2004 Report of the Steering Committee on Dengue and Other Flavivirus Vaccines

Including

Minutes of the SC Meeting

WHO, Bangkok, 26-28 April 2004

Non-confidential version

Contents

1. Introduction: Context of the meeting

The WHO Steering Committee on Vaccines for Dengue and Other Flaviviruses met 26th-28th April 2004 at Siam City Hotel, Bangkok, Thailand. The meeting was separated into two parts, the first two days being devoted to a scientific review on flavivirus vaccine development and vaccination. The third day was reserved to matters of the steering committee, and was a closed meeting for SC members and temporary advisers only. The scientific review gathered some 200 attendees from academia, government, private sector and non-profit organization, with very strong representation from the region. Proceedings of the meeting are being published in the journal *Vaccine*. The scientific meeting was co-sponsored by the Thai Ministry of Public Health.

The meeting was opened by Dr. Vallop Thaineua, Permanent Secretary of the Ministry of Public Health (MoPH), who informed the attendees about the strong support by the Ministry for control of dengue. There were 30,000 dengue fever (DF) cases last year and almost 200 children died of dengue (DEN). The ministry has been looking forward to a DEN vaccine since 1970s and is looking forward to working with scientists around the world to develop a vaccine. Also, the ministry is interested in an improved JE vaccine.

Prof A. Sabchareon (Mahidol University, Thailand) welcomed attendees on behalf of local organizers, and Drs Kurane (NIID, Japan), Hombach (WHO) and Kieny (WHO) thanked the local organizers and informed the meeting that this was an exciting time due to new candidate DEN and Japanese encephalitis (JE) vaccines in clinical trials. The meeting would review DEN vaccine development and DEN cohort and epidemiologic studies, plus JE vaccine development, epidemiology & vaccination, the contribution of newly established programmes by PATH and the Gates Foundation, and an update on other mosquito-borne flaviviruses of major public health importance.

Finally, Dr. S. Chunsuttiwat (MoPH, Thailand) reminded the attendees that Prof Natt just passed away 3months ago and his major role in the development of a candidate live DEN vaccine and that much had been learnt from his contributions to DEN vaccine development.

2. Objectives and Strategies of the Steering Committee

2.1 Dengue

Overall objective: facilitate the development of safe, effective and affordable vaccines against dengue severe disease, and support activities related to disease monitoring, and introduction of vaccines.

Strategies:

- Support targeted research on new dengue vaccines and their evaluation through direct funding or setting of research agendas;
- Facilitate evaluation of new vaccines by providing a platform of exchange of information for vaccine developers (clinical trials task force), and the provision of guidance on population-based trials;
- Support the establishment of models for early evaluation of candidate vaccines;
- Provide normative support and make available standardized research materials (jointly with QSB).

2.2 Japanese encephalitis

Overall objective: support the development of second generation JE vaccine that is safer, requires fewer doses, and is more amenable to integration into national immunization schemes in disease-endemic countries, and provide support to measures aiming at accelerated vaccine introduction.

Strategies:

- Support the development of new JE vaccines through co-ordination, technical advice and direct funding of accompanying measures;
- Provide normative support and make available standardized research materials; provide guidance on evaluation of vaccine candidates (jointly with QSB);
- Provide technical support to activities related to disease-burden assessment, vaccine utility and accelerated vaccine introduction.

2.3 Other flaviviruses (West Nile Virus, Yellow Fever Virus, tick-borne encephalitis virus)

Overall objective: observe and regularly review disease-burden and vaccine development efforts; provide advice on an ad hoc basis, in particular in relation Yellow fever vaccine safety.

3. Dengue Vaccine Development

3.1 Vaccines at preclinical stage of development

Dr. L. Markoff (FDA, USA) started the scientific session describing the generation of the "Mutant F" candidate vaccines by site-directed mutagenesis of 3'non-coding region stem loop (SL) in infectious clones of all four DEN viruses. Mutations in the SL affect host range of flaviviruses and bind cell proteins. The DEN1 Mutant F was shown to replicate in vertebrate LLC-MK-2 but not in mosquito C6/36 cells. The DEN1mutF was selected from a low passage, human virulent strain, Western Pacific, and was attenuated for growth in C6/36 cells. DEN1mutF is attenuated, immunogenic, and protective in a rhesus macaque model. Using similar strategy, DEN3 and DEN4mutF viruses were created and shown to be restricted for replication in C6/36 cells. To assemble a tetravalent vaccine candidate, a DEN2mutF will be generated starting from a non-virulent DEN2 virus.

Discussion: Questions were raised on the genetic stability of mutant F, which should be verified by sequence analysis from virus recovered from immunized macaques. There was encouragement to move into clinical evaluation of this candidate.

Dr. R. Kinney (CDC, USA) reported on studies with DEN2 strain 16681 PDK53 vectored chimeric DEN vaccines. The DEN2 PDK53 backbone virus is safe, immunogenic and replicates poorly in *Ae aegypti*. This attenuated strain has been developed at Mahidol University and is licensed to Sanofi-Aventis. It has 3 dominant mutations in order of dominance NS1-53 >5'NCR-57 >NS3-250. There are no mutations in the E protein. Chimeras have been made using attenuated vaccine strains DEN1 16007, DEN3 16562 and DEN4 1036. Attenuation mutations are stable in Vero cells. Phenotypically, the chimeric viruses are temperature sensitive in LLC-MK-2 cells, crippled in C6/36 cells, non-neurovirulent in ICR newborn mice and generate a low viremia in monkeys. The tetravalent chimeric candidate vaccine gave a good immune response in mice and no interference. Monovalent and tetravalent formulations gave low or undetectable viremias and good neutralizing antibody titers in cynomolgus monkeys, with the exception of DEN2, showing a weak response.

Discussion: Viral interference was mentioned as explanation for low immunogenicity of DEN2 in tetravalent formulation, and studies are being repeated. No mosquito competence studies have been done yet.

Dr. C. Weeks-Levy (Hawaii Biotech, USA) reported on a candidate recombinant subunit vaccine based on expression of the DEN virus E protein in Drosophila S2 cells. The current candidate vaccine is tetravalent with 4 DEN 80% E plus NS1. The latter contributes to efficacy of subunit vaccine by increasing interferon gamma production. Mice immunized with 5mg 80%E+NS1 give 100% protection and the tetravalent candidate induces high titer neutralizing antibodies in mice and monkeys. Three non-human primate studies are in progress and results correlate with mouse data. Challenge studies are about to commence. Studies with proprietary adjuvants indicate that immunogenicity of the candidate vaccine can be increased.

Discussion: There was discussion whether NS1 was really needed as component of the vaccine, given the strong antibody response elicited to the E protein. More data were also

requested on the duration of the immune response. A phase I study is in planning for late 2005.

3.2 Vaccines in clinical development

Prof A. Sabchareon (Mahidol University, Thailand) described long-term surveillance of individuals immunized with the candidate Mahidol/Sanofi-Aventis Pasteur live, attenuated tetravalent vaccine. Over a duration of 4-5 years, no vaccine recipient had developed severe DEN disease, but there were evidences of dengue disease as well as subclinical infection. In the last two years, two vaccine recipients out of 104 (one child and one adult who received vaccine formulations 3313 and 3212, respectively) developed the clinical picture of DF. DEN1 or DEN2 viruses were detected in these cases, demonstrating breakthrough infection despite the presence of vaccine-induced neutralizing antibodies of 1:35 and 1:25, respectively. At four years post immunization, 71% of adult and 87% of child vaccinees had neutralization titers >1:10 - <1:30 to all four DEN viruses whereas 29% of adults and 35% children had neutralization titers > 1:30. It was concluded that 4-5 years after vaccination the candidate tetravalent vaccine did not worsen or enhance DEN infection. In addition, there were very high levels of antibodies in 22 vaccinees who had subclinical infections, indicating that the antibodies may help reduce severity of disease.

Discussion: It was speculated if subclinical JE infection may help provide protection to severe DEN, but exposure to JE was considered low in that region. In absence of flavivirus exposure, antibody titres gradually wane.. The need to define threshold protective antibody titres was reiterated.

Dr. I. Kurane (NIID, Japan) reviewed the last meeting of the WHO DEN clinical trials taskforce on behalf of Dr. F. Ennis who was unable to attend the meeting. Full minutes of the task force meeting have been prepared elsewhere and are available from WHO secretariat. In brief, progress was reported on the GSK/WRAIR live, attenuated tetravalent candidate, that has been studied in different formulations in 164 adults for safety and immunogenicity. A superior formulation (No. 17) had been identified that will be evaluated in a pediatric trial as a next step. The Acambis candidate ChimeriVax-DEN had successfully been tested in a monovalent formulation (DEN2) in phase I studies, and a tetravalent formulation was reported to be in preparation for clinical evaluation. The US- NIH approach is based on a deletion mutation (Δ 30), originally introduced into DEN4. Phase 1-2 studies have been conducted with the monovalent formulation, and tetravalent formulations are at preclinical stage of development. Progress was reported on UK-NIBSC / WHO efforts to establish candidate vaccine standard sera. Much of the meeting was devoted to discussion and review of draft guidelines for the production and quality control of tetravalent live attenuated DEN vaccines (see section 3.5). In this context, the role of the monkey neurovirulence test for DEN vaccines, attenuation markers in DEN and cell substrates for live vaccines were discussed in further detail.

3.3 Characterization of immune responses

Dr. R Jarman (Walter Reed, USA), on behalf of Dr W. Sun, described studies to characterize the humoral immune responses following vaccination. The project is supported by a grant from WHO. This study was conducted with human volunteers vaccinated with a candidate live, attenuated tetravalent vaccine, that is licensed to and co-developed with GSK. Volunteers were subsequently challenged with low passage DEN1 and 3. Technology is being developed to measure the binding of antibodies to DEN E proteins via Biacore surface plasmon resonance technology. Preliminary results suggest that the relationship of association/dissociation and neutralizing antibodies have some predictive value for

protection. Low levels of IgG3 may be associated with reduced protection. While the Biacore technology appears powerful, more studies are needed to confirm findings.

Discussion: further use of the model, more detailed analysis of the role of Ig subclasses and other parameters were greatly encouraged. The role of this model for screening candidate vaccines remained controversial. There is also a need to better define challenge strains.

Dr M. Guzman (IPK, Cuba) reviewed data on dengue epidemics in Cuba from 1977-1997. There was a large DEN1 epidemic of DF in 1977 involving 400,000 cases followed in 1981 by a DEN2 epidemic of 300,000 DF cases and 10,000 DHF cases, including 158 fatalities (children and adults). In 1997 there were 5000 confirmed cases of DEN2, including 205 DHF cases of which 12 were fatalities (adults). The 1997 DEN2 epidemic was considered more severe than the 1981 DEN2 epidemic. Both of these epidemics were due to Asian genotype viruses. Serological studies showed that there was a high level of monotypic neutralizing antibodies 20 years post infection. There was a low level of heterotypic neutralizing antibodies to DEN2 Asian genotype while there were higher levels to DEN2 American genotype in DEN1 primary infections. However, the DEN1 sera had low titers to other DEN serotypes while sera from DEN2 infections had a higher level of cross reactivity to different DEN serotypes. It remains to be confirmed if these findings relate to increased risk of severe dengue in secondary heterotypic infections.

Discussion: It was felt desirable that such type of study should also be done for DEN3 infection. Others enquired whether these observations were truly dengue-specific, or whether they reflect repertoire and affinity maturation processes of a normal dynamic antibody response.

Dr. P. Keelapang (Chiang Mai, Thailand) reported studies on the neutralization of DEN viruses by anti-prM monoclonal antibodies (mabs). Most of the mab's are IgG and were derived from early phase of infection (day 1-4). This study is supported by WHO. Five of the mabs had no neutralizing activity while the other five had weak neutralizing activity against only a few of the panel of 23 DEN strains examined. In some cases, plaque size reduction was observed, indicating that anti-prM antibodes might interfere with intracellular virus formation. In comparison, 8/10 mabs would enhance DEN1 infection 100-fold or greater, if appropriately diluted. Thus, prM may play role in enhancement but a weak role in neutralization.

Discussion: The PI was encouraged to continue these studies which were considered promising. It was also mentioned that anti-prM antibodies have potential to be used as an early diagnostic marker capable to distinguish between different flaviviruses.

3.4 Sero-epidemiological studies on DEN infection and trial site identification

Dr. S.Tassniyom (Khon Kaen University, Thailand) described a prospective cohort study on DEN infection in 3000 primary school children in of Nakorn Khon Kaen municipality, Thailand, which is currently in the planning phase. Aim is to study immune responses and virological parameters over the course of sequential infections, moreover incidence of symptomatic versus asymptomatic disease will be determined. The study will have two groups: one group will be bled annually while the other group will be bled as and when children develop pyrexia. Teachers will check daily for any child with pyrexia. Once the child identified, his/her temperature will be measured to confirm fever. Laboratory tests will involve neutralization assays for DEN and JE viruses as well as RT-PCR and ELISPOTs.

Dr. W. Tuntaprasart (Mahidol University, Thailand) described a sero-epidemiological survey in Ratchaburi Province where there is a maximum incidence of 150 DHF cases per 100,000 population. Incidence data are collected since 1992, and there has been a steady decline at province level, while strong variability has been observed at sub-district level. The study site is Nongtalaug and the study population is 283 schoolchildren in Hingong subdistrict. 200 (71%) were DEN immune and 83 (29%) nonimmune. In a follow-up 1 year later (July 2000-June 2001), examination of 192 samples showed that 9.4% children seroconverted with neutralizing antibodies, including 7/68 children who were originally IgG negative. Different from other studies, higher dengue transmission was observed during dry season.

Dr. T. Endy (WRAIR, USA) reported on a prospective cohort study of DEN virus transmission and disease in primary school children in Kamphaeng Pet, Thailand. This is a collaboration between AFRIMS, University of Massachusetts (USA) and the Thai MoPH that began as a five-year study in 1998. Each year a January baseline serum is taken followed by bleeds in June, August and November. Children are followed by active surveillance based on school absenteeism. During the first 5 years of the study, symptomatic disease was seen in 7.9%, 6.5%, 2.2%, 14.9% and 5.2% of children for 1998-2002, respectively. The ratio of unapparent to symptomatic disease was 1.5:1.0, which was different to previous studies by Halstead and Burke showing a 10:1 ratio. The unapparent to symptomatic ratio differed by DEN virus: DEN3 had the most symptomatic disease, and DEN1 and DEN2 the least symptomatic cases. All 12 schools in the study had DEN cases but incidence varied between schools. Also the DEN virus varied by year, 1998: DEN3, 1999: DEN2, 2000: DEN2, 2001: 3 serotypes and 2002: three serotypes. Hospitalization rates varied between 4 and 30% and by school. Interestingly, each school had a “symptomatic” year followed by very “unapparent” infection year suggesting that the presence of heterotypic antibody may be important in modulating infection. Children are vaccinated against JE and impact on DEN is not known. Endy and coworkers also investigated the economic impact of DEN. In Thailand, hospitalized cases involved on average 9.1 days, including 4.3 days pre-hospitalization and 3.5 days in hospital. The financial loss per family is estimated as $61 (which is in the range of a monthly income) and ranked #9 out of 10 childhood diseases. The cost of 5 day illness due to DEN was 2659 Baht. Economic impact varied by school depending of disease severity. Overall, DEN is a significant economic expenditure in Thailand and a DEN vaccine has potential reduce economic burden. Funding has been secured and the study will continue.

Discussion: there was discussion on the DEN virus distribution between apparent and unapparent infection, and it was felt that once again, DEN3 appeared different from other DEN viruses. Differences in DEN virus circulation was observed despite geographic proximity. Interest was expressed to use this field site for vaccine trials.

Dr. P Singhasivanon (Mahidol University, Thailand) described the application of Geographic Information Systems (GIS) to the selection of potential phase III vaccine trial sites in Thailand. DEN disease incidence varied by year and by region/province. GIS was used over 4-10 year period to identify areas to be considered suitable for trials. Two areas were shortlisted including Muang district in Ratchaburi province 100km from Bangkok. According to preliminary data, these regions have consistently higher dengue disease incidence. Ratchaburi Regional hospital is one of 8 sentinel sites in Thailand to look at DEN cases. It has 855 beds, including 119 beds for pediatrics. Work is in progress to identify subdistricts with increased DEN incidence. Currently, Thai MOPH has approved an epidemiological study of dengue infection in children age 3 – 10 years in Ratchaburi Province.

Dr. N Thi Kim Tien (Institut Pasteur, Ho Chi Minh City, Vietnam) described a potential DEN phase III vaccine trial site in Long Xuyen, An Giang Province, near Ho Chi Minh city. This effort is a collaborative study between Institut Pasteur, An Giang Hospital and Sanofi-Aventis. Dr Tien described a prospective DEN hospital-based surveillance study from April 2002 to May 2003. In a preceeding preparatory phase, a retrospective analysis was done for 1996-2000. The Pediatric ward of An Giang hospital had 1007 patients (3mon - 15 years) of whom 572 (57%) had laboratory confirmed DEN, 182 (32%) had shock and 118 (65%) had all 4 criteria for DHF. Virus isolation showed 95 DEN2, 10 DEN4 and 7 DEN1 viruses. Most cases occurred in children beyond the age of 5 years. The hospital-based study is followed by a community-based prospective study covering 2003 - 2005.

Discussion: this site was considered as another suitable site for DEN vaccine trials. Questions were raised on prevalence of JE and vaccination policies.

3.5 Standards and guidelines

Dr M. Ferguson (NIBSC, UK) presented a report on a collaborative study aiming at assessing suitability of reagents to be calibrated as standards for immune readouts in DEN and JE vaccine development. She presented a summary of the studies involving 8 participants in 6 countries to evaluate 6 DEN serum samples in neutralization tests using cells and viruses provided by NIBSC. The goal is to get a candidate standard that has reasonable titers against each DEN virus. The SC was requested to make a recommendation on the use of the tested mono- and tetravalent sera as international standards. In addition, Dr Ferguson presented data on development of JE standards by testing different sera representing immunization with different vaccines, and individuals naturally infected. There were 5 participants, all from different countries, who tested 3 virus strains: SA14-14-2, Nakayama and Beijing-1. The results showed that the homologous strain gave higher neutralizing antibody titers than heterologous strains. Overall, the results indicate that virus used in assays affects antibody titers.

Discussion: The JE data caused a controversial and suggested that more studies are necessary. There was also concern that no standardized protocol had been used in this study.

Drs J Shin (WHO) and K. Eckels (WRAIR, USA) presented the results of discussion on a draft document for WHO guidelines for the production and quality control of live attenuated

dengue vaccines. This document is being proposed as guidance for those manufacturing vaccine for safety and potency. The first draft in 1997 was rejected, a second draft was updated in December 2003, and a final review is expected in Nov 2004 by the WHO Expert Committee on Biological Standardization. Drs Shin and Eckels then presented a thorough overview of the various parameters that were discussed and are included in the draft document.

Dr M.J. Cardosa (Sarawak, Malaysia) discussed the guidelines for the evaluation of dengue vaccines in populations exposed to natural infections that was produced by WHO/TDR in 2002. While this document is a useful introduction into the subject, it was considered being too generic and not addressing some pertinent issues for dengue vaccine population trials. Clinical endpoints (DF or DHF) remained, among others, as controversial items. She stated that information would be needed on duration of immune response, boostability from natural infection to maintain neutralizing antibody levels, efficacy, immunogenicity as well as ethical considerations.

Discussion: It was suggested that a group of volunteers review/draft a document, including participants of industry.

3.6 Pediatric dengue vaccine initiative

Dr S. Halstead (PDVI) gave an overview of the Pediatric Dengue Vaccine Initiative (PDVI) that benefits from a grant from the Bill and Melinda Gates Foundation and some additional funding from the Rockefeller Foundation. The initiative's main thrust is to (1) establish field sites suitable for sero-epidemiological studies and vaccine trials, (2) to support research into safety aspects of dengue vaccines, and (3) to build an economic case for the introduction of pediatric dengue vaccines. The Director designate is Harold Margolis. Dr Halstead stated that PDVI proposes to establish at least 2 dual use field sites in dengue endemic areas for vaccine testing. These will be in areas of high dengue endemicity where no other flaviviruses are circulating, no flavivirus vaccine is administered and 3-4 DEN viruses co-circulate. PDVI has received 22 letters of intent and has recommended that four sites to be evaluated and full proposals requested. Two are in SE Asia and 2 in the Americas. Other studies by PDVI focus on dengue vaccine safety and PDVI received 69 applications of which 11 were funded. In collaboration with WHO, PDVI is currently sponsoring a neutralization workshop in Thailand where representatives of 12 labs from endemic countries around the world are conducting DEN virus neutralization tests. This includes repeating the studies Dr Ferguson reported on using same sera in one lab by different workers at same time.

Discussion: on the PRNT workshop, there was concern expressed that industry had not been involved in this exercise. Also the desire was expressed that resources should be made for research into the development of a functional readout more amenable to large sample numbers.

4. Japanese Encephalitis

4.1 Status of new vaccines

Dr. N. Kanesa-Thasan (Acambis, USA) gave a update on development of Chimerivax-JE using the ChimeriVax platform technology. This second generation JE vaccine is produced to high yields on serum-free Vero cells. It was stated that ChimeriVax-JE was less reactogenic compared to current inactivated JE vaccines. Safety testing of Chimerivax-JE in suckling mice, adult mice, monkeys and infectivity for mosquitoes as well as genetic and antigenic stability were reviewed. A phase I clinicial trial compared ChimeriVax-JE to YF Vax control and showed that prior immunization with YF Vax does not affect immunogenicity. There was an anamnestic response to JE antigen. Currently, Acambis is undertaking a clinical trial in Australia looking at safety, tolerability, and durability of ChimeriVax immunity over 2 years. To date, only one serious adverse event at 38 days post immunization (possible acute viral illness) has been reported. Available data suggest that a one-dose regimen is sufficient to induce lasting immunity. In collaboration with WHO, the company now plans to initiate a first clinical trial in a disease-endemic country that will be conducted as an age de-escalation study in Thai children. Safety and immunogenicity will be compared to commercial, inactivated JE vaccine.

Discussion: on vaccine administration, it was suggested that the vaccine was suitable for epidermal delivery, leading to virus uptake by Langerhans cells. Acambis considers testing the vaccine using a new skin delivery device ("OnVax", manufactured by Becton Dickinson). The manufacturer was encouraged to proceed with the development of the vaccine for pediatric indication. Regulatory hurdles might be considerable for this live recombinant vaccine.

Dr. S. Manabe (BIKEN, Japan) described the company's approach to produce a Vero cell derived inactivated JE vaccine, allowing the company to discontinue its production of mouse-brain derived vaccine. He reported that BIKEN had undertaken a phase I study involving adults and then moved directly into a small scale phase III study. This first phase III trial involved healthy children aged 6-90 months (N=110/group). Designed as a randomized, single-blinded study comparing the candidate against the mouse-brain derived vaccine in a two-dose regimen, it showed a sero-conversion rate of 100%. The new vaccine elicits slightly higher antibody titers than the original mouse brain derived vaccine. No serious adverse events were reported. Overall, preliminary data indicates the cell culture based vaccine to be safe and efficacious.

Discussion: Licensing strategy is planned on the basis of non-inferiority to existing vaccine using immunological readouts.

Dr. I. Kurane gave a presentation on behalf of Dr Y. Kino, Kaketsuken. The company has successfully completed pre-clinical and phase I study of a Vero cell derived inactivated JE vaccine and phase III studies are in progress. This is a randomized, double blind clinical trial involving healthy children, 6-90 months of age. The children have been immunized twice, 1-4 weeks apart, and will be boosted at one year. Development and licensing strategies are similar to BIKEN.

Discussion: in relation to both vaccines, there was question on crossprotection against infection by other JE genotypes. While the vaccine shows lower titres against other (non type II) genotypes, some considered it protective based on previous clinical experience with mouse-brain derived vaccine. The issue remained controversial, in particular in relation to individuals being otherwise flavivirus naïve.

Dr Y. Yu (NICPBP, China) reported on the current status on production and quality control of SA14-14-2 vaccine, a live, attenuated vaccine that has been developed in China and used since 1988. The vaccine is produced on primary hamster kidney cells (PHKC). Chinese producers are currently involved in upgrading production facilities and QC processes in order to meet GMP standards. The vaccine is currently produced at three institutes (Chengdu, NICPBP and Wuhan), and major investments have been made at Chengdu. A new GMP standard building has been constructed, including a SPF animal breeding and primary colony facility. There are 3800 breeding hamsters and Chengdu started using SPF hamsters in Feb 2004 at the rate of 4000 SPF hamsters per month. The maximum capacity of the facility is 32,000 hamsters per month. Genetic analysis of the E protein gene of SA14-14-2 showed no mutations following 20 passages in PHKC. No genetic changes have been detected in any of the vaccine lots produced from 1987-2002. Furthermore, up 50 million doses of vaccine are produced each year (some 20-25 million doses coming from Chengdu) and no serious adverse events have been reported. Neutralizing antibody responses have been measured in children. One dose of SA14-14-2 in 69 children gave a GMT 20.22 and 91.33% of children seroconverted whereas two doses of P3 killed vaccine in 73 children had a GMT of 16.51 and 64.38% of children seroconverted. Dr Yu stated that 2 doses of SA14-14-2 are used for immunization in Beijing and no cases of JE in children have been reported in Beijing following the introduction of SA14-14-2.

4.2 JE epidemiology and vaccination strategies

Dr Zhi Yi Xu (IVI, Korea) provided an overview of the epidemiology of JE in Asia and stated that disease burden was overall underestimated due to limited diagnostics. He used Bali, Indonesia as an example where healthcare was accessible and affordable. The annual incidence rate is approximately 7 per 100,000 and the outcome of the disease was 10% mortality, 43% permanent disability and only 47% recovery with no sequellae. Despite these staggering figures, long-term morbidity due to JE is under-investigated, and more studies are needed in this area. Dr. Xu stated that disease burden in Indonesia is similar to that found in different countries. He described a retrospective cohort study of long-term disability in Shanghai, China, that examined markers of disability, including neurological and psychological sequellae. Twenty-two percent of JE patients had neurological sequellae and 28% had low IQ. To investigate the cost effectiveness of vaccination, the cost of JE in DALYs was calculated. A non-vaccinated group had 488 per 100,000 outcome with 122 fatalities per 100,000 with a loss of 7440 DALYs. This compared to a loss of only 405 DALYs in population immunized with two doses of SA14-14-2 and 552 DALYs lost following five doses of P3 vaccine. It was estimated that P3 vaccine saved $408,272 and SA14-14-2 vaccine saved $579,210 compared to the costs of treatment of non-immunized JE cases. Such data should provide powerfull incentive to introduce programmatic JE vaccination in context of the EPI programme. Dr Xu pointed out that although JE vaccination is very effective in China, JE vaccine is not an EPI vaccine in most provinces and there are still 10,000 cases reported annually. (Post-meeting note: China has in the meantime introduced JE vaccination into the EPI scheme).

Discussion: There was agreement that surveillance of JE needs improvement, which should come along with improved diagnostic tools. In addition, rational guidelines on vaccination where urgently needed, as populations are experiencing both under- and over-vaccination.

Dr S. Chunsuttiwat (Thai MOPH) described JE disease burden in Thailand and other countries where JE is found. There are reports of JE from 4/10 South East Asia Region countries and 7/8 West Pacific Region countries totaling 15-30,000 cases per year. JE vaccination has been introduced into the EPI programme of Thailand and coverage has been steadily increased. JE cases have dropped from 400-1000 cases before 1990 to under 100 cases after 2000. While JE constituted previously some 40% of cases of viral encephalitis, this figure has now dropped to 15%. A major factor in reduction of JE disease burden has been the introduction of vaccination, while vector control efforts and changes in agricultural practice have been supporting this trend. This involved technology transfer of JE vaccine manufacture from Japan, and today the vaccine is locally produced. Vaccination was initially introduced into the 8 provinces with the highest incidence of JE, increasing to 34 provinces in 2001 and all 76 now. Coverage for JE2 is 87%, and for JE3 76%. The first vaccine was based on strain Nakayama but this was changed to strain Beijing-1 in the late 1990s. It costs 5443 Bahts (US$136) per patient for medical care for acute JE, but indirect costs are much higher. As with other vaccines, as disease incidence drops, concerns about vaccine safety find increasing attention.

Dr. L. Markoff (FDA, USA) reviewed options for evaluation of new JE vaccines for licensure using surrogate markers instead of clinical endpoints. He stated that a large scale clincial trial, similar to that undertaken by C. Hoke in Thailand with inactivated vaccine, would be unethical and impractical. Hoke et al showed there were 51 cases of JE per 100,000 in the control group compared to 5 cases per 100,000 in the immunized group. Dr. Markoff estimated that a new clinical trial would need 247,000 individuals based on an incidence of 10 cases per 100,000. Thus, there is a need to define efficacy and demonstrate that a new vaccine should not be inferior to current licensed vaccine. Surrogate markers of protection are needed, for example, the YF 17D vaccine uses a LNI of 0.7. However, although there is evidence of a correlation between neutralization and protection, the neutralization assay would need to be standardized. One possibility was to use the approach for hepatitis B and hepatitis A vaccine studies to define surrogate(s). There are a number of animal models for JE virus, including mice, hamsters, rabbits, monkeys. Dr Markoff described mouse and monkey models and thought that this was a “Plausible approach” to establish surrogate(s) based on neutralization test, immunization and challenge animal model. Nonetheless, a large scale human safety trial will still be needed, involving some 3000 to 5000 subjects.

Discussion: It was felt that the US FDA Animal efficacy rule (21 CFR parts 314 and 601) was less applicable to new JE vaccines. Participants were informed by the secretariat that WHO will be conducting a dedicated consultation with the goal to defining immunological measures suitable to be used as surrogates of efficacy.

Dr J. Jacobson (PATH, USA) described the newly established PATH JE programme that is part of the Children’s Vaccine program in PATH and is funded by Bill and Melinda Gates Foundation. Dr. Jacobson stated that JE was an orphan disease not recognized outside Asia. One of the barriers to effective JE control was poor recognition of the disease and that she was aiming to establish JE surveillance so that countries are aware of the problem. She stated that syndromic surveillance is used in countries that have successful vaccination programs. India, Indonesia and China have disease surveillance programs now. Furthermore, the Chinese Government has decided that JE vaccines will no longer be used in campaigns and will be incorporated in EPI vaccine in provinces where JE is a problem. There would be a meeting to discuss surveillance at WHO headquarters later this year. Her second goal was to advance an improved vaccine that is better than the current mouse brain-derived vaccines. Currently, the most promising candidates are SA14-14-2 and ChimeriVax-JE. A programmatic interaction with WHO is anticipated.

5. Other Flavivirus Vaccines

5.1 West Nile

Dr J. Roehrig (CDC, USA) reviewed trends in West Nile disease (WN) in North America. He started by describing the epidemic in the United States. WN virus (WNV) arrived in the US in 1999 and has rapidly spread through much of North America. In 2003 the epicenter was in Colorado. He described enzootic and epidemic transmission cycles and how dead bird surveillance can be used as an indicator of human disease. He reported the "Top ten" WNV positive birds and that the American crow has a case fatality rate of 100%. The "Top 10" mosquitoes revealed that WNV infects more mosquito species than St Louis encephalitis virus. Many mammals and alligators are infected by WNV. Numbers of human cases have increased over time but this is in part due to intensified surveillance for mild WNV. The human epidemic curve is the same as the equine one. Disease severity in humans is associated with increasing age. In addition to the traditional mosquito-borne route of transmission other routes of transmission have arisen, including transmission via blood transfusion. From July 1, 2003, the entire US blood supply is being screened for WNV. Up to 1 in 250 donations are positive in some areas. To date there are 225 bird species and 49 mosquito species that are hosts for WNV, consequently there is widespread WNV activity in the US, Canada and Mexico. Currently, there are no approved antivirals or human vaccines. Veterinary vaccines of inactivated type are used in equines.

Dr. S. Whitehead (NIH, USA) presented data on behalf of his colleague Alex Pletnev on WN vaccine development at the NIH involving two candidate vaccines, WN/DEN4 chimera and WN/DEN4delta 30 chimera, based on a DEN4 virus backbone. These viruses show reduced replication in mouse Neuro2A and human SH-SY5Y neuroblastoma cell lines. The candidate vaccines are attenuated in suckling and adult mice although WN/DEN4Δ30 is more attenuated than ?WN/DEN4. The candidate vaccines are not efficacious in geese but are in horses. The WN/DEN4 chimera is better than WN/DEN4Δ3 in equines, and both give better immune responses than the Fort Dodge inactivated vaccine. The WN/DEN4 is attenuated, immunogenic and protective in Rhesus monkeys. Also, the vaccine candidates show decreased rate of dissemination in mosquitoes. Currently, the WN/DEN4Δ30 chimera is vaccine lot prepared and certified for human use.

Dr. T: Monath (Acambis, USA) described the construction of ChimeriVax-WN as a candidate WN vaccine. Acambis has introduced three mutations into the WNV E protein gene to eliminate neurovirulence, and assessed lack of neurovirulence in 8 day old suckling mice given 10E5 pfu. The mutations are:: 316 A□ V, 107 L F and 440 K R Three GMP production lots at final scale have been prepared in a 100L bioreactor. The yield is 8.4-8.6 log10 pfu/ml. The chimera is significantly less neurovirulent than 17D in monkey neuroviurlence test, has reduced replication in primary human hepatic cells and is not capable of oral infection of mosquitoes. One dose of Chimerivax-WN is better than two doses of Fort Dodge inactivated vaccine in the hamster model. There were no deaths nor viremia in the monkey challenge model and.9/12 monkeys had neutralizing antibodies on challenge. A Phase I clinical trial is in progress. Acambis believe the vaccine has veterinary applications as it immunizes and protects horses. However, it does not immunize avian species.

5.2 Yellow Fever

In the final scientific presentation of the meeting, Dr. A. Dabbagh (WHO) reviewed the WHO strategies on vaccination and surveillance of YF, and challenges in their implementation. She presented an overview of YF in Africa and South America and described the increased incidence (reemergence) of YF in the last 20 years. Since 1988 there has been encouragement by WHO that YF should be put into routine immunization and mass vaccination campaigns. The vaccine can be co-administered with measles. However, the number of countries at risk from YF has increased from 20 to 34 of the 44 endemic countries during the period from 2000 to 2004. Although YF vaccine coverage is low, routine infant immunization programmes in addition to single mass vaccination campaign are very effective as shown by efforts in Gambia and Trinidad. Nonetheless, there are limited resources for implementation of vaccine coverage and the 6 million doses in reserve/stockpile are not sufficient to meet the needs of all endemic countries. It is noteworthy that the suspected and confirmed case definitions for YF have become more sensitive since 2001. But differential diagnosis from other tropical diseases is a major issue. To overcome this problem, the African YF lab network is being given training in ELISA diagnostics plus integration with the measles lab network. However, there is no proficiency training and only a limited number of laboratories are participating in the program. Dr. Dabbagh presented an overview of the safety issues for YF vaccine and the recent reports of vaccine-associated diseases involving neurotropism and viscerotropism. Although of concern, the risk of severe adverse events is still very low. Significantly, there are many examples of HIV positive individuals receiving vaccine but none have been found to succumb to a vaccine-associated disease. Clearly, more studies are necessary to understand vaccine safety and efficacy, especially in HIV positive individuals.

6. Closed Session - Restricted attendance

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