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**Report:**

**Workshop on Dengue Burden Studies**

**(Washington, DC, 5-7 November 2002)**

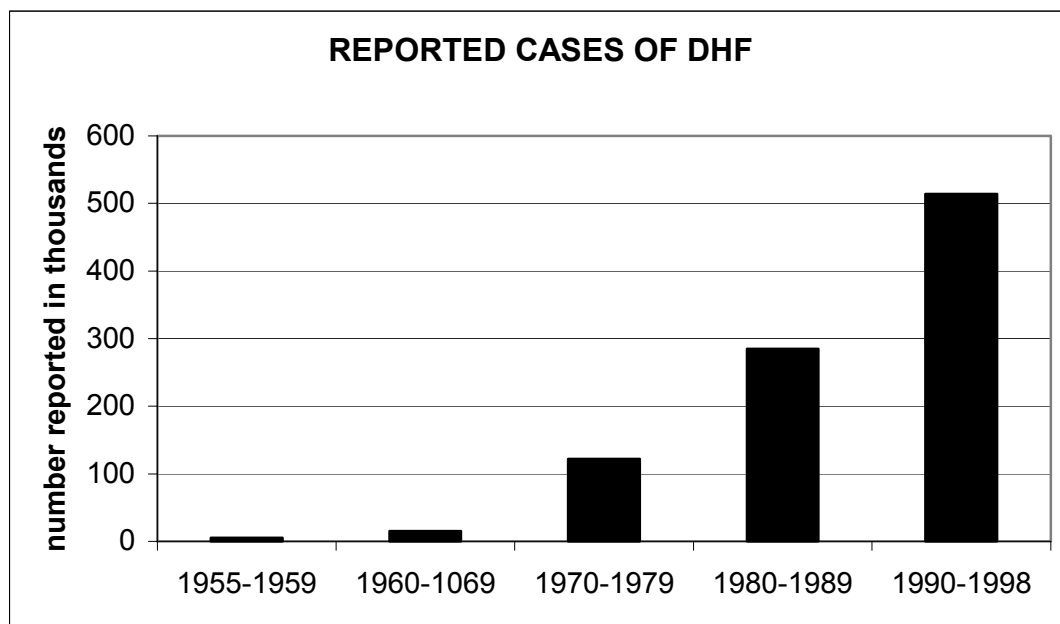
**Convened by**

**The Pan American Health Organization  
The Rockefeller Foundation  
The Pediatric Dengue Vaccine Initiative**

## Executive Summary

### Background

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are caused by the mosquito borne virus, dengue virus, of which there are four antigenically distinct serotypes. It is estimated that annually these viruses cause at least 20 million infections worldwide leading to some 24,000 deaths (WHO, [http://www.who.int/health\\_topics/dengue/en/](http://www.who.int/health_topics/dengue/en/)). The alarming rise in dengue hemorrhagic fever in the world today is illustrated most starkly by the chart below which represents data from the World Health Organization (WHO) showing the rise of DHF cases over the last four decades. Indeed the first two years of the new millennium has seen outbreak after outbreak of DHF not only in Southeast Asia where DHF has been seen for half a century, but also in many countries of South and Central America.



*Source:* WHO; adapted from [http://www.who.int/health\\_topics/dengue/en/](http://www.who.int/health_topics/dengue/en/)

While there is no doubt that severe dengue is spreading from countries in Southeast Asia to countries in the Pacific and in the Americas, there is also no doubt that many international efforts into the development of dengue vaccines have led to a number of promising vaccine candidates which may offer some solutions to the control of this disease. The Pediatric Dengue Vaccine Initiative (PDVI) is committed to promoting and facilitating the development of a vaccine which would be safe and effective for children in the developing world where endemic transmission of dengue puts millions at risk.

In the effort to facilitate the development of a pediatric vaccine against dengue, it is necessary to obtain not only epidemiological and statistical data on the actual numbers of people affected, but also to obtain meaningful data on the burden of illness to the social system and the community. In other words, we need to begin to design and carry out good studies which will provide a more complete picture of what it costs us to have the spread of

DHF continue in this current trend. We need data not only on the monetary costs to health systems of managing each case of dengue infection, DF or DHF, but also need a way to measure the intangible costs to families, to communities and ultimately to the whole social system. Thus the burden of illness studies which PDVI is seeking will provide inputs and insights into the total cost of dengue disease, and will be able to inform policy makers as well as vaccine manufacturers of the benefits of controlling the spread of dengue.

PDVI in collaboration with PAHO/WHO and the Rockefeller Foundation convened a workshop in Washington DC from 5-7 November 2002 in order to begin the process of discussion and consultation to formulate such burden of illness studies from countries with endemic and epidemic dengue today.

### **Format of the Workshop**

A document explaining the rationale for the workshop, including the agenda had been circulated prior to the convening of the workshop (Appendix 1) and participants arrived in Washington DC with some idea of what burden of illness research they would be interested in carrying out in their countries. The workshop was designed to bring together interested researchers with resource persons who could assist in providing some inputs into the final project plan as well as to share ideas and information with participants from other countries. This was to be achieved through a series of presentations by key resource persons followed by breakout sessions during which participant groups assisted by a facilitator would engage in discussions with resource persons of their choice.

Presentations from resource persons were very comprehensive and included:

- A study of the views of policy makers to a dengue vaccine.
- Preliminary data on pharmaco-economics of treatment of dengue cases in one hospital in Malaysia.
- The economic burden imposed on the families of dengue cases, in a study in Thailand.
- An insight into how willingness-to-pay studies are done.
- A socio-cultural perspective on illness and health, and the value of exploring local perspectives.
- A look at dengue haemorrhagic fever as it emerges in Bangladesh.

On the final day of the workshop, participants had an opportunity to present to the whole group a sketch of what projects they had planned.

### **Participation**

The workshop was attended by scientists, doctors and public health professionals from the government sector as well as universities and research institutions from 14 countries in Asia and the Americas. Resource persons and facilitators came from diverse backgrounds and countries and provided their assistance and expertise in fields ranging from economics,

statistics, public health and virology. The individuals who attended the workshop are listed in Appendix 2.

### Country Presentations

On the final day, participants from 14 countries gave presentations on the dengue situation in their countries and talked about what kind of studies they felt would be most useful for them. Seven of the countries were keen to do community based studies while six were planning hospital based studies. All but two countries had a cost or economic component planned and a few wished to include also socio-behavioral and/or entomological studies to their projects. A summary is shown in the table below.

**Summary of Components Addressed in the Proposed Projects from Each Country**

Country	Community based	Hospital based	Cost/Economic component	Socio-Behavioral	Entomology	Other
Bangladesh	✓		✓	✓	✓	
Brazil	✓		✓		✓	
Cambodia		✓				
Guatemala		✓	✓			
Indonesia	✓		✓	✓		
Laos			✓	✓		✓
Malaysia	✓		✓			
Nicaragua		✓	✓			
Panama		✓				
Philippines	✓		✓	✓	✓	
El Salvador		✓	✓			
Thailand	✓		✓			
Venezuela		✓	✓			
VietNam	✓		✓			

The breadth of experience brought to the workshop by the participants was formidable. Different countries were at different stages in the progression of dengue from sporadic to endemic and epidemic, from DF to DHF, from emerging to established infection, from urban to rural. All had insights to offer and all had different needs.

### Recommendations

The workshop deliberations established that the spread of dengue virus is of serious concern to all the countries represented. Participants have the interest and commitment to design and carry out burden of illness studies which have the potential to inform decisions about public health intervention for disease control. Thus, some of the many issues that participants have thought about are listed here:

- A wide range of studies should be supported from many different countries to provide comparative data and a flow of information and experience through the dengue affected regions.

- Studies need not be limited to measuring the cost of hospital care for severely ill patients.
- The socio-cultural dimension to dengue disease in different settings would be informative and useful.
- The burden (financial, psychological, social) to a family of having a dengue-ill child needs to be better defined and better recognised.
- The cost of improved vector control and disease surveillance needs to be factored into our estimates of burden of illness.
- Innovative alternative methods of dengue control need to be considered.
- The cost of care and care-giving associated with non-specific febrile illness due to dengue or less severe dengue illness needs to be estimated.
- This requires a means of estimating the true incidence of infection and disease which is not DHF.
- Most surveillance programs in place are passive and will not provide data on the true incidence of dengue infection since the proportion of very ill to mild cases is thought to be small. It is expected therefore that there are many more dengue infections which are unrecognized, which also contribute to the burden of illness.

Although this workshop was organized to discuss studies about burden of illness, other important issues about dengue disease were found to be of interest as well, and some means of supporting investigations into these should be found.

- In particular, some participants pointed out that there was a great difference in clinical outcomes in different settings in some countries. This is due to late recognition of the syndrome, or delayed presentation. Participants called for more training opportunities for clinicians. Although differences in clinical outcomes in different settings is likely to be an equity issue (differences in access to health care, remote from health care centers, inability to afford health care, differences in allocation of resources to healthcare centers) it seems also that socio-cultural studies into the reasons for such differences may contribute to developing more effective health education material.
- Accuracy of laboratory diagnosis and standardization of these methods was another issue of concern to some participants.

Participants were also interested in the wider program of research leading towards the management and control of dengue, including questions of pathogenesis, virulence, strain differences and strategies for vaccine design. It is clear that there is much yet to be done to understand dengue, but that the number of vaccine candidates under development should offer us hope that dengue will one day be controlled.

Finally, the participants were given recommendations to prepare final protocols and a date in January 2003 to present the proposal to PDVI for consideration. To start out with, a project from each of the Regions (America and Asia) were to be considered for funding, and the rest pending the availability of further funding.

As a follow-up note, 10 proposals were presented by nine countries. A brief summary of these can be found in Appendix 3.

## Appendix 1

# Workshop on Dengue Burden Studies

(Washington, DC, 5-7 November 2002)

Convened by:

The Pan American Health Organization  
The Rockefeller Foundation  
The Pediatric Dengue Vaccine Initiative

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## Background

Dengue has become a major international public health concern, spreading geographically in incidence and severity. Before 1970, only 9 countries worldwide reported dengue hemorrhagic fever, a number that has increased more than four-fold and continues to rise. Dengue viruses are now transmitted in nearly 100 tropical countries and it is estimated that each year 50 -100 million dengue infections occur with 250 – 500,000 cases of dengue hemorrhagic fever (DHF) and at least 2-3000 deaths reported, mostly of children (1,2). The 20-21<sup>st</sup> century dengue pandemic directly grew out of contemporary demographic and life-style trends - the population explosion, urbanization and rapid transportation of large numbers of people. In view of the difficulty and expense of national programs of mosquito abatement, dengue vaccines offer a realistic and near-term solution for the control a major global health problem.

*Surveillance systems and Problems:* Hospitalized DHF cases and deaths have been reported annually to the Western Pacific and Southeast Asian Regional Offices of the WHO for more than 30 years. In the early decades of this period, most countries in the two regions subsidized universal in-patient care through national hospital systems. Since dengue is an urban disease, it has been estimated that this reporting frame was nearly complete. In recent years, progressively more outpatient and in-patient care has been provided by the private sector. Case reporting from the private sector is notoriously incomplete.

The modern dengue pandemic arrived in the American region in 1977. There, already a significant portion of medical care was provided by the private sector, resulting in under-reporting. In the Americas, dengue was introduced into naïve populations resulting in high infection and clinical attack rates in adults. Each year, thousands of cases of dengue fever (DF) have been reported and following the pattern in SE Asia, dengue syndromes in the Americas have become more severe.

As a result of the above factors a number of problems confound an accurate assessment of the illness burden imposed by dengue. First, the symptoms of dengue fever (DF) are difficult to distinguish from other common febrile illnesses. DF and DHF may not be suspected or recognized in many places. Second, DHF cannot be diagnosed using clinical judgment alone. Laboratory tests (hematocrits and platelet counts) are needed to correctly identify a case of DHF and, ideally, virologic or serologic tests to confirm it. Laboratory equipment to perform a complete array of diagnostic tests is often not available either in health centers or nationally. Third, the case definitions differ among countries, with some reporting only laboratory-confirmed cases whereas others reporting clinically diagnosed cases as well. Some countries report cases and deaths from DF and DHF separately; others report DF and DHF combined. Problems of over- and under-diagnosis, incomplete reporting and delays also weaken surveillance for dengue. Finally, proper surveillance of dengue should also include the monitoring of serotypes circulating in the population. The introduction of a new serotype may be an important indicator of future epidemics of DHF. In many countries laboratories need considerable strengthening to monitor circulating serotypes (3).

Since the surveillance systems from country to country are not standardized, the private-public sector mix is not known, and diagnostic criteria are not evenly applied internationally, the true burden of dengue is unclear.

*Estimating Incidence Rates:* Other than national reporting systems, hospital based descriptive studies provide some useful epidemiologic information (4-11). However, usually their denominator is unknown, making it impossible to calculate incidence rates. Longitudinal prospective studies follow subjects over a period of time and can provide incidence rates but only for the year(s) of study. A half-season study in Bangkok in 1980 followed children aged 4 to 16 years of age (12). Over a seven-month period, among susceptibles there was a dengue infection rate of 47/747 (6.3%). Seven of 47



children with a documented second dengue infection were hospitalized. The part-season and part-childhood DHF hospital admission rate was 7/1757 (40/10,000). In the same year, in Rayong, Thailand, the incidence of dengue infection in 251 seronegative children over a 12-month period was 39.4% (13). Among the 18,154 children, aged less than 15 years resident in the study area, there were 127 DHF cases reported to national health authorities (69/10,000). Of the total, 89 were serologically proven dengue (55 DHF cases); 3 inconclusive and 22 without adequate specimens for diagnostic study. Hospitalized cases that might have been dengue totaled 114 (63/10,000). A seroepidemiological study in Yogyakarta followed a cohort of children 4 to 9 years of age from 1995 to 1996(14). The total dengue infection rate was 536/1837 (29.2%). The outpatient consultation rate for fevers was 107/1837 (5.8%), of which 11/107 (10.3%) were confirmed as dengue. The hospital admission rate for DHF/DSS was 0.4% (7/1837) and 1/1837 (0.05%) child died of a DSS-like illness. The hospitalization rate in the latter study was similar to that in the Bangkok study. Both of these studies included only a portion of all children at risk for dengue infections and omitted most fatal cases (not enrolled in study). Since age-specific hospitalization rates are known to vary markedly, data from a selected childhood sample cannot be extrapolated to the whole population. Only the Rayong study reported total hospitalizations for all at risk children. This brief review illustrates the limitations in using published prospective studies to calculate incidence data as they were designed as risk factor studies.

*Dengue Control Efforts:* All dengue-endemic countries support *Aedes aegypti* abatement programs using a combination of national and local funding. Dengue control programs include larviciding at the household level and in public places, e.g., schools and hospitals, and adulticiding, often at locales where DHF cases have been reported. Despite early success achieved in controlling *Aedes aegypti* during the period 1930-1960 as a part of the hemispheric program to control yellow fever in the Americas (15), recent national programs have rarely been effective. Except for those supported by strong central governments in Cuba and Singapore, modern *Aedes aegypti* control programs are in disarray (16). The development of a vaccine offers the only effective promise for the long-term control of dengue infection (17, 18). A recent analysis showed much more favorable cost-effectiveness of a dengue vaccine compared to an integrated vector control strategy since the latter has to be enforced/delivered repeatedly to provide effective protection (19).

## **Pediatric Dengue Vaccine Initiative (PDVI)**

Dengue 1-4 are single-stranded RNA viruses that usually produce short, self-limited illnesses in humans and readily induce life-long immunity. In a subset of these cases, the more severe DHF occurs, and this has been associated with secondary infections by a dengue type different from the one that caused the primary infection. Related viruses, yellow fever and Japanese encephalitis, are successfully prevented by live-attenuated vaccines. The goal is to develop tetravalent (D1, D2, D3, D4) vaccines that can protect against DF and /or DHF. Existing technologies have resulted in several robust dengue vaccine candidates, many in Phase 1 or 2 testing. The challenge is to determine those candidates that best provide long-lasting protection against all four dengue viruses and that are safe for large-scale administration (one concern being the possible sensitization of vaccine recipients). At a meeting convened by the Rockefeller Foundation and the International Vaccine Institute in Ho Chi Minh City, Vietnam, December 5-8, 2001, a consensus was reached among attending scientists that a safe, broadly protective dengue vaccine for children can be achieved *in a matter of years* by a focused, intense effort.

The Pediatric Dengue Vaccine Initiative (PDVI) has been formed to coordinate and support a comprehensive effort to raise awareness and work with public and private partners to accelerate the development and introduction of a dengue vaccine that is appropriate, safe and accessible to children in endemic countries. Initial specific goals include the following:

- To energize advocacy and fund-raising.
- To commission country surveys needed to better define the burden of dengue illness, to understand its public health impact, and to obtain information on the pediatric dengue vaccine market.
- Field-testing of candidate dengue vaccines.
- To improve vaccine safety by directing funds to research on the mechanisms that protect humans from dengue infections.
- To support development of improved dengue vaccines.

Enhanced developing country science capacity and public health should be a planned beneficiary.

*Purpose of Burden of Illness Studies:* The Final Report of the Working Groups of the 2001 Vietnam meeting included recommendations that a mechanism be found to plan, commission and analyze country surveys to improve understanding of dengue disease burden, assess current surveillance systems, design improved surveillance systems and promote their adoption. Based upon past experience, particularly with the introduction of hepatitis B vaccines, it is felt that several country-specific burden of disease data will be crucial to the policy and health prioritization debates, in cost-of-illness analysis, in informing decisions on dengue research, and in budgeting for the development, field-testing, and acquisition of future dengue vaccines. To the extent possible, similar studies should be commissioned in selected dengue-endemic countries. Because representatives from PAHO, WPRO, SEARO were present at the Vietnam meeting, it was agreed to organize a follow-on meeting to be attended by representatives of member countries from the three regions in Washington, D.C. in November 2002 under co-sponsorship of PAHO and the Rockefeller Foundation.

These burden of disease studies will also assist in the identification of potential sites where future vaccine trials, especially phase III efficacy trials, could be conducted. An accurate determination of the incidence of DF and DHF in selected populations is a pre-requisite for the estimation of sample sizes in the design of efficacy trials. (For instance, incidences of DHF of 0.4% per year may necessitate 10,000 to 20,000 dengue-negative volunteers to be followed over 2-3 years, to detect a protective efficacy of 40-50%). Different vaccine field evaluation sites (in different regions) may be needed to assess the efficacy of different types of candidate vaccines, in different populations, and against different dengue virus types (although some of that could be done as post-licensing phase IV trials)

Over and above preparing for future vaccine trials, these burden of disease studies will reflect and address the needs of each country. Preparation and conduct of the studies will increase in-country capacity for diagnosis and surveillance. The results from these studies would be of extreme usefulness for advocacy and control efforts.

## **Mekong Basin Disease Surveillance (MBDS) Network**

The MBDS was established in 1999 with representatives from six member countries (Cambodia, China, Lao PDR, Myanmar, Thailand and Vietnam). The objectives of the MBDS are to strengthen sustainable national capacities in disease surveillance, outbreak investigation and response; to strengthen human resource development in the area of field epidemiology, and to establish a sub-regional network for disease surveillance and information exchange. The MBDS held a meeting on December 9, 2001 on the epidemiology and surveillance of dengue in the Mekong Basin countries. Each participant gave a brief presentation of the dengue situation in his/her country. This was

followed by discussion on a review on existing epidemiological data on dengue from the Mekong Region countries (20). The participants also discussed possible methods to quantify the burden of dengue. It was agreed that there are many purposes for collecting burden of disease data on dengue over an above the vaccine goal, particularly for strengthening surveillance systems.

## **Preparatory Activities prior to the Workshop**

*Asia:* Currently dengue is endemic in all continents but the burden of disease is greatest in Asia, where in many countries DHF is a leading cause of pediatric hospitalization and death. The countries belonging to the WHO Southeast Asian region are stratified in terms of dengue endemicity (21). In Indonesia, Myanmar and Thailand, epidemics have been caused by all four virus serotypes during the past 20 years, multiple virus serotypes are circulating, there is high morbidity in children and epidemics occur in urban centers every 3 to 5 years. In Bangladesh, India, Maldives and Sri Lanka, DHF is an emerging disease, epidemics are becoming more frequent, multiple virus serotypes are circulating, and the disease is spreading within countries. In Bhutan and Nepal, there are no reported cases and endemicity is uncertain. Thirty-three of the 37 countries belonging to the WHO Western Pacific Region have epidemic dengue (22). Singapore has been the one country in the region, which has been able to maintain a low incidence of dengue through an integrated mosquito control program incorporating source reduction, health education and law enforcement implemented since 1969 (23,24).

The strengths and shortcomings of the national reporting systems for dengue in Bangladesh, Cambodia, China, Indonesia, Lao PDR, Malaysia, the Philippines, Thailand and Vietnam were explored and discussed during visits to these countries by PDVI Senior Adviser, Dr Scott Halstead, and PDVI coordinator, Dr Jacqueline Deen, in May 2002 and during a meeting held in Bangkok on June 20, 2002 (see Meeting notes, Appendix A). During the meeting, country representatives and members of the MBDS expressed their willingness to join the effort of planning strategies to better define the burden of dengue.

From July to October 2002, Denise DeRoeck, a vaccine policy consultant, will conduct a policymaker survey on dengue in Vietnam, the Philippines, Indonesia and Cambodia. The objective of the survey is to document the perceptions of key policymakers and influential professionals concerning the extent and seriousness of dengue in their country; the minimum criteria that they would require in dengue vaccines, in terms of cost, performance and vaccine characteristics; feasible or preferable strategies for the introduction and use of future dengue vaccines; and the types of data policymakers require to facilitate decisions concerning the field-testing and implementation of future dengue vaccines. Information from the surveys will help in the planning of the burden of disease studies to make its objectives responsive to the needs and priorities of dengue-endemic countries.

*Latin America:* The first DHF epidemic in the Americas occurred in Cuba in 1981. Subsequently 24 other countries in the Region have reported DHF and its incidence shows a marked upward trend (25). In 2001 alone, there were more than 609,000 reported cases of dengue in the Americas, of which 15000 were DHF. Not only is the number of cases increasing as the disease is spreading to new areas, but explosive outbreaks are occurring (26).

The present status of dengue surveillance and laboratory diagnosis was discussed in the context of establishing DengueNet, a global surveillance system, with eight countries and territories in the American region at a meeting organized by PAHO and WHO, 9-11 July 2002 in San Juan, Puerto Rico. During this meeting representatives from PAHO and the PDVI discussed dengue burden of illness studies individually with delegates from Latin American countries. All expressed an interest in preparing study protocols and attending a follow-on meeting in November. Further

discussions and protocol preparation will be carried out by e-mail correspondence with the planners of the November meeting.

## **Objective of the Workshop**

The objective of the workshop is to review, refine and prepare study proposals to define the epidemiologic, economic and social burden of dengue illnesses. Expected outcomes are several finished country-level budgeted proposals for the study of the burden of dengue.

## **Format of the Workshop**

Prior to the workshop, preliminary discussions with potential principal investigators from Asian and Latin American countries were held, including the dissemination of guidelines for proposals to study the burden of dengue (see Appendix B). The guidelines include those for prospective community-based studies, economics studies, socio-behavioral studies, and studies on using routinely collected data. Country representatives who expressed interest were requested to prepare proposal frameworks, which would be finalized during the workshop with the assistance of epidemiologists, health economists, social scientists and surveillance experts. As much as possible, these burden of disease studies are tailored to the capabilities and needs of each country and on their own, would be beneficial to the national dengue program.

The format of the workshop will be mainly group discussion to clarify points and reach agreement regarding standardization of the proposal formats so that studies are comparable across countries. There will also be working group sessions during which time country-level proposals will be finalized. This will also be an opportunity for proposals other than those based on the guidelines can be discussed. Epidemiologists, health economists, social scientists and other experts in the field will facilitate the workshop. The agenda is shown in Appendix C and a list of participant and facilitators in Appendix D.

## **Follow-Up to the Workshop**

At the conclusion of the workshop we expect the following near-final proposals:

- 3 study sites that will assess existing national reporting systems and use routinely collected data to assess the burden of dengue over 3 years
- 4 prospective, community-based surveillance sites over 3 years. The criteria for selection of study sites will include: the expected disease burden, research experience of the investigators, the submitted budget, and the likelihood to become a vaccine evaluation site
- 1 to 2 proposals that will focus on other complementary issues

The proposals will be submitted to funding agencies. These include the Bill and Melinda Gates Foundation and the Rockefeller Foundation. A workshop report will be prepared to include the standardized guidelines as amended with the consensus of the group, the budgeted proposals and a plan on how to move forward.

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## Appendix A: Meeting Notes—Planning Dengue Burden of Disease Studies (Bangkok, June 20, 2002)

Participants: S Halstead, H Oshitani, R Breiman, N Chantha, O Vandine, R Kusriatuti, S Archkhavongs, R Capeding, K Bunthamcharoen, S Chunharas, P Kantipong, S Kongsin, G Rasul, P Sawanpanyalert, J Suaya, P T Nga, D Thac, L Yuhua, L R Petersen, L von Seidlein and J Deen.

0915 – Dr Scott Halstead presented the history and *objectives of the PDVI*, as follows:

- To better define the burden of dengue and conduct cost-effectiveness studies of a future dengue vaccine. This process will be started today.
- To conduct a policymaker survey.
- To organize and support several new field sites where dengue infections can be studied and ultimately where Phase 3 trials can be conducted.
- To support and strengthen dengue research, particularly on the question of vaccine safety and vaccine research and development.
- Advocacy and fund-raising.

He explained that this meeting was called to specifically consider the generic issues in defining the dengue burden of illness. During the meeting, models of dengue disease burden studies will be presented and the participants will be asked whether they would be interested to develop a proposal (with assistance) during the next few months. Proposals should be ready for presentation at the global meeting sponsored by PAHO in November 2002.

0930 – Participants introduced themselves.

0945 – Discussion on *measuring the burden of dengue* - Representatives from Thailand, Vietnam, Indonesia, the Philippines, Bangladesh, China, and Cambodia presented and discussed the strengths and shortcomings of their national dengue reporting systems. Scott Halstead suggested that one option of better defining the burden of dengue would be by strengthening national disease reporting systems and using the data that these systems provide.

1330 – *Quantifying the burden of dengue using DALYs and QALYs* – Dr Suaya explained the data that would be needed and the process for calculation. The information needed would include: incidence, duration, quality of life, days of school lost/productivity lost, product lost due to care, hospital and government cost. This information would be needed for each of the categories of dengue infections, clinical DF, DHF/DSS and death. Dr Kongsin brought up the issue of demand for the dengue vaccine.

1430 – The International Vaccine Institute's experience with *prospective community-based, burden of disease studies* - Dr von Seidlein described the DOMI (typhoid, cholera and Shigella) program, started in 1997. Components of the burden of disease studies include surveillance, socio-behavioral and economic studies and collection of existing data. The studies are population-based with passive surveillance. The population size varies from country to country. Census is done at the beginning and at the end of the study. Health utilization surveys are done to estimate the number of persons coming to the surveillance health sites.

Dr Breiman highlighted some issues:

1. Normally when vaccines are available, they are handed to the Ministries of Health for possible implementation. The DOMI program turned around the construct whereby, information is gathered prior to the availability of the vaccine.

2. The methodology and microbiologic methods are standardized and comparable across sites. Whether a passive approach would be appropriate for dengue is not known.
3. Multiple sites crossing over cultural issues help make the study more useful to a larger geographic area.
4. Characteristics of the ideal study site include: endemicity of the disease, manageability, logistics, limited number of hospitals,

Dr Petersen described the active surveillance system of individuals under 15 years old in an area in Vietnam. Whenever a case was suspected, a card is filled out and blood is collected and submitted to the primary health care center for a complete blood count and dengue serology and to Pasteur Institute for viral isolation and PCR. 80% of the reported cases are males. It has been relatively easy to set up because the local people are very interested and involved. The key elements include laboratory procedures close-by and local investigators who want to make it work. This project was started 3 months ago.

1600 – Dr Halstead *summarized the discussions*. He requested the participants to think about proposals that could be submitted for funding. Various options are possible, depending on the country's capacity and needs. Consultants could come to work with the countries.

After a discussion, it was decided that participants from this meeting would be contacted and asked whether they would be interested in developing a proposal. If yes, they should submit:

1. A statement of interest and intent
2. Brief description of the type of study and potential locations
3. The objective(s) of the study
4. Brief description of the method(s)
5. The expected output
6. The budget
7. Assistance that will be needed to develop the proposal

1700 – The meeting was adjourned.



# Appendix B: Guidelines Sent to Potential Principal Investigators

## 1. Guidelines for Dengue Prospective Community-Based Studies

### Introduction

To learn more about the epidemiology and clinical burden of dengue, one method would be to conduct a surveillance of populations residing in defined catchment areas. Health care providers in a catchment area will be requested to send/report all cases of fever of 7 days or less presenting to them. This passive surveillance will allow us to estimate the incidence of dengue infections severe enough to warrant clinical attention. In addition, each site will determine the additional types of information that they believe would be important to collect during the surveillance study.

Prospective seroepidemiologic studies to estimate the dengue burden of disease require the following:

- a defined population denominator that will allow calculation of incidence rates in the community;
- good surveillance to optimize the detection of febrile episodes and perform laboratory confirmation;
- an appropriate laboratory method to diagnose dengue infections;
- a study duration of 3 years or more since epidemics of DF/DHF occur, resulting in year-to-year variation of the disease burden;
- inclusion of a wide age band since epidemiologic patterns vary from country to country and is important when considering the target populations for future immunization; and
- multiple sites since the epidemiology of dengue varies from country to country, there are several vaccine candidates in different stages of development and there may be delay or termination of activities in any one or more of the study sites.

The first step towards prospective surveillance studies is to draft a protocol that could be used in various sites, so as to get comparable results. Potential primary investigators from various countries in Asia and Latin America will be invited to a workshop from November 4 to 6, 2002 in the Washington DC area to develop proposals with the help of epidemiologists, health economists, and a social scientist. The submitted proposals will be ranked based on the expected disease burden in the study area, the likelihood for the study area to become a vaccine evaluation site, research experience and the submitted budget. Final selection will be determined by the amount of research funding available and the potential study site's ranking.

### Background Data Needed for Preparing Proposals

Ideally, the following general information on the potential study population should be outlined prior to the November workshop:

- a. Map(s) of potential study population(s), with geographical boundaries;
- b. The age (0-11.9 months, 12-59.9 months, 5-14.9 years, 15-40 years, >40 years) and gender distribution of these populations, if available.
- c. The incidence of DF, DHF and dengue-related deaths by age-group, if available
- d. The stability of the populations (migration rates), if available;
- e. The sources of outpatient and inpatient care, both private and public; information on how accessible this care is to the population (geographically and financially), as well as about the

- extent to which the target population receives alternative health care for fever (e.g., from pharmacists, traditional healers) would be ideal.
- f. The proportion of consultations with the clinical diagnosis of DF/DHF *from clinic data* (to estimate the burden of dengue on out-patient/clinic facilities).

Data under b and c, if available, will be used to calculate sample size.

## **Proposed Study Methodology (to be discussed during the November workshop)**

### **a. Preparation of the Communities**

Prior to the start of the study, it is recommended that efforts be made to obtain community support. Discussions about the study should be undertaken with community leaders in order to obtain their endorsement. Health practitioners (medical and alternative) will be encouraged to report/send all residents of the study area with fever of 7 days or less requiring clinical attention to a surveillance center. One method to increase participation in the surveillance is to offer reliable and free laboratory tests (e.g. complete blood count and follow-up hematocrit values).

### **b. Baseline Census**

At the outset of the study, a census of the source population will be conducted. In order to keep track of residents who present for care of fever, each person in the census will be assigned a unique identification number. It is also useful to distribute to each resident, an identification card giving the identification number and birth date, the household address and the name of the household head. On the back of the card will be instructions in the local language stating the health benefits and locations of the study treatment sites. Residents will be encouraged to bring this card to a treatment site when presenting for medical care. It is recommended that the census of the source population be done just prior to the start of surveillance for dengue infections.

### **c. Surveillance Centers**

Each study site will develop a plan of how to capture all episodes of fever requiring clinical attention among the study population. Surveillance centers may be set-up independently or within the premises of health centers, hospitals and medical practitioners. Every resident of the study population who is brought to the surveillance center for fever of 7 days or less will have several pieces of information entered into a clinical research form. Since an individual may be brought more than once over several days of fever to one or more surveillance centers, the clinical log form will have a carbon copy given to the patient, parent or guardian, which will be presented during subsequent visits. Blood will be collected during the initial visit to a surveillance center for a complete blood count and dengue test. The optimal diagnostic test for dengue will be determined. The laboratory results will be given back to the patients and his/her physician within a reasonable time frame so that these can be used in the clinical management.

A field worker will visit the individual within 1 to 2 weeks after the collection of the first (acute phase) blood sample to request for a follow-up (convalescent phase) blood sample. During the follow up visit, the field worker will confirm the individual's demographic data and ID number. A follow-up form will be completed to record hospitalization, outcome and any signs and symptoms still present. The total number of days off from school or work, as appropriate, will be recorded. Determination of cost-of-illness (economics component) may be integrated into these follow-up visits.

Health care personnel at the surveillance centers will be trained in the appropriate assessment, treatment and referral of patients suspected to have DF/DHF. The *Integrated Management of Childhood Illness* (adapted by country) provides current WHO guidelines appropriate for the management of children less than five years of age with fever. There are also WHO guidelines for the management of DF/DHF appropriate for all age groups. Patients will be referred for hospitalization as appropriate.

The records of each hospitalized suspected DHF case will be reviewed by a pediatrician who is not associated with the study and without knowledge of virologic and serologic results. WHO case definitions of DHF/DSS will be used which define DHF as

- Presence or history of fever for 2 to 7 days,
- Hemorrhagic tendencies,
- Thrombocytopenia of 100,000 cells per m<sup>3</sup> or less, and
- Evidence of plasma leakage manifested as a rise in the hematocrit equal to or greater than 20% above average, a drop in the hematocrit following volume-replacement treatment equal to or greater than 20% of the baseline, or signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia

DSS is defined as all of the above four criteria for DHF plus evidence of circulatory failure. Cases of dengue etiology not meeting the criteria for DHF/DSS will be classified as DF.

A minimum of three months will be required for start-up before the two-year surveillance begins. This period will be devoted to development of clinical research forms and training health workers and supervisors on the appropriate collection of data and of specimens, as well as on the standard approach to patients with fever. It will also be devoted to conducting a “dry-run” of surveillance in order to correct major problems before definitive surveillance begins.

#### **d. Supervision of Surveillance**

It is recommended that a trained physician-supervisor visit each surveillance center on a regular basis. At the beginning of the surveillance period, such visits will be frequent, e.g. once per week. Later, as the study progresses, judgment can be used in deciding to decrease the frequency of such visits, but in no case will it be less frequent than once every other week. During the visits, the supervisor will check to make sure that the facility is equipped with all supplies necessary to conduct the surveillance and that the registry log book and clinical research forms are being completed properly.

The principal investigator will check all supervisory forms on a regular (e.g., weekly) basis so that corrective actions can be instituted as quickly as possible. Regular meetings of personnel involved in the study will be instituted, so that any problems that may arise can be discussed and solutions identified.

#### **e. Close out Census and Serology**

At the end of the first year and at the end of the 2-year surveillance period, a repeat census will be conducted. To facilitate the interim and closeout censuses, it is recommended that the baseline census be computerized and printed into books, with one page devoted to each household. Each household page would give the name, age, sex, and identification numbers of each member. Additional data fields will be included for entry of the following information about each household member: whether the person had migrated out (and when); whether person had died; and whether fever had occurred in the past month and the names of all health centers where care was sought. Spaces will also be included for addition of new household members and dates of births and in-

migrations. Moreover, blank pages will be included for addition of new households. A verbal autopsy will be done for each death to determine the likely cause of death.

#### **f. Data Management**

Data management programs will be required for data entry from each form and for automatic checking to determine that the entered data for each record are complete and consistent. Problems noted (missing data, inconsistent data) will be printed out; one or more members of a “data team” will then be responsible for updating those errors that can be resolved by inspecting the original data forms or by inspecting information from other data files. It also will be important to be able to link records from related data files. For example, for each treatment visit, it will be important to link the related census record, if it exists, as well as the related laboratory results record. Errors in linkage (missing linkage or linkage of records of different individuals) require detection and, if possible, resolution via correction of erroneous information in individual records.

#### **g. Data Analysis**

The analysis of disease burden will focus on the incidence of dengue infections, DHF episodes and on the incidence of dengue-related deaths.

- The incidence of dengue infections will be calculated, as the number of dengue infections detected during each year of surveillance divided by the person-time at risk (approximated, in person-years, by the average of the number of persons in the baseline and close-out censuses).
- The incidence of DHF episodes will be calculated, as the number of DHF episodes detected during each year of surveillance divided by the person-time at risk (approximated, in person-years, by the average of the number of persons in the baseline and close-out censuses).
- The incidence of dengue death will be calculated, as the number of dengue deaths noted in the close-out census among persons in the baseline census, divided by the person-time of follow-up contributed by the population in the baseline census. Person-time for this calculation is one year for each person present in two sequential censuses, one half year for persons lost to follow-up between the censuses, and the time from onset of surveillance to death for persons who died during the surveillance period. Individuals present at the first and the third, close out census but absent at the time of the interim census after one year may have to be interviewed about residence status following the close out census. The proportion of such deaths that might be related to dengue can be judged by the proportion of febrile episodes detected in the surveillance centers that are associated with dengue.

#### **h. Size of the Required Study Population**

The size of the population needed will be determined by the need to estimate the following with suitable precision: 1) the incidence of dengue mortality in persons <5 years, >5 to 15, >15 years of age; and 2) the incidence of dengue fever in persons <5 years, >5 to 15, >15 years of age. In a previous 1-year prospective study done in Yogyakarta, among 1837 children 4 to 10 years of age, there were 11 episodes of fever requiring medical attention that were confirmed as dengue, with one death (5 dengue-related deaths/10,000 children 4-10 years of age/year).

### **i. Health Utilization Survey**

The aim of the health utilization survey is to explore the percentage of individuals living in the study catchment area that actually makes use of the surveillance centers. The results from the health utilization survey will help estimate the accuracy of the incidence data that are collected. The health utilization survey can be integrated into the baseline and follow-up census.

### **j. Socio-Behavioral Studies**

Socio-behavioral studies may also be conducted in the surveillance study population. The objective of these studies is to describe preventive behaviors and health seeking practices related to dengue from the perspective of community leaders, residents, and members of the health system. The research will describe past experiences with vaccination programs, and possible barriers and facilitators to the acceptability and accessibility of a future dengue vaccination program.

### **k. Economic Studies**

Economic studies may be done in conjunction with the epidemiologic surveillance or done alone. The objective of economic studies is to determine the health care services and individual patient direct and indirect costs associated with DF/DHF. Data obtained could provide an estimate of costs of an illness episode averted, as a partial measure of the country-specific savings that could result from the introduction of a dengue vaccine (i.e. cost effectiveness).

## **2. Guidelines for Dengue Economics Studies**

An estimated 50-100 million cases of dengue fever occur annually, including 250 to 500 thousand cases of dengue hemorrhagic fever and 24 thousand deaths, mostly in children. Currently, there are no licensed dengue vaccines. Research is ongoing and there are several candidate vaccines under development. Once these vaccines are available it will be crucial to know the true disease burden. These economic and disease burden data will be of particular interest to dengue-endemic countries where decisions will need to be made regarding the implementation of newly developed vaccines. It will be important to demonstrate the cost-benefit of vaccine use compared to the cost burden of each episode of dengue and costs to governments for prevention and vector control activities. To provide an estimate of costs of an illness episode averted, as a partial measure of the country-specific savings that could result from the introduction of a dengue vaccine, various methodologies may be employed.

Identification and measurement of direct medical costs during hospitalization

- a. Identification of patients
- b. Identification and measurement of resources used
- c. Calculation of the cost of hospitalization per patient

Identification, measurement, and valuation of direct medical costs

- a. Interview of physicians regarding common practices in treating patients using a standardized data collection form.
- b. Validation using a review of 10 charts per patient with dengue per doctor and/or observation of 10 physician encounters with dengue patients

Identification, measurement and valuation of out-of-pocket expenditures including direct medical and non-medical costs and productivity losses

- a. Convenience sampling using caregivers of newly admitted/consulting patients
- b. Initial interview to include ambulatory and emergency room utilization prior to hospitalization/consultation. Subsequent interviews every 2-3 days (for hospitalized) patients and every other day (for out-patient consultations) to obtain data on days lost from work, travel costs and out-of-pocket expenditures using a standardized data collection form

Valuation: Value of a bed-day

- a. Recurrent Costs
  - Ascertain personnel costs per bed-day in ER/Ward/ICU
  - Add hospital overheads (laundry, cleaning, security, records, housekeeping, administration, etc per bed-day; but exclude pharmaceuticals and diagnostics)
  - Add back diagnosis-specific pharmaceutical and diagnostic cost.
- b. Capital Costs: Obtain current purchase cost annualized over 20 years (buildings) and 5-15 years (equipment) at discount rate of 3%.

Costs in the community and to the government for prevention and vector control activities

### **3. Guidelines for Dengue Socio-Behavioral Studies**

Socio-cultural research including both quantitative and qualitative methodologies can provide important information for understanding health practices, and real and perceived susceptibility to particular diseases with relation to multiple variables including gender, ethnicity, socio-economic status, and social relations within a dynamic historical, political, and economic context. These data can be utilized for the development of health programs in terms of the cultural appropriateness of their content, strategies for program implementation, and removal of potential barriers to delivery and participation, as well as the development of relevant evaluation tools and measures.

The proposed research is to describe preventive behaviors and health seeking practices related to dengue from the perspective of community leaders, residents, and members of the health system. The research will describe past experiences with vaccination programs, and possible barriers and facilitators to the acceptability and accessibility of a future dengue vaccination program.

#### **Phase One: Qualitative/Ethnographic Research**

##### **a. Community Mapping**

The purpose of the community mapping is to understand the socio-cultural-geographical patterns of human interaction and behavior. The community mapping will also allow the researchers to make decisions regarding sampling for both the qualitative and quantitative research phases, and to track the physical distribution of research participants. The mapping could potentially be used in the future during a vaccination trial to track patterns of participation rates by place.

##### **b. Open-Ended Semi-Structured Interviews**

The semi-structured interviews will be conducted with members of the health system including biomedical health practitioners, pharmacists, traditional healers, members of religious organizations (as relevant to providing health services), and other community members engaged in prevention and

treatment of illnesses, e.g., through herbal medications. Semi-structured interviews will also be conducted with community leaders and residents.

### **c. Socio-Cultural Calendar**

A subsample of individuals or care-givers will be asked to complete an additional brief interview designed to develop a socio-cultural and economic annual calendar to assess times of the year when groups of individuals or care-givers may be more or less able to access health care, e.g., because of lack of employment during certain seasons households may have less money, and potentially more or less able or willing to seek health care or to participate in a vaccination program. We will select a subsample of individuals/care-givers from each of the three groups (leaders, members of the health system, residents), and within these groups representative of different sectors, e.g., based on age, income, religion.

### **d. Case Studies**

The case studies will provide a means of recording health-seeking practices of individuals or care-givers of children diagnosed with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome through clinics and hospitals. In addition, we will also select individuals or care-givers of children from the community with suspected dengue to include among the case studies, to understand health-seeking practices outside of the biomedical system. The interviews will take place as soon as is feasible after the individual presents at the clinic and/or hospital and is diagnosed. The initial interviews will be retrospective in terms of what the individual or caregiver did in response to symptoms leading up to going to the clinic or hospital. Likewise, among individuals or care-givers identified in the community, the interview will be retrospective to determine what health-seeking practices have been used up to the time of the interview.

### **e. Key Informants**

Key informants can provide necessary baseline information on beliefs and behaviors related to dengue, its prevention, diagnosis and management. Preliminary information on the explanatory model of dengue in the research area(s) (e.g. perceptions of the etiology of dengue; perceptions of the signs and symptoms of dengue fever, dengue hemorrhagic fever and dengue shock syndrome; local preventative and treatment practices for dengue) will allow the researcher to formulate a basic disease model in the study site. From the key informants the researchers will also gather information to: understand household decision-making related to health care seeking; delineate health seeking behaviors associated with specific signs (e.g. high-grade fever, weakness, etc); determine assessment and management of suspected dengue cases by health providers; identify conceptions of and practices related to illness prevention; understand past experiences with vaccination programs; and determine potential barriers to a dengue vaccine program.

## **Phase Two: Household Surveys**

Household surveys will be developed from the data collected during the initial qualitative phase. The survey will provide more generalizable data on such variables as perceptions of severity, vulnerability, causes of dengue, health seeking practices, and perceptions of need and acceptability of a dengue vaccine.

The interview questions will be read to the respondent by the interviewer so as to minimize any difficulties related to rates of literacy, and to make data collection consistent within and across sites

regardless of literacy levels. Since we do not anticipate particularly personal questions on the survey, there should not be issues related to revealing sensitive information to the interviewer.

### **Phase Three: Data Analysis**

#### **a. Qualitative**

The qualitative data will be analyzed initially at an "ideational" level, thus we will be most concerned with what is said in the context of the interview, how the different parts of the interview fits into single or multiple discourses, and relationships between the texts of interviews within and between individuals or care-givers and groups. Qualitative interview and participant-observation data will be entered into a word processing program, so as to be compatible with use in a text-organizing program, e.g., Ethnograph. Texts will be coded in Ethnograph. In order to ensure the validity of the coding, a sample of texts will be double coded by two individuals or care-givers.

#### **b. Quantitative**

Two basic kinds of quantitative analyses will be used in conjunction with the survey data. The first will involve simple descriptive statistics including frequencies, means, standard deviations, and ranges of responses in order to describe the basic demographics, conditions and attitudes of respondents at each research site, e.g., frequency of episodes of dengue, average income level. Cross-tabulations will also be used in order to describe variations across groups within the population of conditions and attitudes. Descriptive analysis will be performed on all relevant variables prior to inclusion in subsequent higher order analyses. Distributions will be analyzed using standard graphical techniques. Appropriate transformations will be made to the data to address the various underlying statistical assumption, whether the test be parametric or non-parametric. Correlation matrices and principal components factor analysis will be used to determine the extent of multicollinearity.

The second level of analysis will involve univariate, multivariate, conditional logit and probit techniques. These analyses will be utilized to further explore issues related to the health seeking practices of the respondents, and prediction of vaccination acceptability and accessibility. Through the use of multivariate procedures, one can account for the individual contribution of each variable and describe the portion of the dependent variable explained by the combination of a set of theoretically meaningful variables. Two different multivariate approaches will be used: linear and logistic regression and structural equation modeling.

## **4. Guidelines for Using Routinely Collected Data to Quantify the Burden of Dengue**

### **Background**

The Pediatric Dengue Vaccine Initiative (PDVI) is conducting a policymaker survey on dengue in Asian countries. The preliminary results point towards the need for disease burden data for dengue. While there are plans to collect prospective incidence and mortality data through community-based disease surveillance, these data will be limited to the specific areas in each country where the projects are to take place. There may be regional variations in disease incidence. Similarly, longer-term trends will not be detected by the proposed studies. To complement these community-based data and to address policymakers' expressed need for nationwide data, we propose to systematically collect



epidemiological data on dengue from national reporting systems, hospitals, and other unpublished sources prospectively.

The inherent limitation of using routinely-collected data sets is that they rarely relate the numerator to any population base. There may be overlap between different sources and none are complete. Diagnosis of DF, DHF and DSS are mostly based on clinical criteria which may not be adhered to strictly or vary from country to country. DF and DHF may be reported separately or combined. Nevertheless, these routinely collected data will be able to provide an idea of the magnitude and nature of the problem and allow comparison between several countries, particularly if the limitations of the data are recognized and some form of standardization between countries is done. The data may also allow estimation of the burden of dengue relative to other conditions in outpatient and in-patient health facilities and in the public and private sector.

Combining the results of community-based and routinely-collected data will provide a more comprehensive estimate of the incidence and mortality of dengue in Asian countries.

To launch this activity, representatives from the PDVI (Scott Halstead and Jacqueline Deen) have been visiting countries in Asia in May 2002. A meeting with country representatives was held in June 2002 in Bangkok to discuss various methods to quantify the burden of dengue, including the use of routinely-collected data. A workshop is planned for November 2002 in Washington DC to harmonize data collection methods and data management.

### **Variables of Interest (To be discussed before finalization)**

Population-based data on the incidence and the mortality of dengue may be inaccurate, incomplete, or unavailable for each participating country. This will be addressed by conducting an initial assessment to find out the weaknesses and limitations of the national reporting system, followed by recommendations to improve the system. Since changes may be difficult to implement in the short-term, a method called here “triangulation” will be applied. Triangulation refers to the use of several indirect measurements to estimate the variable under investigation. For example the hospital-based national reports may combine dengue fever and dengue hemorrhagic fever together. To calculate the incidence of dengue hemorrhagic fever, the fraction of DHF in reporting hospitals among all dengue cases can be calculated and used to estimate the proportion in the national reports. Another example is incomplete national reporting due to non-inclusion of private sector patients. Health utilization data of the population (private versus public) may be used to quantify the proportion that is excluded from the national reporting system. Similar approaches may be available for an indirect measurement of dengue mortality.

<b>Primary, Essential Data</b>
<ol style="list-style-type: none"> <li>1. Incidence of dengue fever, dengue hemorrhagic fever and dengue shock syndrome</li> <li>2. Dengue – related mortality rate</li> </ol>
<b>Secondary Data</b>
<ol style="list-style-type: none"> <li>1. Age specific incidence of dengue fever, dengue hemorrhagic fever and dengue shock syndrome</li> <li>2. Age specific dengue mortality</li> <li>3. Age specific dengue incidence and mortality, compared to that from other important diseases</li> <li>4. Total number of cases requiring admission versus number of cases treated as outpatients</li> <li>5. Total domiciliary episodes versus episodes requiring care at health centers</li> <li>6. Total episodes in rural settings versus urban settings</li> <li>7. Predominant dengue serotype(s) by area and by year</li> <li>8. Duration of hospitalization for dengue fever, dengue hemorrhagic fever and dengue shock syndrome</li> </ol>
<b>Potential Data for Triangulation</b>
<ol style="list-style-type: none"> <li>1. Domiciliary incidence of fever</li> <li>2. Fraction of the cases who seek care within the private and public health care system</li> <li>3. Fraction of laboratory-confirmed dengue of clinically-diagnosed dengue</li> <li>4. Incidence of fever seeking out-patient care</li> </ol>

## Sources of Data

Dr Debrati Guha-Sapir has conducted an analysis of the existing epidemiologic data (1990 to 1999) on dengue in the Mekong region countries. A similar retrospective analysis would be useful for the other dengue-endemic Asian countries. For prospective collection of data, the following are potential sources of data.

- *Government statistics:* In each of the study countries, the government collects data on dengue. We expect it will be possible to capture in each country for every year government statistics. The data on incidence, mortality and seasonality will be collected from government statistics on a national level.
- *Hospital data:* The collection of hospital data will be an important contributor to the overall data collection, particularly for triangulation purposes.
- *Data from NGOs* such as MSF, John Snow Society, etc
- *Laboratory data* would supplement overall data collection (e.g. serotype data, fraction of laboratory-confirmed cases).
- *State-level or community-level data* (particularly for decentralized countries)
- *Other sources*, as determined by the principal investigators

## **Methods for Summarizing the Data**

Abstraction forms for data collection (government statistics, hospital data, NGO data, laboratory data and other sources) will be prepared by each country representative then standardized / agreed upon during the November workshop. These forms will be completed and submitted to the PDVI every six months for data entry.

## Appendix C: Workshop Agenda

### Tuesday, 5 November 2002

9:00 AM Welcome/ opening remarks/ meeting objectives, *Jorge Arias, Sarah MacFarlane, Scott Halstead*,  
“The value of dengue disease burden estimates”

9:30 AM The results of policymaker survey, *Denise DeRoock*: “Key policymaker views regarding dengue”

10:00 AM Group discussion on national reporting systems: strengths and weaknesses, *facilitated by Alan Schapira, Chusak Prasittsuk, Jorge Arias, Scott Halstead*

#### *Points for discussion*

1. The WHO DF/DHF estimates
2. Application of clinical case definitions for routine surveillance
3. Laboratory confirmation for routine surveillance
4. Sources of data
5. Reporting
6. Analysis
7. Feedback and use of the data

*lunch*

1:30 PM Group discussion on using routinely collected data to quantify the burden of dengue

3:00 PM Pharmaco-economics of dengue vaccines: data needed to calculate costs and impact, *Don Shepard and Jose Suaya*

Afternoon and evening: The working group discusses using routinely collected data to calculate economic burden, *facilitated by: Don Shepard and Jose Suaya*

⇒ Output: proposals using routinely collected data

## Wednesday, 6 November 2002

9:00 AM Kampongphet, Thailand. Impact of dengue fever/dengue hemorrhagic fever in Thailand at the family and population levels. *Danielle Clark*

9:30 AM Community-based prospective studies, the Bangladesh experience. *Robert Breiman*

10:00 AM Group discussion on community-based surveillance for dengue, *facilitated by: Lorenz von Seidlein and Shabbar Jaffar*

### *Points for discussion*

1. Requirements for the site/population
2. Census and health utilization survey
3. Active versus passive surveillance
4. Surveillance centers
5. Who should be included? Age group, number of days of fever
6. Follow-up
7. Blood collection from patients
8. Repeat cross-sectional studies

*lunch*

1:30 PM Group discussion on cost-of-illness and willingness-to-pay studies, *facilitated by Dale Whittington and Chirstine M. Poulos*

2:30 PM Group discussion on socio-behavioral studies, *facilitated by Lauren Blum*

Afternoon and evening: The working group discusses country-level proposals, including cost estimates, *facilitated by Lorenz von Seidlein, Robert Breiman, Shabbar Jaffar and Danielle Clark*, and incorporating economic and socio-behavioral studies in the surveillance, *facilitated by Dale Whittington and Chirstine M. Poulos*

⇒ Output: community based surveillance, economics and socio-behavioral proposals.

## Thursday, 7 November 2002

Morning: Presentation and discussion of proposals by country representatives

*lunch*

1:30 PM – Concluding remarks – *Jorge Arias, Alan Schapira, Chusak Prasittisuk*

3:00 PM – Planning to move forward – *Jose Esparza, Duane Gubler, Sarah MacFarlane, Scott Halstead*

## Appendix D: Workshop Participants and Facilitators

### Asian Region

#### *Cambodia*

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\* Unable to attend

## Appendix 3: Proposals

The 10 proposals received from nine countries are listed below indicating the principal investigator, title, and budget for each proposal. PDVI acknowledged receipt and replied that they will contact them as soon as possible. The proposals have been forwarded to Scott Halstead and it is understood that Don Shepard and Jose Esparza are reviewing them.

### Proposals

- a. Brazil -Dr Joao Bosco Siquiera - Population-based active dengue surveillance - \$200,200
- b. Cambodia - Dr Or Vandine - Cost analysis of dengue and willingness to pay for a dengue vaccine - \$56,348
- c. Cambodia - Dr Ngan Chanta - Hospital-based study on dengue - \$50,000
- d. El Salvador - Dr Romeo Montoya - Determination de la carga de dengue - \$43,000
- e. Guatemala - Dr Leticia Castillo Signor - Clinical-epidemiological characterization, social and economic contribution of dengue - \$270,449
- f. Malaysia - Dr Peifan Chai - Economic burden of dengue disease in the Klang Valley - \$31,421
- g. Panama - Dr Blas Armien - Dengue disease burden quantification in the Metropolitan Region of Panama City - \$150,000
- h. Philippines - Dr Fidelis Quiza - Dengue burden of illness, entomological determinants, and socio-cultural aspects - \$421,767
- i. Thailand - Dr Sukhontha Kongsin - Dengue cost of illness, willingness to pay for a dengue vaccine - \$140,300
- j. Venezuela - Dr Fatima Garrido - Proyecto de carga de dengue en Distrito Federal y Estado Aragua, Venezuela 2003-2005 - \$29,915 per year