, a group of stakeholders, composed of academic experts as well as vaccine developers, had been conveyed by Dr Edelman prior to the SC meeting, to provide views on the most important elements to be addressed in the revised guidelines. The specific comments were presented at the SC meeting to open a plenary discussion on content and process.

Discussion: One major discussion item was on case definitions needed for field efficacy trials. An effort to evaluate case definitions in the Americas as compared to Asia, coordinated by TDR with support from the European Community (EC), is under way and was discussed later in the day by Dr. Guzman (see item 4.4). The difference of clinical presentations between the Americas and Asia was highlighted. It was noted that the WHO classification is very strict and that many endemic areas do not have the equipment or trained personnel to implement. It was also considered to categorical, and often severe cases are found without signs of hemorrhage. It was agreed that caretakers need management guidelines rather than a strict classification scheme, and that physicians need criteria for early triage. However, it was stressed that a case definition for a clinical trial might not need to be the same as the one used in public health practice. The case definitions for trials must be unequivocal and be validated, they should be uniform in order to compare data across trials. Moreover, it is desirable to link them to distinct health outcomes in order to be able to measure health impact of interventions. Most likely, the primary endpoint for efficacy studies will likely be mild disease with laboratory confirmation to allow feasible sample sizes. Vaccine prevention of severe disease will be conducted as a secondary endpoint; it will be important to know how well vaccine does to prevent severe disease. Current surveillance efforts, passive and active, are important and case definition validation is vital. It was suggested that Phase 4 discussion should be in a separate chapter. Also, the indirect benefits of vaccination should be considered (i.e. community benefit or herd immunity).
A working group was identified to advance the guidelines led by Dr. Edelman with membership including Drs. Anna Durbin, Frank Ennis, Duane Gubler, Maria Guzman, Scott Halstead, Eva Harris, Bruce Innis, Jean Lang, Lew Markoff, Jose Rigau, Arunee Sabchareon, Wellington Sun, and David Vaughn. A draft will be circulated by Dr. Edelman for editing through the summer with a meeting possible in September.

3.4 Dengue Classification and Detection

Dr Maria Guzman (Istituto Pedro Kouri, Havana) presented an overview of a large collaborative project (“DENCO”) on dengue which is financed by EC. Overall, some nine institutions are participating, covering the American and Asian region, and overall scientific coordination is with TDR. The project is grouped into work packages which have the following objectives: (1) Gain new knowledge on pathophysiology relevant both to improved clinical management and to vaccine development; (2) Clarify the clinical distinction between mild and severe dengue by developing an evidence-based prospectively generated classification scheme; (3) Develop and test clinical management guidelines and hence reduce morbidity and mortality; (4) Assess novel vector control tools to reduce vector densities below epidemic threshold levels; (5) and Assess and document the timely translation of research findings into policy and practice. Work package 1 includes virological and immunological studies with the main of linking virological features with clinical outcomes. Virus isolates will come from work package 2, and it is anticipated that some 500 isolates, from both regions, will be fully sequenced. Work package 2 includes research on dengue classification and case management in the form of a prospective study. Work package 2 also includes validation of two NS1 diagnostic kits. In the first year, a prospective, hospital-based study is being conducted. Patients older than 6 months of age with less than 7 days of fever and with suspected dengue will be enrolled. The gold standard for severity will be the degree of medical intervention. In the second year, findings will be used to revisit the WHO clinical guidelines and case classification system. It is anticipated that the drafting and peer review process to establish new guidelines will be completed by 2008.

Discussion: The need for standard procedures was emphasized to ensure that enrollment of “suspected dengue” leads to similar cohorts at the different sites. There are protocol defined definitions of “intervention”. It was clarified that these studies should help to build the evidence to critically review, and possibly adapt the existing WHO guidelines for case classification and management. Lab capabilities will vary by site; some will have access to nearly real-time diagnosis. Enrollment as late as 7 days will decrease virus isolation rates though it will allow a thorough testing of NS1 antigen detection kits (BioRad and PanBio). Mortality is an outcome measure though it was questioned how this would be used is half of deaths are iatrogenic due to fluid overload (at least in Southeast Asia). Three thousand cases are anticipated to be enrolled during the first year. Improved guidelines will be critical not only for case management, but also for comparing disease burden estimates and for defining proper and relevant endpoints for the assessment of vaccine and drug candidates.
3.5 TDR/PDVI Dengue Acute Phase Diagnostic Study

Dr José Pelegrino (WHO/TDR) reported on progress towards a comparative study to assess commercial acute phase dengue diagnostics. A dengue serum specimen bank has been established by TDR and PDVI for the purpose of providing specimen panels to facilitate diagnostic test development, evaluation, and quality assurance. A dengue diagnostics workshop was held on 4-6 October 2004 in Geneva, Switzerland with a subsequent working group meeting 25-26 July 2005 in Winnipeg, Canada with a follow-up meeting 8-10 February 2006 in Bangkok, Thailand. The evaluation of IgM tests was identified as a priority, even though new antigen-based tests should also be studied. Specimens will be donated and maintained in eight network sites in seven countries. Panels will be prepared and stored at reference laboratories. Proficiency testing of the reference laboratories has been completed. A seven-member SC has been established that will (1) review proficiency test results from reference and evaluation laboratories; (2) review progress in panel development; (3) decide which laboratories in the network will evaluate which tests; (4) review evaluation results and recommend dissemination and (5) resolve problems related to the specimen bank and the network, and call meetings of the network as necessary. A specimen panel composition has been proposed (200 for sensitivity, 150 for specificity). There are seven companies participating in the first round of assay evaluation. There is currently 100% concordance between results at the two reference laboratories. Proficiency evaluation of the evaluation laboratories is under way. Findings from the evaluations of kits on the market will be published jointly by TDR and PDVI, and companies will be identified.
4. Partner Activities

4.1 The PDVI Strategic Plan

Dr Duane Gubler (University of Hawaii) presented on behalf of PDVI, and in his function of chair of the Board, their interest is to foster “public-private product development partnerships” with the goal to accelerate the evaluation and introduction of dengue vaccines for use in developing countries. While the goals of PDVI have not changed, there has been some reprioritization of objectives that include formation of strategic partnerships, supportive research and development, vaccine evaluation, and vaccine access. Public sector partnerships include WHO/IVR, WHO/TDR, US Army/Navy/CDC/NIH, Mahidol University, Pedro Kouri, Taiwan CDC and others to include ministries of health. Supportive R&D includes diagnostics development for correlates of protection and severe disease and standardization of assays for the diagnosis of acute infections. Vaccine evaluation efforts include the development of a consortium of field sites for efficacy and effectiveness testing and contributing to guidelines for vaccine evaluation. Vaccine access efforts include disease burden measurements, cost-effectiveness studies, and vaccine recommended use practices that might influence vaccine purchase and use by national authorities.

Discussion: It was noted that there is an increased emphasis on product development. However, there remains a knowledge deficit to understand protection at the molecular level that requires further study. In that context, it was mentioned that PDVI has attracted new talent to the dengue field, and that a network was being established that deserved further support. In fact, the next investigators network meeting is scheduled for early June in Virginia. It was noted that PDVI has many mid-term objective yet short-term funding (2008). Donors have advised PDVI to plan for the future.

4.2 US NIAID Dengue Programme

Dr Patricia Repik (US NIAID) reported that while NIAID has traditionally funded basic research, there has been a new emphasis over the past five years to look for more industry input and to fund product development. The NIAID does in-house flavivirus vaccine development work on dengue, WNV, and TBE. Within the Division of Extramural Activities, six dengue projects are funded (recombinant subunit, virus-like particles, replicon, and DNA vaccines), three WNV projects (recombinant subunit and attenuated), one JE vaccine project, and one TBE project (recombinant subunit vaccine). Each of these projects was outlined. NIH has 5 current program announcements that will further develop flavivirus vaccines.
Discussion: The likelihood of funding for these programs is similar to the overall current 14% funding rate. The University of Massachusetts PO1 grant was not included in the list of funded projects but has contributed significantly to the field. Proposals can be submitted from overseas particularly if they offer research opportunities not possible in the US. There is not special incentive for pediatric grants. Flavivirus grants make up a small subset among all research areas funded.
Dr Barrett provided an overview on the current discussion on YF vaccine safety issues, and in particular on the rare viscerotropic and neurotropic adverse events. The YF vaccine is one of the most efficacious vaccines available today. Initially introduced in the 1930s, and likely conferring a lifelong protection from a single dose, the vaccine has overall shown an excellent safety profile. There has been reporting of occasional severe adverse events, and the vaccine associated neurotropic disease has been long recognized, with some 26 cases since 1945 (16 in infants under 7 months of age leading to the recommendation not to use in infants under 9 months of age). All cases have been in primary vaccinees, with a risk calculated at 0.3 per 100,000, the case fatality rate is below 5%. In contrast, vaccine associated viscerotropic disease has been recognized only since the 1990s with 26 cases showing 50% mortality and a risk of 1.6 per 100,000 immunizations. These vaccinees develop a classic YF disease. Vaccine genome sequences has been recovered from patients, and do not point towards reversion mutations. All cases have been observed in primary vaccinees, and the risk seems to be highest in people above 60 years of age, and in individuals with depressed T cell immunity (i.e., thymectomized). Host genetic factors may contribute to the adverse outcome. There have been 3 cases reported in 2004 and 2005 (US military, Spain, China). The CDC has a registry and it is clear that in most cases for travelers the risk of disease is much higher than the risk of significant AEFI as incidence rates remain high in endemic areas. More research is needed, also into the safety of vaccinating HIV infected individuals. There is also a need to strengthen the safety database from use of the vaccine in disease endemic countries, where the vaccine still has a paramount public health importance.

Discussion: It was stated that the vaccine is only 50% effective in HIV patients but no increased risk from vaccination has been observed. It is unknown what genetic difference in the host predisposes to severe AEFI; perhaps a deficit in innate immune responses for YF. The rate of serious AEFI in endemic areas is unknown; none have been reported. In the Ivory Coast, 2.6 million doses of vaccine were given but no serious AEFI were identified. However, the sensitivity of the AEFI reporting might not have been appropriate.
6. Japanese Encephalitis

6.1 Report from SAGE

Dr Chunsuttiwat reported from the last meeting of the Strategic Advisory Group of Experts (SAGE). SAGE was established by the Director-General of WHO to provide guidance on the work of WHO in relation to immunization, vaccines, and biologicals. At its meeting on 10-11 April 2006, SAGE had a dedicated session on JE immunization at the request of WHO Regions, in order to provide advice in relation to JE immunization, surveillance and related laboratory work. Background to this request is the increased interest by JE endemic countries in the Region to strengthen JE immunization, and to introduce the live, attenuated SA 14-14-2 vaccine. SAGE acknowledged the public health importance of JE in the Asia Pacific region and recommended that surveillance be improved and increased. SAGE acknowledged that significant work has been conducted on the evaluation of the safety and efficacy of the SA 14-14-2 vaccine. The JE Program at the Program for Appropriate Technology in Health (PATH) was commended for its work to confirm the target product profile, to address safety questions highlighted by the GACVS, and for its collaboration with the manufacturer towards submission of a dossier for vaccine prequalification. The negotiation of a special public sector price was applauded. SAGE recommended that if countries plan for introduction of that vaccine, they have to assure the proper regulatory oversight that should be given to vaccines that are important bilaterally. In the longer run, the desire was expressed that the vaccine should become prequalified. SAGE also recommended that the WHO position paper on JE immunization should be updated.

6.2 SA 14-14-2: Confirming the Target Product Profile

Dr Mansour Yaïch (PATH) overviewed clinical trials activities related to confirming the product profile for the SA 14-14-2 live-attenuated JE vaccine. PATH has partnered with the Chinese manufacturer Chengdu Institute of Biological Products to answer several remaining questions in order to confirm the target product profile of a single dose given to infants at 9 months of age, concomitantly with measles vaccine. Towards that goal, a trial in the Philippines will establish immunological and safety non-inferiority of JE vaccine given with measles vaccine; a clinical report from this 600 infant study is expected in August 2006. A site in Sri Lanka has been selected to see if those children who have already been vaccinated with inactivated JE vaccine can be boosted with SA 14-14-2; protocol development is underway for 400 volunteers. Site selection is underway for a study to look at antibody responses following JE vaccination in subjects with preexisting dengue antibody.
Following the licensure of SA 14-14-2 in India in February 2006, the Indian authorities have requested a couple of additional studies. This includes a viraemia study in 24 healthy adults following vaccination, and a small scale post marketing surveillance study. The protocol for the post marketing surveillance safety study in 1000 volunteers should receive final approvals in May for the start of enrollment in June 2006.

Discussion: For the viraemia study, volunteers will be screened for dengue, JE, and WNV; JE is not known to circulate in the study state. Virus will be isolated from blood in Vero cells and RT-PCR will be performed on blood also. There are no plans for isolate sequencing but specimens will be archived. The vaccine virus has previously been shown not to replicate in mosquitoes. A Korean study showed that SA 14-14-2 does boost the priming with inactivated vaccine, though that study enrolled limited numbers of volunteers. While levels of NtAb are low after a single dose, recipients boost well and may provide a lifetime of protection. There will be 11 years of follow-up after one dose to look at long-term protection in China, and data from Nepal are expected to become available soon (5 year follow-up); if NtAb levels drop, volunteers will be vaccinated again to look for anamnestic NtAb response.

6.3 SA 14-14-2: Vaccine Introduction in India and Strategies for Post Marketing Surveillance

Dr Paul Francis (WHO India) discussed the strategy for introduction of the SA 14-14-2 vaccine in India. The 2005 seasonal epidemic of JE accounted for 6584 cases in India, including 1765 deaths reported from 11 states. Recommendations of the National Technical Advisory Group in favor of JE immunization were released in October 2004 and March 2006. So, far JE immunization has been limited to some high-risk districts in Andhra Pradesh, and indigenous vaccine production has been low. New vaccination strategies will be based on imported SA 14-14-2 vaccine. The vaccine has been granted a time-limited special license by the drug controller of India for that purpose. Vaccine will be phased in between 2006 and 2009 due to limited availability of vaccine. There will be a one-time targeting of all children 1-15 years of age with subsequent introduction of the vaccine into the universal immunization program. The successful implementation of the campaign (12 million doses) will be taken as a decision point for introducing vaccination into routine programmes. Dr Francis provided some additional details on the post marketing surveillance study, which will cover children of 1-15 years of age, with active follow up on days 1, 7, 14 and 28. Additional studies as discussed in the previous presentation are planned along with strengthening of the AEFI detection program. For AEFI, a First Information Report will be submitted within 24 hours followed by a Preliminary Investigation Report within 7 days and a Detailed Investigation Report within 3 months. This will be a challenge when administering 30-40 million doses a year.

Discussion: It was clarified that the Chinese manufacturer has made a commitment to provide adequate amounts of vaccine per plan. The 1000 children safety data may not be available before the vaccine is included in the routine immunization programme in the identified districts. There was some discussion on the sample size, and it was stressed that the size of 1000 is based on logistical capabilities and is not intended to identify rare serious adverse events; instead, authorities will depend on the routine AEFI reporting system for that. There is ongoing effort to link the PMS study to the
AEFI by using the same reporting forms. The India NRA have requested animal
toxicity studies; results are expected in early June 2006. While a WHO
prequalification file is being put together, a country may bilaterally license the vaccine
and assure safety and quality using its own control authorities, as it has been the
decision of India. Vaccine technology transfer from China to India is not anticipated.
NtAb will be assessed at the National Institute of Virology in India. China has agreed
to price concessions for export to countries with a GDP less than $1000.

6.4 Planned WHO Network of Sentinel Countries for AEFI Surveillance

Dr Adwoa Bentsi-Enchill (WHO/QSS) reported on a network of sentinel
countries for PMS with emphasis on monitoring the safety of newly introduced
vaccines. Only 35% of 192 Member States have a functioning AEFI program
(all 27 industrialized countries and 41 non-industrialized countries though 15 of
those require external support). A collaboration with PAHO established a 5-country
network in March 2006 with 5 new countries anticipated by the end of 2006 with an
initial focus on rotavirus vaccines. They will use a “stimulated passive surveillance”
approach combined with active sentinel surveillance using the network protocol and
private and public sector health facilities to search for selected AEs and serious AEs.
Appropriate denominator data (doses given) will be important. Surveillance will
continue for 2-3 years following the introduction of each new vaccine. Implementation is expected in the fourth quarter of 2006.

Discussion: While the system is currently vaccine specific and operates on the
basis of specific PMS protocols, just having a network will help increase sensitivity
of reporting of AEFI for all vaccines. For inclusion of JE, the network would
need input on how best to identify rare AEFI associated with that vaccine.
Current participating countries were identified on the basis of a population over
6 million and political stability. Vaccine effectiveness is not a target of the programme,
and vaccine safety is the focus. This programme tries to make AEFI surveillance
more effective through a network and will focus on vaccines made in Europe yet not
distributed in Europe. PMS was defined to be more like Phase 4 vaccine studies and
to be distinct from AEFI efforts.

6.5 Discussion on Adverse Events Following Immunization (AEFI)
Monitoring and Post Marketing Surveillance

Dr Ichiro Kurane (Japan National Institute of Infectious Diseases) presented on
routine surveillance for AEFI. When a vaccine is given to a healthy individual a high
standard of safety is expected. There are limitations to identify risk pre-licensure
due to limited sample sizes. It is therefore important to have post-marketing
AEFI reporting systems. At a bi-regional meeting on Japanese encephalitis
(March 31-April 1, 2005, Bangkok, Thailand), functioning AFEI systems in
Southeast Asia (11 countries) and the Western Pacific region countries were discussed.
Functionality ranged from fully functional to no system. WHO Global Training
Networks should help to improve capabilities in these regions. In Japan, three systems
are used that include passive (anyone can report any symptoms following vaccination),
targeted (vaccines are asked to compete a form following vaccination), or safety
information reporting by companies and physicians of collected AE information.
6.6 PATH Activities in Support of JE Immunization

Dr Julie Jacobson (PATH) gave an update on the JE Project at PATH, focusing on aspects not covered by previous discussions. The vision of the project is to eliminate clinical JE and avoid the unnecessary death and disability caused by this disease through a vaccination strategy. Emphasis is on demonstrating the impact of the strategy in several countries and settings. Towards that objective, PATH supports several countries to gain the data they need for informed decision making. In Indonesia, a six-province study has demonstrated JE in all 6 provinces (just one thought to be endemic previously). In Cambodia, surveillance for meningoencephalitis will start this year with treatment guidelines effective not just for JE as vaccination decreases the JE burned, encephalitis cases will still occur due to other etiologies. In Vietnam, two provinces have been selected for intensified surveillance and to link case reporting with laboratory diagnosis. In China, the project will transition live vaccine to replace inactivated vaccine in the EPI and will intensify surveillance for JE to improve the program. Two commercial diagnostic kits were evaluated at AFRIMS and two have moved forward to field testing in Nepal. In the area of vaccine introduction, India began SA 14-14-2 vaccination two days ago and Sri Lanka is preparing to transition to live vaccine in 2007. Through these efforts there has been increased support coming from partners, the establishment of a WHO lab network is ongoing, and JE was discussed at the SAGE. International donors are supporting countries, such as the World Bank in Nepal, and the Asian Development Bank in Vietnam. GAVI may request an Investment Case for JE vaccine later this year.

Discussion: Several meeting participants commended Dr Jacobson and PATH for the excellent work that has been done. The JE Project is funded through 2008 and probably through 2010 through the Gates Foundation. The Project will adapt its focus as vaccines are being introduced. It was stated that SA 14-14-2 cost around ten cents per dose in the multi-dose vials form GAVI eligible countries, but will cost $2 per dose in individual dose vials. There was concern about decreasing vaccine availability and coverage in China. Dr Jacobson replied that just one of four production facilities in China provides vaccine for export so there may be shortages for a year or so but production should then be able to meet demand. It is estimated that 40-50 million doses are need each year for routine vaccination (excluding catch up vaccination). In relation to vaccine registration in India, inspections on Chinese manufacturing facilities have taken place by Indian authorities. Additionally, there will be batch release testing in India. A new facility will be built in China for export vaccines meeting cGMP criteria. This plant will be subject to the WHO prequalification application.

6.7 Update on Pediatric Development of New JE Vaccines

Dr Shailesh Dewasthaly (Intercell, Austria) provided an update on Intercell’s JE vaccine IC51. In his presentation, he focused on the clinical evaluation of the vaccine, as well as the company strategy to bring the product onto different markets. IC51 is a purified, inactivated and adjuvanted (alum) vaccine grown in Vero cells. The virus strain is SA14-14-2, which has been obtained from China, and has not been rederived. Multiple batches of clinical trials material have been produced at Intercell’s facility in Livingstone, UK. To meet requirements for adult indication, reproduction toxicity studies are ongoing in rats. Passive transfer studies in mice to
correlate PRNT titers and protection using two different strains of JEV are ongoing. Clinical evaluation for adult indication is advanced, and phase 3 testing started in September of 2005. A total of 4900 volunteers have been enrolled. Apart from basic safety and efficacy, studies are looking at long term immune responses to see when booster doses will be needed, assess concomitant administration of another traveler’s vaccines (hepatitis A vaccine), and accelerated administration of vaccine (double initial dose and 0-14 day dosing). Standard regimen is two doses of vaccine at day 0 and 28, using 6 microgram of antigen per dose. Product registration will be sought from the FDA and EMEA, the latter having granted orphan status this year. The company plans to file in 2006 with licensure anticipated in 2007 in the US and 2008 in Europe. Intercell has partnered with Biological E in India and CSL in Australia for manufacturing (Biological E) and distribution. A dedicated pediatric development plan is being set up with Biological E. License application for pediatric indication is expected in late 2007. While the initial production capacity will be 5 million doses per year, it is expected that after successful technology transfer to Biological E the total capacity will be beyond 20 million doses, in particular to meet the demand from endemic countries. The company will seek product prequalification. The company is also investigating into formulating the vaccine with a different, proprietary adjuvant IC31, with the expectation to reduce the initial round of vaccination to a single dose.

Discussion: In relation to the immunological evaluation of the pivotal non-inferiority study, it was specified that the manufacturer will use the homologous SA 14-14-2 strain for neutralization assays. The choice of this virus allows the laboratory work to be done at BSL2 level. However, a subset of samples will be tested against Nakayama and Beijing virus. It was also noted that this immune response evaluation will compare a two dose regimen (IC51) against a three dose schedule (JE-Vax), requiring a careful analysis of results, as number of doses also impacts the quality of the response. In relation to boosting requirements, current data show persistence of antibody over the observation period of two years. Post marketing studies will determine the need for subsequent booster doses.

Dr Niranjan Kanesa-Thasan (Acambis) reported on progress with candidate vaccine ChimeriVax-JE. The ChimeriVax platform, building on the Yellow fever 17D vaccine virus, is widely used by the company for flavivirus vaccine development, and the JE candidate is the currently most advanced product. While extensive preclinical work has been done on ChimeriVax-JE, this presentation focused on the clinical development and licensure strategies. The target product profile of this live, attenuated vaccine includes single dose administration for all ages beyond nine months, and the suitability for co-administration, in particular with measles vaccine. Contraindications will be immune suppression, pregnancy and lactation. These features would make the product attractive for endemic country pediatric use. However, clinical evaluation is currently most advanced for adult indication. The final formulation is lyophilized with a titre of 4log pfu. Ongoing adult studies assess long-term immunogenicity (H-040-005), safety and dose ranging (H-040-007) and a safety and tolerability non-inferiority study between single dose ChimeriVax-JE and three dose JE-Vax (H-040-008). Pivotal phase 3 studies are being conducted in the US and Australia in a multicenter setting for immunogenicity (H-040-009, N=816) and safety (H-040-010, N=2000). The immunogenicity study is powered to show non-inferiority to JE-Vax (one dose versus three doses), by measuring seroconversion (cut off 1:10 titre) and GMT. The safety study will assess reactogenicity of a single dose of vaccine versus placebo.
For pediatric indication, Acambis has announced a joint venture with Bharat Biotech/India and a phase 2 study is being planned (H-040-004) to assess safety and tolerability of ChimeriVax-JE compared with inactivated mouse brain vaccine (Kasauli) in healthy children and infants (<10 years to =9 months old) without prior JE immunity. Assessment of potential interaction of measles vaccine (Serum Institute of India) with ChimeriVax-JE is also being planned.

Discussion: Several questions addressed the issue of vector immunity (yellow fever) and its impact on other flavivirus infections. Data from Latin America however do not suggest that yellow fever vaccine immunity confers protection against dengue disease. Similarly, it seems unlikely that ChimeriVax-JE protects against yellow fever. Studies assessing cellular immunity are ongoing and may provide some insight into possibly cross protective immune responses. There were also questions in relation to the planned pediatric studies, their sample sizes and plan for licensure. However, the full clinical development plan was not yet revealed, but it was stated that Acambis/Bharat were seeking licensure in India by 2007.
7. General discussion and recommendations

In accordance with WHO procedures, a session of restricted attendance, without participation of representatives from the private sector, was held for general discussion of formulation of recommendations to WHO. The following key recommendations were made:

- Guidance document for plaque reduction neutralization tests to assess dengue immunity: a draft will be produced under lead of Dr. John Roehrig for peer review after the summer break; if possibly, the draft should be presented to ECBS;

- establishment of validation panels for dengue PRNT: it was recommended that the precise composition should be endorsed subsequent to a further written consultation with vaccine developers, and that an implementation plan be established under the lead of Dr Artsob. This task should be distinguished from efforts to establish proficiency panels for lab testing, as well as from effort to establish an international reference reagent. The latter two could be envisaged once a validation panel is established;

- guidance document for clinical evaluation of dengue vaccines: Under lead of Dr Edelman, a timeline has been recommended for production of a draft, and review by a small drafting team; a final manuscript for peer review should be produced by end of 2006;

- disease focus of the SC: while it was acknowledged that the SC should primarily focus on dengue and JE; it was recommended that WHO should regularly monitor vaccine development efforts against other flaviviral diseases, such as West Nile, tick borne encephalitis and others;

- workshop on correlates of protection: it was recommended that the report be published in a peer reviewed journal, and that recommendations in relation to research needs should be specified;

- WHO was encouraged to continue its interaction with PDVI in relation to vaccine evaluation and introduction; it was also recommended that WHO will maintain a watching brief on new vaccine candidates that may lead to next generation vaccines.
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The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

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

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

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

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

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

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