



## **Strategic Plan**

# **Dengue Vaccines: The Role of the Pediatric Dengue Vaccine Initiative**

**June, 2006**

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## Executive Summary

Dengue fever is a mosquito-borne disease, primarily of children, which occurs in all tropical countries. Dengue fever, with its severe consequences of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), results in substantial morbidity, mortality and economic losses. The magnitude of these consequences is significant and is comparable to those of other infectious diseases of children.

Dengue can become a vaccine preventable disease. The disease is caused by four Flaviviruses - dengue types 1 – 4. Other Flavivirus diseases- namely, yellow fever, Japanese encephalitis and tick borne encephalitis – are controlled by effective vaccines. A number of dengue vaccine candidates are in different stages of pre-clinical and clinical evaluation. However, none has entered clinical trials to determine efficacy, effectiveness and safety.

Dengue is one of the more challenging vaccines presently under evaluation. A dengue vaccine must provide protection against infection by four different viruses. The vaccine must provide durable, long-term protection against infection with all dengue viruses because of the unique ability of some infections to produce severe consequences in persons previously infected with another dengue virus (immune enhancement). In addition, there is the need for new and improved dengue diagnostics and assays for vaccine evaluation and for monitoring the effectiveness of vaccination programs.

This Strategic Plan provides a long-term vision for accelerating evaluation of candidate dengue vaccines and introduction of safe, effective and affordable vaccines in the national immunization programs of dengue endemic countries. It also lays out required activities to accelerate development and evaluation of new and improved dengue diagnostics and assays.

The Plan defines the role of the Pediatric Dengue Vaccine Initiative (PDVI) in achieving this accelerated progress. The PDVI is a program of the International Vaccine Institute, Seoul, Korea and is funded by the Bill and Melinda Gates Foundation and the Rockefeller Foundation.

The PDVI has designed four major programs for implementation by the end of 2010.

- **Formation and operation of Strategic Partnerships:** The success of dengue vaccine evaluation and introduction will rest on formation and operation of partnerships with public and private organizations. The PDVI will join or form partnerships with organizations developing and evaluating dengue vaccines and diagnostics and with public sector organizations involved in introduction of vaccines into national immunization programs.
- **Supportive Research & Development:** There exists a strong development pipeline for dengue vaccines. However, a range of research and development activities is required to advance candidate dengue vaccines to large-scale clinical testing. Gaps exist in the diagnostic tests and assays required to evaluate dengue

vaccines. PDVI will undertake activities directed at development, evaluation and standardization of diagnostic tests for acute dengue virus infection, and improved assays to measure immunity to dengue virus infection and to identify persons at risk of antibody enhanced disease.

- **Vaccine Evaluation:** The PDVI will undertake activities to support evaluation of dengue vaccines in large-scale clinical trials (Phase 2b, Phase 3) and population-based effectiveness studies. Activities include creation of a consortium of vaccine evaluation field sites in dengue endemic countries; working with partners to revise guidelines for evaluation of the efficacy, safety and effectiveness of dengue vaccines in large-scale clinical trials; and developing provisional dengue vaccination strategies.
- **Vaccine Access:** Robust estimates of the disease and economic burden attributable to dengue and of the economic and prevention effectiveness of dengue vaccination strategies are required to support investment by private and public partners to make dengue a vaccine preventable disease. In addition, PDVI will work with partners to develop and promote plans for national and international vaccine procurement and distribution and develop effective communications about dengue as a vaccine preventable disease.

This Strategic Plan identifies specific objectives to ensure the achievement of each of these program goals. Progress toward these objectives can be measured by the milestones described in this Plan.

## Introduction

The Pediatric Dengue Vaccine Initiative (PDVI) was established to provide public sector leadership to accelerate development, evaluation and introduction of dengue vaccines. It was founded at a meeting in Ho Chi Minh City in December 2001 to review dengue vaccine development. Meeting participants concluded that an international initiative to promote dengue vaccine evaluation and introduction was timely in light of recent progress in vaccine development<sup>1</sup>.

Initially supported by the Rockefeller Foundation and the International Vaccine Institute (IVI), the PDVI received a \$55 million, 5-year grant from the Bill and Melinda Gates Foundation in 2003. Combined with approximately \$1.7 in grants from the Rockefeller Foundation, the PDVI has established programs to accelerate evaluation and introduction of dengue vaccines. A Board of Counselors (BOC) (see Appendix 1) provides oversight for the PDVI. The day-to-day scientific direction and management is provided by the Director, Dr. Harold Margolis, who comes from a career at the US Centers for Disease Control and Prevention where he had a variety of senior roles including leadership of the viral hepatitis program.

The PDVI is a program of the IVI, an International Organization established in 1997 by treaty under the Vienna Convention of 1969; 38 countries and organizations have signed the Establishment Treaty. The IVI was founded to improve the health of children in developing countries through the development, evaluation, introduction and use of new and improved vaccines via a dynamic interaction among scientific and public health communities, and industry. It has over 150 professional and support staff, and programs throughout Africa, Asia, and Latin America. The IVI is governed by a Board of Trustees, chaired by Prof. Ragnar Norrby, Director General of the Swedish Institute for Infectious Disease Control, and its day-to-day operations are managed by the Director-General, Dr. John Clemens (See Appendix 2 - IVI Board of Trustees). The IVI is housed in a state-of-the-art facility on the campus of Seoul National University Research Park<sup>2</sup>. [Change to current IVI annual report.]

Vaccines have repeatedly been shown to be the most cost-effective means of infectious disease prevention. However, the evaluation and introduction of new vaccines is a complicated and costly process. Steps include meeting regulatory requirements to show vaccine safety and efficacy, changing public health policy to incorporate a new vaccine into health care practice, mobilizing funds at the national and international level to ensure sustained availability, and monitoring vaccine effectiveness to ensure that it achieves the desired effect of reducing disease burden.

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<sup>1</sup> Almond, J., et al., *Accelerating the development and introduction of a dengue vaccine for poor children*, 5-8 December 2001, Ho Chi Minh City, VietNam. *Vaccine*, 2002. **20**(25-26): p. 3043-6.

<sup>2</sup> *IVI Annual Report*. [http://www.ivi.int/publication/annual\\_report/2004/ivi\\_annual\\_report\\_2003\\_2004.pdf](http://www.ivi.int/publication/annual_report/2004/ivi_annual_report_2003_2004.pdf), 2004.

The development cost of a pharmaceutical is estimated to be on the order of \$1 billion<sup>3</sup> and costs for development and successful launch of new vaccines are likely to be similar. Because vaccine companies cannot accord sufficient priority to development of vaccines needed by the poor in developing countries, several foundations, most notably the Bill and Melinda Gates Foundation and the Rockefeller Foundation, have supported product development partnerships (PDPs) to facilitate the timely development, evaluation and introduction of new vaccines<sup>4</sup>.

The limitation in resources available to PDPs, including the PDVI, has the following implications. They must work in partnerships with private and public sector institutions to make value-added contributions to the field. They must set realistically achievable goals within available resources. Last, they must help mobilize substantial additional resources to ensure the achievement of their overall goals of improved health.

Various studies have identified certain characteristics of successful PDPs<sup>5</sup>. These include the creation and management of a portfolio of products rather than focusing on just one or two leads, and creation and promotion of a global network of collaborators.

The evaluation and introduction of one or more pediatric dengue vaccines affordable to developing countries will require the efforts of many parties – academia, non-profit organizations, for-profit vaccine and diagnostics manufacturers, governmental agencies, international health agencies and others. This Strategic Plan seeks to show how each party can contribute. Of particular importance is the requirement for collaboration between the public and private sectors. Each sector has essential skills and capabilities that are critical in achieving the outcome of accelerated vaccine evaluation and introduction. The PDVI will work on a portfolio of vaccine candidates with companies in developed and developing countries to ensure the sustained availability of safe, effective and accessible dengue vaccines. The PDVI will also form partnerships with public sector agencies including the World Health Organization (WHO), developed and developing country government agencies, research institutes, and universities. These partnerships will be a critical means for mobilizing the needed additional resources to achieve success as indicated by introduction of dengue vaccine into one or more dengue endemic countries and making dengue a vaccine-preventable disease<sup>6</sup>.

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<sup>3</sup> DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, *The price of innovation: new estimates of drug development costs*. Journal of Health Economics, 2003. **22**: p. 151-185.

<sup>4</sup> Towse, A., *Estimates of the Medium Term Financial Resource Needs for Development of Pharmaceuticals to Combat Neglected Diseases*. 2004.

<sup>5</sup> Moran M, A Ropers., J Guzman, J Diaz, C Garrison, *The new landscape of neglected diseases*. 2005, [www.wellcome.ac.uk](http://www.wellcome.ac.uk). Wellcome Trust: London.

<sup>6</sup> Kettler, H., K. White, and S. Jordan, *Valuing Industry Contributions to Public-Private Partnerships for Health Product Development*. 2003, The Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, [www.globalforumhealth.org/filesupld/ippph/Valuing.pdf](http://www.globalforumhealth.org/filesupld/ippph/Valuing.pdf).

# The Need and Opportunity for a Dengue Vaccine

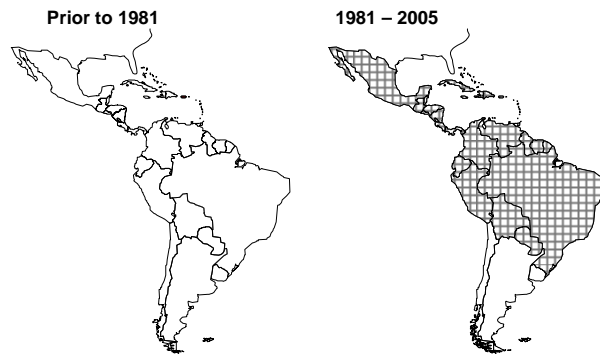
## *The burden of dengue infection*

Dengue is a major global health problem, primarily of tropical and subtropical areas. The 20-21<sup>st</sup> century dengue pandemic is the direct result of changes in demographic and economic trends – namely, the population explosion, urbanization, and rapid movement of individuals both within and between countries. Dengue is a mosquito-borne disease caused by each of four Flaviviruses – dengue virus serotypes 1–4. Diseases caused by other Flaviviruses - yellow fever, Japanese encephalitis, tick-borne encephalitis - can be prevented by live-attenuated and inactivated vaccines. This success provides confidence that dengue will become a vaccine-preventable disease.

Dengue virus infection often produces a self-limited, febrile illness – dengue fever (DF) - that is often painful, and in its severe forms can lead to dengue haemorrhagic fever (DHF), including dengue shock syndrome (DSS), which can rapidly progress to death. These dangerous forms of the disease occur in an estimated 5% - 10% of dengue patients and children are particularly at risk. Patients with DHF require hospitalization and 30% - 40% of children progress to DSS. Life-long immunity to the infecting dengue virus serotype occurs among those who recover from the infection.

Since World War II, dengue has spread through more than 100 tropical countries causing tens of millions of cases of dengue fever (DF) annually. Figure 1 shows the rapid spread of DHF in the Americas.

**Figure 1. The Emergence of Dengue Haemorrhagic Fever in the Americas**



Although disease reporting is poor, WHO estimates that 500,000 cases of DHF occur annually, with an average 5% case-fatality rate, or about 20,000 deaths<sup>7</sup>. Disease incidence is highest during the rainy seasons, which occur during the summer and fall in countries located above the equator and during the winter and spring in countries below the equator. In addition to endemic infection, epidemics of DF and DHF occur regularly and exact a significant economic and health toll. In the poor dengue endemic countries of Asia and the Americas, studies have found the burden of dengue to be approximately 1,300 disability adjusted life-years (DALYs) per million population, which is similar to the disease burden of other childhood and tropical diseases and of tuberculosis in the same regions<sup>8 9</sup>.

While supportive intensive care can be life-saving, specific antiviral or other drug treatment for dengue is not available. The *Aedes aegypti* mosquito, the primary vector for dengue, most often circulates during daylight hours, and thrives in small amounts of water that collect in items around households and living areas. The only available preventive measure for dengue is comprehensive mosquito control. Trying to control dengue mosquito vectors has been an ongoing challenge over the past several decades, has not been successfully sustained and has had little long-term impact on disease (Figure

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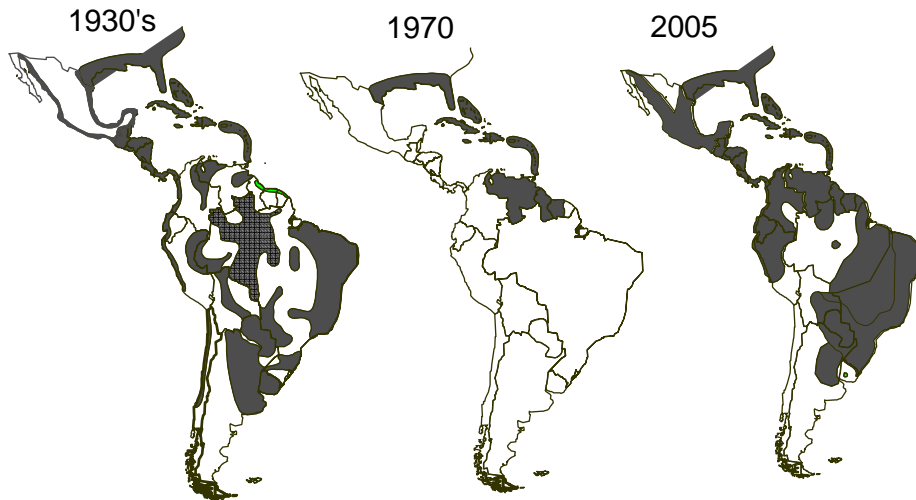
<sup>7</sup> Rigau-Perez, J.G., et al., *Dengue and dengue haemorrhagic fever*. Lancet, 1998. **352**(9132): p. 971-7.

<sup>8</sup> Meltzer, M.I., et al., *Using disability-adjusted life years to assess the economic impact of dengue in Puerto Rico: 1984-1994*. Am J Trop Med Hyg, 1998. **59**(2): p. 265-71.

<sup>9</sup> Gubler, D.J. and M. Meltzer, *Impact of dengue/dengue hemorrhagic fever on the developing world*. Adv Virus Res, 1999. **53**: p. 35-70.

2)<sup>10</sup>. Although, the Grand Challenges for Global Health Program of the Bill and Melinda Gates Foundation awarded over \$20 million to produce genetically modified mosquitoes that would not transmit dengue<sup>11</sup>, these projects have long time horizons, and must address issues such as distribution systems and environmental impact.

**Figure 2. *Aedes aegypti* Distribution in the Americas**



Dengue is an important disease concern for tourists, guest workers and the military in endemic countries. Although the true incidence of dengue among travelers to endemic countries is not known, several surveillance studies illustrate the magnitude of the problem. Among returning travelers with febrile illness, dengue is the most common diagnosis from every region (Americas, Caribbean, Southeast and South Central Asia) except sub-Saharan Africa (12a-NEJM article). Self-reported incidence of dengue fever among Israeli travelers to Thailand in 1998 was as high as 3.4 per 1000 and among returning German air travelers, the highest rate of disease was in travelers returning from Southeast Asia (26.5/100,000), followed by the Indian subcontinent (8.2/100,000) and Central and South America (8.3/100,000)<sup>12,13</sup>. In addition, reported disease rates fluctuate

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<sup>10</sup> Teixeira, M., MdC Nascimento Costa, ML Barreto, E Mota, *Dengue and dengue hemorrhagic fever epidemics in Brazil: what research is needed based on trends, surveillance, and control experiences?* Cad. Saude Publica de Janeiro, 2005. **21**(5): p. 1307-15.

<sup>11</sup> Anonymous. *Grand Challenges in Global Health: Background on the Initiative and Research Projects*. [Electronic] 2005 [cited 2005 June 27]; Available from: [http://www.gatesfoundation.org/nr/downloads/globalhealth/GCGH\\_Grants\\_Backgrounder.doc](http://www.gatesfoundation.org/nr/downloads/globalhealth/GCGH_Grants_Backgrounder.doc).

<sup>12</sup> Wilder-Smith, A. and E. Schwartz, *Dengue in Travelers*. New England Journal of Medicine, 2005. **335**(9): p. 924 - 932.

<sup>13</sup> Freedman, D., et al., *Spectrum of Disease and Relation to Place of Exposure among ill Returned Travelers*. New England Journal of Medicine, 2006. **354**: p. 119-30.

in concordance with epidemics in the dengue endemic regions. High rates of dengue have been reported among troops deployed to endemic countries, with highest rates occurring during seasonal epidemics. This documented high risk of infection should make dengue vaccination a routine preventive measure for travelers, the military and guest workers to dengue endemic parts of the world.

Dengue affects all age groups and all socioeconomic sectors. In most countries of Southeast Asia nearly all of the adult population has been infected with one or more dengue virus serotypes. Dengue is considered the most serious acute communicable disease of children in countries of Southeast and South Asia, and there has been a rising trends in disease reported to the WHO over the past decade. At peak epidemic times in Myanmar, as many as 70 children with severe DHF may present to a single children's hospital in a day, 20 of them with the potentially fatal DSS<sup>14</sup>. Dengue is endemic in most countries of Latin America and the Caribbean and severe forms are now affecting increasing numbers of children and adults.

### ***The status of dengue vaccine development and evaluation***

Since dengue virus was first grown in cell culture more than 50 years ago, the goal has been to produce a safe and effective vaccine. There is agreement among experts that a dengue vaccine should confer long-term immunity against all four dengue virus serotypes because of the theoretical potential for immune enhanced disease or Antibody Dependent Enhancement (ADE) in persons partially immune (protected) from immunization. ADE can occur when an individual previously infected with one of the dengue viruses is infected with a second dengue virus. The body has a hyperimmune response to the second virus.

A number of candidate dengue vaccines have been developed and evaluated in pre-clinical or small clinical trials (see Table 1). All vaccine candidates include the four dengue serotypes and have been produced by a number of virus attenuation methods or as a subunit vaccine of recombinant proteins. Other techniques have been used to develop prototype vaccines and have had more limited evaluation. These include naked DNA, DNA shuffling, and other virus vectors.

Sanofi Pasteur began with live, attenuated vaccines developed by Mahidol University, Bangkok derived by cell culture passage of clinical isolates of each dengue virus serotype. Evaluation in a series of Phase 1 – 2 clinical trials showed good immunogenicity, but high rates of reactogenicity and viremia, suggesting inadequate attenuation of at least one dengue virus serotype. Subsequently, Sanofi Pasteur obtained licenses to genetically engineered live-attenuated chimeric vaccine candidates for each dengue serotype from Acambis, Inc. Each is produced by inserting the relevant dengue envelope and pre-membrane genes into the non-structural genome region of the attenuated 17-D yellow fever vaccine virus, which results in an infectious clone that

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<sup>14</sup> Thu, H.M., et al., *Myanmar dengue outbreak associated with displacement of serotypes 2, 3, and 4 by dengue J. Emerg Infect Dis*, 2004. **10**(4): p. 593-7.

expresses its respective serotype-specific antigen. In Phase 1 clinical trials, serotype-specific dengue vaccines were shown to have good immunogenicity, minimal reactogenicity and low viremia. A tetravalent vaccine formulation administered in a 2-dose schedule is being evaluated in adults in a Phase 2 clinical trial.

GlaxoSmithKline, in collaboration with the Walter Reed Army Institute for Research (WRAIR), has developed a live-attenuated vaccine for each of the four dengue virus serotypes. These serotype-specific vaccines were derived by cell culture passage of clinical isolates. When evaluated in Phase 1 clinical trials, the monovalent vaccines showed good immunogenicity and low rates of reactogenicity. These individual vaccines have been evaluated in Phase 2 adults trials, and recently in children. When administered in combination in a 2-dose schedule the composite candidate vaccine has shown good immunogenicity and low reactogenicity rates, although there has been some variability in overall rates of seroconversion.

Attenuated, serotype-specific, vaccine candidates have been developed by the US National Institutes of Health (NIH), National Institute of Allergy and Infectious Disease (NIAID), Laboratory of Infectious Disease. These vaccine candidates are prepared by: 1) site directed mutagenesis of a dengue type 4 virus to produce attenuation, or 2) insertion of serotype-specific envelope and pre-membrane genes into the non-structural genome region of a dengue type 4 virus to produce infectious clones. Monovalent vaccine candidates are being evaluated in Phase 1 clinical trials, with the best candidates moving to Phase 2 clinical trials in adults, followed by step-down trials in children and formulation into a tetravalent vaccine. These vaccine candidates have been licensed non-exclusively to Biological E of Hyderabad, India and Butantan in Sao Paulo, Brazil.

**Table 1. Dengue Vaccine Candidates**

<b>Developer</b>	<b>Partner</b>	<b>Approach</b>	<b>Formulation</b>	<b>Status</b>
Mahidol University	Sanofi Pasteur	Cell culture passage of clinical isolates	Tetravalent	Phase 2 trials <b>No longer being evaluated</b>
Walter Reed Army Institute of Research (WRAIR)	GlaxoSmithKline	Cell culture passage of clinical isolates	Tetravalent	Phase 2, adults and children
Acambis	Sanofi Pasteur	Chimeric infectious clones. Yellow fever vaccine virus (nonstructural) + dengue envelope & preM genes	Tetravalent	Phase 2, adults
US National Institutes of Health (NIH)		Chimeric infectious clones. Dengue-4 $\Delta$ -30 virus (nonstructural) + dengue envelope & preM genes. Attenuated $\Delta$ 30 dengue-4 virus	Monovalent	Phase 1, adults
	Biological E			
	Butantan			
US Centers for Disease Control and Prevention (CDC)	InViragen	Chimeric infectious clones. Dengue-2 virus (nonstructural) + dengue envelope & preM genes	Monovalent	Preclinical
Hawaii Biotech	Hawaii Biotech	Recombinant envelope and non-structural protein (NS1) subunit	Monovalent	Preclinical

Other candidate vaccines are undergoing preclinical studies. A subunit vaccine containing recombinant envelop and NS1 proteins developed and produced by Hawaii Biotech has completed immunogenicity studies in monkeys that show production of neutralizing antibodies and protection from viremia following wild-type dengue virus challenge. Monovalent chimeric, live attenuated vaccines using an attenuated dengue type-2 virus backbone have been developed by the CDC Division of Vector Borne Infectious Diseases and licensed to InViragen, LLC. of Fort Collins, CO. These vaccine candidates generate neutralizing antibodies in mice and monkeys. It is anticipated that both the recombinant and the chimeric vaccines will go into Phase 1 clinical trials in the near future. DNA vaccines developed by the Naval Medical Research Center and WRAIR has also successfully protected non-human primates from viremia upon challenge with wild-type dengue viruses.

In sum, there are a number of vaccine candidates using different approaches and several vaccine companies are making substantial investments in these vaccines. These developments provide optimism that one or more will progress through clinical testing to licensure in the next several years.

### ***The status of dengue diagnostics***

Prior to their commercial availability within the last 15 years, dengue diagnostics were available only in a limited number of government supported research laboratories in the Americas and Asia. Even today with commercially available diagnostic tests, the accurate diagnosis of acute dengue virus infection, including primary and secondary infections, requires a laboratory with capacity to perform several immunodiagnostic assays and to carry out virus detection by cell culture or nucleic acid detection. A number of research based assays are required to determine if a person is immune to infection from a specific dengue virus serotype, whether a person has cross reacting (heterotypic) antibody to dengue viruses and whether a person had been infected with a Flavivirus other than dengue.

The development in the early 1990's of an ELISA to detect IgM antibodies to dengue virus and its subsequent commercial availability has improved the capability to diagnose acute dengue virus infection. However, IgM antibody to dengue becomes detectable only 4-7 days after onset of fever, which limits its usefulness in the clinical setting, where patients often present within 2-4 days of fever onset. In addition, these tests have not been rigorously evaluated against a panel of well characterized specimens. In one limited evaluation, the positive predictive value of several commercially available tests was <70%. Recently there has been increased effort to develop tests to diagnose acute infection more accurately, including nucleic acid detection in various amplification formats and ELISAs to detect circulating NS1 antigen. However, these tests are available only in specialized laboratories that produce their own reagents.

Assays for serotype-specific antibody against infection include the plaque reduction neutralization test (PRNT), an IgG ELISA and a hemagglutination inhibition (HI) assay. As with most dengue diagnostics, these tests are not commercially available, except for the IgG ELISA, and have rarely been evaluated against panels of well characterized serum specimens to determine their sensitivity, specificity and positive or negative predictive values. Even for the PRNT, there is not good correlation of results between research or reference laboratories performing the assay.

Well standardized assays for acute infection and serotype-specific protective antibody to dengue virus infection are needed for vaccine evaluation. While sponsors of vaccine trials will qualify existing assays to meet regulatory requirements, there is the need to have assays that are comparable between groups conducting clinical trials. In addition, when dengue vaccine becomes available, the ongoing assessment of its effectiveness will require the accurate diagnosis of acute infection and well standardized assays to measure long-term protection.

## Programs

PDVI has four major program areas: development of strategic partnerships, supportive research and development, vaccine evaluation, and vaccine access. These programs are directed to providing value-added information, coordination and resources to the process of vaccine evaluation and introduction and diagnostic development, evaluation and use (see Figure 3). In this section, each of these programs is discussed in two sections: Background and Work Plan.

### *Strategic Partnerships*

#### Background

The development, evaluation and introduction of new vaccines each require formation and sustained operation of a network of partners. No one organization can carry out all the diverse tasks required to achieve the accelerated evaluation and introduction of a vaccine. In addition, for PDPs to be successful, it is important they establish and maintain a dynamic portfolio of product leads<sup>15</sup>. These leads can vary by technical approach or by developers of similar approaches. The important thing is that PDPs not put all resources in “one basket.”

The PDVI has taken advantage of the opportunity to affiliate with several established partnerships working in the areas of dengue vaccine development, diagnostics, basic and public health science, clinical care, and prevention. In the public sector, the oldest network is the WHO Flavivirus Steering Committee which meets regularly and has addressed and supported research, and issued guidelines related to dengue clinical care, vaccine development and evaluation, diagnostics, surveillance and prevention. In addition, the UNICEF/UNDP/WHO Special Programme for Research and Training in Tropical Diseases (TDR) addresses dengue diagnostics and WHO has a program for global dengue surveillance - DengueNet<sup>16</sup>. Other public sector groups with long-term involvement in dengue vaccines and diagnostics development include the US Army and Navy (i.e., WRAIR, AFRIMS, NAMRU-2), the CDC, the NIH, Mahidol University in Bangkok, the Pedro Kouri Tropical Medicine Institute in Havana, the Ministry of Public Health in Thailand, the Taiwan CDC, and other ministries of health in Southeast Asia and the Americas, usually through their regional WHO organizations.

In the private sector, there has been long term commitment to vaccine development by the large firms Sanofi Pasteur and GlaxoSmithKline and by one biotechnology firm, Hawaii Biotech. Recently a number of additional firms have joined the effort to produce a safe and effective dengue vaccine that reflects increased recognition of the market

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<sup>15</sup> See Reference 4

<sup>16</sup> <http://www.who.int/csr/disease/dengue/denguenet/en>

potential and possibly reflects a new more favorable attitude by firms toward “neglected diseases.” (See preceding section and Text Box 1) In addition, a number of companies have produced dengue diagnostics and several are in the process of developing new diagnostics, including PanBio, BioRad, Standard Diagnostics and Roche Molecular Diagnostics.

### **Text Box 1. Changes in Private Sector Interest in Diseases of Developing Countries**

Recently, the Wellcome Trust released a report (see ref. 5) on “neglected diseases”, which showed that since the year 2000, previously neglected diseases (i.e. diseases of poor countries) are no longer being neglected by major pharmaceutical companies. This change is due in large part to a broader and more comprehensive understanding of self-interest by the pharmaceutical industry. The report’s authors, led by Ms. Mary Moran, noted:

- “Growing public awareness of the fact that developing country health needs are not being met is leading to an increased pressure on the pharmaceutical industry and on public donors.
- “Transformations in the pharmaceutical industry sector since the 1980s have resulted in changes for neglected disease R&D over the past five years.”

The Wellcome study found: “Four of the top twelve multinational companies now have neglected disease R&D units employing over 200 scientists; three others work on a smaller scale. This activity is driven by ‘non-commercial’ motives (i.e. by broader business concerns rather than by returns in the neglected disease market) and is conducted under a new ‘no profit-no loss’ model that provides drugs to developing country patients at cost price.”

The PDVI interacts with the two major private sector vaccine developers (Sanofi Pasteur, GlaxoSmithKline), including inviting their membership on the PDVI Scientific Advisory Group for its Field Site Program for Vaccine Evaluation. PDVI has developed a strong partnership with the WHO and TDR to implement activities that address the need for better dengue diagnostics, evaluation of diagnostic tests and performance of laboratories carrying out these tests, and the establishment of dengue reference laboratories. PDVI is represented on the WHO Flavivirus Steering Committee and interacts with the other WHO programs responsible for dengue vaccines and surveillance. In addition, PDVI interacts with US agencies involved in dengue research, vaccine development and prevention.

The PDVI is developing a portfolio of vaccine programs in the form of partnerships with vaccine manufacturers and developers, as appropriate. For dengue, it has often been the case that prototype vaccine development and their early evaluations have been conducted by public sector institutions (e.g., Mahidol University, WRAIR, NIH and CDC). It is important that PDVI maintain partnerships with all the involved institutions. The nature

of these partnerships will vary in intensity and priority based on how PDVI can most effectively deploy its resources.

Other partnerships will be formed with companies, and research laboratories in the public sector to ensure the development, evaluation, and introduction of appropriate dengue diagnostics<sup>17</sup>.

PDVI has been able to take advantage of pre-existing partnerships. However, PDVI realizes that it must develop new private-sector partnerships as companies come into the field of dengue vaccines and diagnostics to form the most effective network. In addition, PDVI must develop new partnerships in the public sector to accelerate the introduction of safe and effective dengue vaccines.

## Work Plan

In this work plan, we address partnerships for vaccines and for diagnostics.

***Vaccine partnerships:*** Partnerships will be the backbone of PDVI's achieving success in each of its program areas. This will require the formation of new partnerships and maintenance of existing ones. The key partnerships will be with leading dengue vaccine companies, which currently are GlaxoSmithKline and Sanofi Pasteur. Other partnerships will be sought with groups currently developing dengue vaccines or who have acquired licenses for dengue vaccine intellectual property (IP), (see Appendix 3). These companies and their vaccine development partners can be grouped into 3 stages of vaccine development and evaluation – those in pre-clinical testing, those in Phase 1 clinical trials, and those in Phase 2 clinical trials and likely ready to enter large-scale clinical trials (Phase 3 or Phase 2b). Figure 3 shows the current stage of work of the respective companies. In some cases, the licensor, e.g. NIH, has taken the candidate to the stage of development shown in the Figure, but eventually a private sector partner will have to submit the appropriate documents to one or more national regulatory authorities to obtain licensure. The partnerships will be means by which PDVI can make a value-added contribution to these and other companies' efforts.

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<sup>17</sup> We note that there has been rapid progress in development of antiviral agents for early treatment of DF to prevent DHF and DSS. This effort is being undertaken by the Novartis Institute for Tropical Diseases (NITD), Singapore. Although these compounds are undergoing early pre-clinical assessment, their product evaluation timelines could parallel those of dengue vaccines. PDVI and NITD have had preliminary discussions concerning strategies to ensure the best downstream use of their respective products and the sharing of information related to scientific objectives common to both groups.

**Figure 3. Stage of progress of dengue vaccines**

Developer	Producer	Stage of Evaluation				
		Pre-Clinical	Phase 1	Phase 2	Phase 3	Phase 4
Acambis	SanofiPasteur	→				
WRAIR	Glaxo SmithKline	→				
NIH	Biological E	→				
	Butatan					
Hawaii Biotech		→				
CDC	InViragen	→				

**Diagnostics partnerships:** New partnerships will be formed for development, evaluation and production of dengue diagnostics, including production for use in resource poor countries where dengue is endemic. Initially, PDVI will map IP for dengue diagnostics and identify those companies actively engaged in development, evaluation, production and distribution of diagnostic tests for acute dengue virus infection or tests for immunity to infection. Some of this has been done in collaboration with TDR. In April 2005, a joint PDVI – TDR workshop on dengue diagnostics, which included manufacturers, was held to identify activities needed to accelerate development of improved diagnostics for acute dengue virus infection. Following the inventory of IP for dengue diagnostics, the PDVI will begin to develop partnerships with companies active in this field.

Table 2 shows the complementary relationships between the partners and PDVI and how PDVI can make value-added contributions. This Table lays out many of the PDVI program components discussed through the remainder of the Plan and thus gives an overview of the PDVI program in many of its aspects.

**Table 2. Complementary Relationships between Private Sector Partners and PDVI**

Tasks	Private sector (vaccine or diagnostics) companies	PDVI
<b>Supportive Research and Development</b>		
<b>Dengue diagnostic tests</b>		
Evaluation of new and existing diagnostic tests	<ul style="list-style-type: none"> <li>• Development of tests and registration through appropriate regulatory process</li> <li>• Qualify tests for acute dengue infection for vaccine trials</li> </ul>	<ul style="list-style-type: none"> <li>• With WHO, develop and provide Evaluation Panels</li> <li>• Evaluate test kits in WHO designated Reference/ Evaluation labs</li> <li>• Evaluate test kits under field conditions in Field Site Consortium</li> <li>• Provide Evaluation Panel to qualify tests for vaccine trials</li> </ul>
Standardization of plaque reduction neutralization test (PRNT)	<ul style="list-style-type: none"> <li>• Need to qualify and standardize antibody assays for vaccine trials</li> <li>• Expression of antibody results from vaccine trials in international units (IU) to allow for better comparisons</li> </ul>	<ul style="list-style-type: none"> <li>• Development of reagents, standardized protocols and support for training</li> <li>• Development of International Reference Reagent for Dengue to become available from the National Institute of Biological Standards and Control, UK which allows for PRNT results to be expressed in standard units.</li> </ul>
Improved test to measure protective antibody – improved over the PRNT	<ul style="list-style-type: none"> <li>• Use of validated test(s) in vaccine trials and for submission to regulatory agencies</li> <li>• Use of test for long-term studies of vaccine induced protection from dengue</li> </ul>	Development, validation and production of new test(s) as outcome of funded pre-clinical research studies
New diagnostic test to measure antibodies responsible for ADE	Use in vaccine trials, if available, or late in follow-up studies of vaccine safety	Development, validation and production of new test(s) as outcome of funded pre-clinical research studies
<b>Vaccine Evaluation</b>		

<b>Tasks</b>		<b>Private sector (vaccine or diagnostics) companies</b>	<b>PDVI</b>
Clinical studies	Phase 1	Lead responsibility	Potential support for GMP produced vaccine lot to conduct Phase 1 studies
	Phase 2	Lead responsibility	Use of Vaccine Evaluation Field Sites to conduct trials
	Phase 2b	Lead responsibility	Develop Field Sites for clinical trials in children to provide earlier indication of vaccine safety and efficacy. Participate in protocol design or data safety monitoring committee.
	Phase 3	Lead responsibility	Develop Field Sites for clinical trials. Participate in protocol design or data safety monitoring committee
	Phase 4	Co-investigator, vaccine supply	Develop and maintain field sites, lead responsibility for studies
Regulatory affairs		Responsible for all IND and NDA filings	With WHO and others, help develop international guidelines for vaccine evaluation, including trial design  Support WHO and national government efforts to enhance dengue vaccine review capabilities
<b>Vaccine Access</b>			
Prevention Effectiveness Studies		Receive information for decision making, provide information for selected studies	Provide information for decision making through support and evaluation of studies of cost of illness, burden of disease, comparative economic benefits, and quality of surveillance
Development of Dengue Vaccination Strategies		<ul style="list-style-type: none"> <li>• Develop marketing strategies</li> <li>• Receive forecasting of vaccine needs</li> </ul>	Support development of draft international and national recommendations for dengue vaccination strategies
Role of developing country manufacturers in partnership with developed country companies		Information about business assessment	Assess potential role in ensuring access by the public sector
Plans for national and international distribution		Responsible for private sector, provides collaborative access to information about public sector market	<ul style="list-style-type: none"> <li>• Promote procurement and the related mobilization of resources.</li> <li>• Assist national immunization programs in development of plans to include dengue vaccine in their childhood immunization schedule</li> </ul>
Develop communications about		Access to medical and public health	Ensure effective communication

Tasks	Private sector (vaccine or diagnostics) companies	PDVI
dengue as a vaccine preventable disease	communities after vaccine licensure	and information flow through establishment of regional work and advisory groups

**Memoranda of Cooperation:** These agreements are negotiated between PDVI and its private sector partners. The negotiations leading to these agreements are initiated with discussions between PDVI and leadership of the respective private sector organizations about the complementary roles between the PDVI and their organization. A framework for cooperation based on issues of concern to the PDVI (see Appendix 4) is used to assist in negotiating an agreement, which specifically identifies the complementary roles between the PDVI and the company and the activities PDVI will undertake. The agreements consist of a set of standard terms to which are attached various appendices which are detailed work plans for specific activities under the three main areas of PDVI work, i.e., Supportive R&D, Evaluation, and Vaccine Access. These agreements will be reviewed regularly and modified as appropriate.

In large part, PDVI’s success will be measured by how it contributes to extending the arrow tips more quickly to the right in Figure 3.

**Objectives:**

**In developed and developing countries,**

- Establish and maintain the portfolio of *private sector* partnerships required to accelerate evaluation and introduction of dengue vaccines in developing countries, including the development and evaluation of diagnostic tests
- Establish and maintain a spectrum of *public sector* partnerships required to accelerate evaluation and introduction of dengue vaccines in developing countries

**Milestones:**

- Complete a situation analysis, including IP mapping, for vaccines and diagnostics to identify potential private sector partners.
- Establish private sector partnerships through Memoranda of Cooperation and maintain collaborations through implementation of activity plans for specific areas.
- Establish and maintain collaborations with public sector partners in vaccine and diagnostics evaluation and introduction
- Build new partnerships with public sector organizations and agencies involved in vaccine development, evaluation and introduction (e.g., Global Alliance for Vaccines and Immunization, national regulatory authorities, et al.).

## ***Supportive Research & Development***

Despite the promising development of a number of candidate dengue vaccines, it can be predicted that dengue vaccine evaluation will be a difficult endeavor and is discussed in the next section. The major tasks for PDVI in Supportive Research & Development have to do with the development and validation of diagnostic tests and specialized assays. PDVI does not intend to sponsor laboratory studies that would result in development of new vaccine constructs. This work is being undertaken in universities and government laboratories and in companies sponsoring new vaccine development.

### **Background**

The accurate diagnosis of new dengue virus infections requires both virus detection and detection of IgM anti-dengue because of the 4 - 5 day window after onset of fever when the IgM test is negative. While diagnostic tests for IgM anti-dengue are commercially available, virus detection by cell culture, nucleic acid detection (e.g., PCR, NASBA [Nucleic Acid Sequence Based Amplification]) or detection of NS1 antigen in serum require the capacity of a research laboratory that produces the required reagents and performs the tests under good laboratory practices.

The plaque reduction neutralization test (PRNT) is the only assay available to measure immunity to dengue virus infection and reliably differentiate primary from secondary infections. However, the PRNT is performed only in research and reference laboratories, has not been standardized between laboratories, and is not easily adapted to handle large numbers of specimens. To better standardize performance of the PRNT, the PDVI held a training workshop for senior technicians from Asia and the Americas at Mahidol University Center for Vaccine Development in July 2004. Standardized protocols, methods and reagents were transferred to the participants through hands-on performance of the PRNT. In collaboration with WHO and the National Institute for Biologic Standards and Control (NIBSC), United Kingdom, PDVI attempted to produce an International Reference Standard that would allow PRNT results to be expressed in international units (IUs) and improve comparison of results between laboratories worldwide. However, a multi-laboratory, comparison of the proposed international reference reagents showed an unacceptably high level of test variation.

There appears to be increasing interest in commercial production of dengue diagnostic tests. Working with TDR, a series of consultants meetings was held, which included diagnostics manufacturers, to identify needs in this area. Of high priority is the availability of a well characterized evaluation panel to determine the performance of current or future diagnostic tests as well as the performance of laboratories doing these tests. To develop this evaluation panel, TDR has designated and funded two Dengue Reference Diagnostics Laboratories and seven Diagnostics Evaluation Laboratories. A TDR-PDVI consultative workshop was held in July 2005 and developed and implemented a plan to produce a Dengue Evaluation Panel to evaluate diagnostic tests for acute dengue virus infection, which should become available in the last quarter of 2006.

An important consideration in the evaluation of dengue vaccines is that the PRNT, although the only test available, may not provide the best measurement of protective immunity to dengue virus infection. For instance, human challenge studies have shown that some persons are susceptible to infection and disease with the same dengue serotype for which they are PRNT-antibody positive, and some persons negative for PRNT type-specific antibody do not develop disease when challenged with that dengue virus serotype. PDVI is funding pre-clinical research to characterize the types and binding sites of antibodies involved in virus neutralization to develop a better test for dengue immunity. This work has been greatly facilitated by ongoing work on West Nile Virus, another Flavivirus, to answer the same questions. It is anticipated that the results of this research will lead to development of improved diagnostic tests for immunity (natural or vaccine induced) to dengue. The PDVI is prepared to ensure the further development and evaluation of these prototype tests.

A major concern during evaluation of dengue vaccines is that immunization could immunologically prime a vaccine recipient and cause enhanced dengue disease upon later exposure to wild-type virus infection. While there may be some scientific disagreement as to the frequency with which immune enhanced disease occurs, its presence seems well established. Most studies point to antibodies as the primary mechanism of immune enhancement or ADE. What is missing is information about the type or level of antibody(ies) involved and an assay to measure these antibodies. Having an assay to detect ADE-related antibodies would provide an important tool to differentiate vaccine associated ADE from naturally occurring disease. In addition, if ADE is observed following immunization, knowledge about the characteristics of the antibodies involved could accelerate modifying vaccines to eliminate this problem.

Other Supportive Research and Development: Additional research needed to support dengue vaccine evaluation and introduction is discussed in the following sections on Evaluation and Vaccine Access.

## **Work Plan**

PDVI supported research and development will be targeted to fill gaps in knowledge and products thought to have a significant impact on evaluation and introduction of dengue vaccines. Development of the current PDVI supported R&D agenda has been undertaken with input from our Scientific Advisory Groups, WHO co-sponsored consultant meetings and the PDVI Board of Counselors. It is anticipated that additional gaps in knowledge or products will be identified through our strategic partnerships and consultants during the course of dengue vaccine evaluation and introduction. If deemed appropriate, targeted projects to address these needs will be initiated or co-sponsored by the PDVI. Although additional activities in this Strategic Plan (e.g., Vaccine Evaluation, Vaccine Access) have a considerable research and development component, we have included only vaccine-related, pre-clinical and non-clinical activities in this portion of the Work Plan.

Current R&D activities have a heavy dose of basic science because this is thought to be the best pathway for development of the required vaccine and diagnostic products. A

total of 14 pre-and non-clinical research projects have been approved and 13 funded for 3-year periods, with annual renewals based on achievement of defined milestones (see Appendix 5). To maximize the likelihood that PDVI sponsored projects result in outcomes directly applicable to vaccine and diagnostics evaluation, they are being managed as cooperative agreements, with significant technical and program input by PDVI staff. PDVI convenes an annual meeting of its research network to facilitate further collaboration between investigators. These annual meetings will be supplemented by communication and data sharing through web-based portals designed specifically for the investigator network. In addition, to speed development of diagnostic tests, PDVI staff is bringing together small working groups to examine promising results in an effort to most rapidly move this information into production of prototype tests for further evaluation. PDVI anticipates funding early development and evaluation of prototype diagnostic tests resulting from research on protective antibody and ADE. In addition, there is the possibility for funding additional projects identified as important through our strategic partnerships.

***Objectives:***

- Improve dengue diagnostics through standardization of PRNT, validation of dengue diagnostic tests for current and past infection, and development of a test(s) for early, rapid diagnosis.
- Develop an improved antibody test to define protection against dengue infection.
- Develop an antibody test to predict risk of ADE.

***Milestones***

- Define, in collaboration with WHO and TDR, the agenda for standardization and validation of dengue diagnostics
- Produce serum panels to evaluate diagnostics for acute dengue virus infection (IgM, NS1 antigen, nucleic acid detection)
- Produce serum panels to evaluate assays for immunity to dengue virus infection (neutralization tests)
- Develop and distribute guidelines for performance of neutralization assays.
- Establish international reference reagents for calibration of dengue antibody tests
- Develop new test(s) that define protection against infection, including vaccine induced protection, employing the results of PDVI-sponsored studies of dengue envelope structure, binding of dengue antibodies and virus, and blocking of virus entry into target host cells
- Develop a test(s) for ADE employing the results of PDVI-sponsored studies of dengue virus–antibody characterization and interactions
- Produce, through subcontracts, prototype tests developed in the PDVI-sponsored research program
- Complete evaluation of these tests in appropriate clinical trials

- Ensure use of commercially available validated tests in vaccine trials or demonstration projects, and facilitate appropriate distribution in dengue endemic areas
- Prepare and maintain situation analyses of dengue diagnostics for measurement of vaccine safety and efficacy to determine the need for additional PDVI-sponsored research and development.

## **Vaccine Evaluation**

### **Background**

Evaluation takes place at a number of stages in the life of a vaccine, and includes pre-clinical studies in the best available animal model(s) to determine immunogenicity and induction of protection (directly or indirectly), Phase 1 clinical trials to determine safety and immunogenicity of prototype vaccines, Phase 2 trials to determine immunogenicity, age-specific dose-range, and larger trials to show proof of concept (Phase 2b) and vaccine efficacy and safety (Phase 3 randomized, controlled clinical trials). The Phase 3 trial provides the pivotal data for licensure, and Phase 4 population-based demonstration projects (trials) are used to determine vaccine effectiveness and identify rare adverse events under field conditions. Dengue vaccines are in varying stages of clinical development and none is licensed. Each vaccine will have to undergo pre-clinical and clinical evaluation, although some may not require extensive Phase 3 or Phase 4 evaluations.

Companies with vaccines (i.e., Sanofi Pasteur and GlaxoSmithKline) in Phase 2 trials could be expected to enter large-scale (Phase 2b, Phase 3) trials in the next few years barring negative Phase 2 trial outcomes. These manufactures will oversee large-scale trials either with in-house staff or under contract with academic, governmental or clinical research organizations. Discussions between PDVI and these companies will determine the extent to which PDVI may participate in or fund these trials. For the other vaccines currently in the pipeline, the funding pathways are not clear for Phase 2 and Phase 3 trials. In addition, the results of the first large clinical trials of dengue vaccine will determine whether an easily measured determinant of protection is identified, which could facilitate evaluation of other dengue vaccines in Phase 2 and Phase 3 clinical trials to determine equivalent levels of seroprotection and vaccine safety

The question of whether early, population-based clinical studies (Phase 4 trials) will be needed for licensure of dengue vaccines is an important one and cannot be answered unequivocally today. However, there is no doubt they will be needed to provide robust assessments of vaccine safety and the long-term effectiveness of immunization against multiple dengue virus serotypes in large populations. Since the early 1990s, Phase 4 trials have shown their value in the assessment of vaccine effectiveness and safety, and the introduction of new vaccines into childhood immunization programs and for their delivery at the community, provincial and national levels<sup>18</sup>.

Guidelines for evaluation of dengue vaccines have been developed by the Flavivirus Steering Committee organized by the WHO Initiative for Vaccine Research and are an important roadmap for industry and regulatory agencies. However, these guidelines do not fully address important issues such as vaccine trial endpoints (e.g., DF versus DHF), how to assess vaccine efficacy (effectiveness) against each dengue serotype, how to

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<sup>18</sup> Clemens, J., *Thinking downstream to accelerate the introduction of new vaccines for developing countries*. Vaccine, 2003. **21 Suppl 2**: p. S114-5.

account for possible cross-protection afforded by other Flavivirus infections in endemic areas (e.g., Japanese encephalitis), and how to assess vaccine safety (e.g., population size, role of Phase 4 trials). Development of consensus trial designs may permit comparison of clinical trial results for different vaccines performed by different sponsors. WHO has committed to undertake consultations to amend the current guideline with PDVI sponsoring consultants meetings to support this endeavor.

Development of a provisional, evidence-based dengue vaccination strategy or strategies, with well defined options (e.g., early childhood vaccination, the role of catch-up vaccination in older children, introduction strategies and epidemic control) based on available epidemiologic data and expected levels of vaccine efficacy would provide a roadmap for future vaccine evaluation studies. A provisional strategy would evolve as data about dengue vaccine performance become available, and it would provide clear pathways for vaccine evaluation either before or after Phase 3 trials. Examples of questions to be answered for the respective candidate vaccines, which would accelerate vaccine introduction, include the earliest expected age of vaccination (i.e., to determine the role of interference from passively acquired maternal antibody) and interference from other vaccines expected to be administered simultaneously with dengue vaccine (i.e., DTP, Hib, HBV, measles, and yellow fever).

Because dengue is a disease with cyclical peaks in incidence, having access to multiple sites in dengue endemic areas worldwide will increase the likelihood of being able to conduct large-scale, clinical trials (Phase 2b, Phase 3) when an outbreak occurs. In addition, having multiple field sites with dengue surveillance and clinical trial capacity will allow for vaccines found efficacious in a Phase 3 trial to move rapidly into a Phase 4 study before a vaccine is licensed, under an IND and appropriate informed consent.

Having population-based field sites capable of conducting rigorous studies also provides the settings to evaluate new dengue diagnostics, determine the economic burden of disease and study disease pathogenesis and natural history.

While it is anticipated that vaccine companies will want to have oversight of their large-scale clinical trials and trial sites (Phase 2b, Phase 3), we think the PDVI can provide the surveillance platform to identify multiple high incidence sites and assist in development of capacity to conduct clinical trials, including clinical trials of a single vaccine in multiple sites experiencing infection from different dengue virus serotypes.

Since historically, vaccine companies have not developed or sponsored Phase 4 trials in developing countries, PDVI will take on this responsibility. By undertaking management of the field sites and using them for other types of studies related to vaccine evaluation, PDVI will seek to minimize the possibility for field site ‘burnout’ during the period of time between site development and implementation of an evaluation trial.

## Work Plan

Based on extensive consultation with experts in the field, including vaccine manufacturers, the PDVI is in the process of establishing a *consortium* of field sites to conduct real-time dengue surveillance, perform standardized diagnostic testing and develop capacity to conduct clinical trials. These sites could be used for vaccine evaluation and other dengue-related studies. This consortium would be composed of sites fully or partially funded by PDVI, or funded by another sponsor. All members of the Consortium would agree to share surveillance data on dengue, standardize laboratory diagnostic protocols and methods, and diagnostic case definitions.

Development of the scientific basis for design of clinical trials and a provisional dengue vaccination strategy will be done in close collaboration with WHO. These program activities would involve a series of meetings, with conclusions updated as new clinical trial experience, information about performance of the respective vaccines, and epidemiologic data become available. Coordination to eliminate duplication of efforts or having outcomes which are at cross-purposes to each other would be achieved by working through PDVI's strategic partnerships.

The development of an effective consortium of field sites capable of vaccine evaluation will require substantial technical support from the PDVI. This support would include direct funding for some sites, staff and funding support to ensure that all sites achieve common core capacities of active dengue surveillance, standardized dengue diagnostic testing, and clinical and epidemiologic record keeping which meets standards of good clinical practices. In addition, PDVI staff would regularly visit field sites to work with staff. Principle investigators from respective sites would meet regularly to present data and discuss site management, and the sites would be tied together with an internet-based, data management and surveillance reporting system. Some field sites would be provided additional resources to develop prospectively followed cohorts of children for studies of dengue pathogenesis and natural history of infection. In return for access to the field sites, PDVI will encourage vaccine manufacturers to follow consensus clinical trial designs and use validated assays to assess immune responses to the vaccines.

The PDVI has initiated formal discussions with WHO on how best to provide the scientific information needed to revise the current Guidelines for Evaluation of Flavivirus Vaccines. Planning has begun for what will most likely become a series of scientific forums to address issues of dengue trial design and evaluation, and implementation of a dengue vaccination strategy.

### *Objectives*

PDVI support of vaccine evaluation will be directed in three major areas:

- Establishment of field sites for evaluation of dengue vaccines to determine their efficacy, effectiveness, and safety.
- Development of clinical trial guidelines to assess vaccine efficacy, effectiveness, and safety.

- Development of provisional dengue vaccination strategies for dengue endemic and non-endemic countries

***Milestones:***

- Establish consortium of 6 – 10 field sites located in Asia and the Americas to evaluate dengue vaccines
- Through the provision of technical assistance, ensure the capability of field sites to conduct standardized surveillance, dengue diagnosis, record keeping under good clinical practices
- Develop an effective IT and communications network among field sites
- Ensure timely and effective utilization of sites for clinical trials of vaccines and diagnostics and studies of disease incidence, dengue pathogenesis and the economic consequences of disease through the operation of a field site Steering Committee which includes field site directors and other partners
- Conduct meetings with private sector partners to determine how PDVI can make specific contributions to Phase 2b and 3 trials and prepare detailed work plans
- In collaboration with WHO and other partners, develop guidelines for optimum design of clinical trials to determine the efficacy, effectiveness and safety of dengue vaccines.
- Through consultations with public-private partners, develop strategies for implementation of dengue vaccination in endemic countries.

## Vaccine Access

### Background

Experience with hepatitis B vaccine led to the definition of a strategic approach to the introduction of new vaccines in developing countries<sup>19</sup>. The approach laid out five essential overlapping and complementary elements for success:

1. Measurement of disease burden and computation of vaccination cost-effectiveness
2. Conduct of large scale vaccine-introduction trials (Phase 4 trials)
3. Establishment of international and national consensus on the need for the vaccine and recommended use practices
4. Assurance of adequate and competitive supply
5. Creation and sustenance of funding mechanisms to procure the vaccine

Making the investment-case for dengue vaccination, includes measuring disease burden and computing the cost-effectiveness of vaccination compared to vector control programs and possibly anti-viral therapy. This information is essential for national and international policy-makers to be able to determine the priority to be accorded to various vaccines and prevention programs. In the context of scarce resources, they must decide the relative priority of various vaccines, especially with the availability of many new vaccines since 1990 -- hepatitis B, *Haemophilus influenzae* type b, Japanese encephalitis, rotavirus, pneumococcal conjugate, and others.

There is an urgent need to define the global disease burden of dengue. Good epidemiologic data exist for hospitalized cases in most of Southeast Asia and Latin America. However, little data exist for the remainder of Asia (e.g., India) and Africa. Validated models of dengue infection and disease burden need to be developed, which utilize data from population-based seroprevalence and surveillance studies. Such models should provide a mechanism to estimate the expansion factors required to take national and international surveillance data, e.g., WHO's DengueNet, and estimate disease burden. In addition, disease models provide a tool to estimate the effects of dengue vaccination and other control measures on infection and disease burden.

Although dengue vaccines have yet to be licensed and shown safe and effective, it is not too early to initiate regional and international discussions to determine dengue vaccination strategy options for endemic areas and for persons traveling from non-endemic to endemic areas. The presence of a dengue vaccine strategy with recommended practices is needed to ensure that manufacturers, in partnership with agencies such as WHO, UNICEF, and the World Bank, and the developing countries themselves, can effectively introduce a sustainable supply of vaccines.

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<sup>19</sup>Mahoney, R and JE Maynard, *The introduction of new vaccines into developing countries*. Vaccine, 1999. 17(7-8): p. 646-52.

PDVI will be concerned with all forms of IP, defined broadly to include patents, clinical, laboratory and epidemiologic data, know how, trade secrets, trademarks and agreements. IP has become an increasingly important matter for health technology development. The public sector is rapidly increasing its capacities in this area. Public private partnerships involved in vaccine development need to be able to operate in this complex field. The public sector can help ensure access by monitoring and managing IP as appropriate. It is unlikely PDVI will own any patents, but it will be involved (either as a party to the agreement or as an interested third party) in negotiations of licenses for development, production, and distribution of vaccines. The patent landscape of dengue vaccines is relatively simple compared to malaria (see Appendix 3). Our initial analysis indicates that there are no major issues of “patent thickets” that could inhibit the development of a dengue vaccine. Clinical and laboratory data have become important forms of IP, in part because of the further international extension of the principle of Data Exclusivity – the number of years after licensure during which data used to obtain licensure cannot be used by a company other than the company originally obtaining the license. Because PDVI will participate and, in some cases, fund studies generating these IP, it will negotiate appropriate arrangements to ensure eventual vaccine access in developing countries. Know how is often the most important form of IP for vaccines -- it can be more important to know how a vaccine is made than to know what it is made of. Technology transfer may arise as an important means to ensure access in dengue endemic countries. PDVI will promote cost-effective means of licensing and technology transfer to developing country manufacturers when appropriate. Additional issues that PDVI will address include open publication of results and developing strategies to access background IP and to assemble new IP generated by PDVI funded projects,

Ensuring adequate and competitive vaccine supply depends on good communication between users and producers. Producers need to know projected levels of use at various price levels. By encouraging and fostering competition, if possible, public-sector policy-makers can help insure lower yet commercially sustainable prices. Also, it may be desirable to establish production in developing countries to take advantage of cost advantages. Developed country companies are increasingly considering and, in some cases, pursuing this option. The public sector can assist in exploring such options and facilitating their success. In the case of dengue vaccines, the major companies will make their own assessment, but PDVI can facilitate through interactions with government agencies and other key decision makers.

Global purchase systems, such as those of the Vaccine Fund and the Global Fund to Fight AIDS, TB and Malaria, are essential to meet the needs of poor countries. These systems face extraordinary challenges in mobilizing the required resources to purchase vaccines and drugs. The global funds operate using a complex set of policies that has already resolved many important issues, including such controversial matters as regulatory standards and respect for IP. The mobilization of resources for vaccine procurement may be the most difficult challenge, other than resolving scientific questions, facing the vaccine community and will certainly be a challenge for dengue vaccines.

The development and introduction of pediatric dengue vaccines should be conducted with close involvement of key agencies such as WHO, GAVI, UNICEF, governments of developing countries, producers, and others. Regular national and international meetings

will help to air issues and generate consensus. Of particular importance will be interactions with national vaccine regulatory agencies and with the relevant regulatory groups at WHO. The development of this consensus will be affected by many of the activities carried out by PDVI. An important component will be to develop effective communications with health professionals, scientists, other partners and the public about dengue prevention and control, progress in dengue vaccine development, evaluation and utilization, and the PDVI.

**Text Box. The Viral Hepatitis Prevention Board (VHPB) - A model of regional advocacy for disease prevention and control**

The Viral Hepatitis Prevention Board ([www.vhpb.org](http://www.vhpb.org)) of the European Union and WHO European Region, which includes the former Soviet Union, was established in 1992. The Board consists of advisors who are internationally recognized experts in viral hepatitis from member countries, WHO and other partner organizations. The VHPB has had a substantial influence on development and advocacy for viral hepatitis prevention and control (primarily immunization) by issuing guidelines, encouraging actions to improve control and prevention activities, and disseminating information to healthcare professionals, decision makers and opinion leaders. Funding comes from industry, and the University of Antwerp serves as the Secretariat. .

## **Work Plan**

PDVI will support activities to provide, validate and strengthen the scientific and economic information needed to make decisions with respect to dengue vaccine development, evaluation, production and introduction. (See Appendix 7 for a list of already funded activities.) In addition, the PDVI will engage in monitoring, and when appropriate, managing IP associated with dengue vaccines and diagnostics; facilitating development of advocacy to support introduction and utilization of a safe and effective dengue vaccines; developing international and national dengue vaccination strategies and providing national assessments of access to dengue vaccine by the poor.

### ***Objectives:***

- Conduct and evaluate health economic studies to make robust national, regional and international estimates of the cost of illness; the estimated cost effectiveness of dengue prevention through vaccination, including comparisons of different vaccination strategies and vector control programs; the estimated cost-effectiveness of dengue prevention compared to potential treatment with antiviral drugs; the willingness to pay for dengue vaccine and the revenue potential of dengue vaccine when used in various immunization strategies;
- Estimate burden of illness at the national, regional and global level through development of appropriate mathematical models from various data sources;

- Estimate the potential effect on disease incidence of dengue vaccination and different vaccination strategies using mathematical models;
- Working with WHO and others, strengthen the quality of national, regional and international surveillance and reporting for dengue;
- Monitor and manage IP related to dengue vaccines and diagnostics as appropriate
- Collaborate with manufacturers and provide assistance to developing countries with respect to regulatory affairs
- Identify and promote plans for national and international vaccine distribution in the public and private sectors; assess the potential role of manufacturers in developing countries in ensuring access by the poor; and promote creation of funding mechanisms for sustained procurement of vaccine;
- Develop effective communications with health professionals, scientists, other partners and the public about dengue prevention and control, progress in dengue vaccine development, evaluation and utilization, and the PDVI.

***Milestones:***

- Complete, analyze and disseminate data from facility-based cost of illness studies in Asia and Latin America
- Design, implement, analyze and disseminate results of population-based cost of illness studies
- Design, implement analyze and disseminate results of studies of the cost of vector control programs.
- Support development and validation of mathematical models, including user friendly versions, to estimate the burden of disease at national, regional and global levels.
- Conduct projects and activities to assess reporting, data quality, analysis, interpretation and use of information for strengthening of dengue surveillance at the national and global levels
- Conduct comparative health economic studies of dengue vaccination, including different vaccination strategies, vector control and treatment, including anti-viral therapy.
- Undertake economic studies to evaluate how PDVI funds can most effectively be allocated to the complex array of areas involved in vaccine and diagnostic development and introduction.
- Support socio-economic studies to understand the nature of the public and private sector markets; determine willingness to pay for dengue vaccines on the part of the public and governments; attitudes of the public and private health sectors towards dengue as a vaccine preventable disease; and the value and consequences of social mobilization during dengue epidemics and the potential effects on immunization strategy and vaccine supply.
- Establish and implement IP management policies and capacity.
- Assess the desirability and feasibility of dengue vaccine production in developing countries through discussions with vaccine manufacturers, development of terms of agreement with potential manufacturers, and support of a technical and economic feasibility study.
- Establish strong communications and advocacy with health professionals, scientists, regulatory officials, and other partners through development of a comprehensive,

authoritative web site; creation of regional dengue prevention groups and publication of a Newsletter

- Prepare a detailed assessment of the various strategies and related costs for ensuring a continuing supply of dengue vaccine through both international and national procurement as one or more vaccines are approaching the market.

## Organization and Operations

In recognition of the magnitude of the effort and the demand for a focused, highly specialized and multi-faceted program based at the International Vaccine Institute, the PDVI has been designed to address all critical issues, either directly itself or through appropriate partnerships. The Board of Counselors, which provides oversight to the PDVI, is a group of highly qualified individuals with expertise in one or more areas of PDVI work.

The IVI is well suited to host the PDVI for several reasons:

- It has extensive networks in Asia, and other developing regions, with vaccine investigators, ministries of health, and international organizations.
- It has completed a number of important studies in areas related to PDVI programs such as burden of disease and policy studies, epidemiological assessments, clinical trials, Phase 4 trials, and socio-economic studies.
- It has a laboratory program that could provide support to PDVI surveillance studies.
- Its Board of Trustees includes individuals who can be effective in supporting the achievement of PDVI goals.
- It has collaborative relationships with vaccine companies in both developed and developing countries including the key companies concerned with dengue vaccines.
- It has established administrative capabilities for global programs of vaccine research and development.

The PDVI has divided its work into the program areas described in this Plan.

- Strategic Partnerships
- Supportive R&D
- Vaccine Evaluation
- Vaccine Access

There will be a specific Director for three of the program areas – Supportive R&D, Vaccine Evaluation and Vaccine Access. These Directors provide the required technical expertise, consultation, oversight and program management. The Strategic Partnerships program area is the lead responsibility of the Deputy Director of the PDVI. Assisting the Director is a Senior Advisor and a Senior Advisor for strategic program development, who also serves as the Director for Vaccine Access. As the need arises, the PDVI will contract with consultants to provide the specific expertise needed for program development and implementation.

In launching the PDVI, two Scientific Advisory Groups (SAGs) were formed. These SAGs have provided excellent support and guidance to the conceptualization and launch of the programs and activities for the cost of illness studies, targeted research towards the development of improved diagnostics and for understanding safety issues with respect to dengue vaccines, and for the development of vaccine evaluation field sites. These

programs are well underway and they should achieve their objectives in the near future. With the increase in the size and breadth of expertise of the Board of Counselors, it will assume the continuing oversight responsibilities for the Supportive R&D, Vaccine Evaluation and Vaccine Access Programs, as well as the Strategic Partnerships formed by the PDVI.

To assist the Director, the PDVI has formed a Scientific and Technical Advisory Panel, which includes most members of the SAGs, as well as members with expertise to address new challenges to provide assistance as appropriate with special issues.

Most of the work of the PDVI will be conducted in dengue endemic countries or through subcontracts with qualified groups at research and academic centers in both developed and developing countries. Certain activities will be conducted directly by PDVI staff. For example, the Vaccine Access program will be managed by PDVI staff who will be deeply involved in the detailed execution of its various components. The administrative management, including human subjects review, of the PDVI program will occur according to established IVI guidelines and procedures. The primary program management office resides in Seoul, with a satellite in the United States to support the large number of PDVI supported programs in the Americas and Europe. These offices operate under the same administrative guidelines and use a secure web portal to share documents and information in a seamless manner.

Overall, it is expected that PDVI core staff may increase to approximately 10 - 15 full time equivalents varying over time. This staff complement is comparable to that seen in other similar programs such as the Global Alliance for TB Drug Development. PDVI may station PDVI staff in one or more of the Phase 4 sites. In addition, PDVI will call on individuals in collaborating organizations and will, as appropriate, support their salaries.

## **Timeline**

No dengue vaccines have been shown to be safe and provide efficacy in preventing infection. To estimate the timeline to accelerate evaluation and introduction of one or more dengue vaccines, we have made certain assumptions about program activities described in this Plan leading to the completion of population-based effectiveness trials (Phase 4) of one or more vaccines in 2015 and limited vaccine introduction. Based on current results from Phase 2 trials, we estimate that one or more dengue vaccines could enter into large-scale (Phase 2b or Phase 3) clinical trials in 2008, recognizing that a trial site would have to be established in advance of the annual ‘dengue season’, which is usually in the summer-fall north of the equator and winter-spring south of the equator.

With respect to time lines, these depend significantly on whether a manufacturer decides to conduct a Phase 2b or a Phase 3 trial at the next juncture. If a sponsor conducts a Phase 2b trial, this will have to be followed by a Phase 3 trial to determine vaccine safety and efficacy. However, if a Phase 3 trial is conducted and efficacy is shown in a single ‘dengue season’, the results of such a trial could be available in 2009-2010 at the earliest. It is our assumption that any tetravalent dengue vaccine shown to have efficacy in a single Phase 3 trial would quickly need to enter into a Phase 4 population effectiveness

trial to demonstrate safety and protection against multiple dengue serotypes over time. In a best case scenario, a Phase 4 trial could be initiated 2010.

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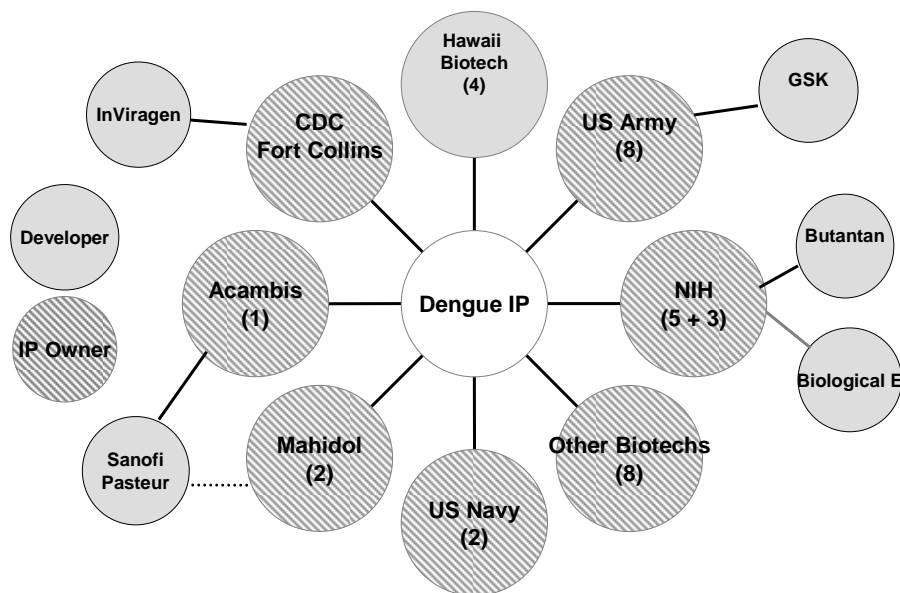
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## Appendix 3: IP and licensing arrangements for dengue vaccines

Figure 4 is a picture of the current IP and licensing arrangements for dengue vaccines. The blue circles are organizations that hold patents for various dengue vaccines. The Yellow circles are organizations that have licenses from the IP owners. One organization (Hawaii Biotech) is both an owner and a developer. The numbers in parentheses are the number of patents owned plus (in the case of NIH) the number of pending applications. It is the pending NIH applications that are licensed to Biological E and Butantan. The dashed line from Mahidol to Sanofi Pasteur indicates that the licensed vaccine is no longer under development.

**Figure 4. IP and licensing arrangements for dengue vaccines**



The data to construct Figure 4 were obtained by conducting searches on [www.uspto.gov](http://www.uspto.gov) using the search terms “(Dengue or Flavivirus) and Vaccine” in the Abstract. We also searched at [www.ep.espacenet.com](http://www.ep.espacenet.com) using the same search terms in Advanced Search. In addition, we interviewed officials at various organizations (T. Monath, Acambis; L. Salicrup and M. Rohrbaugh, NIH; Richard Kinney, CDC; J. Roehrig, CDC; D. Vaughn, USAMRMC; J. Lang, Sanofi Pasteur) who confirmed the validity of the data. The data are current as of December 2005.

PDVI is also assessing the IP landscape for diagnostics.

# **Appendix 4: Suggestive Term Sheet on which to base early discussions with potential private sector partners**

## **Pediatric Dengue Vaccine Initiative at the International Vaccine Institute PDVI/IVI**

### **Terms for Consideration Memorandum of Cooperation with Company**

#### **1. Commitment to have study results published**

To move the broad field of dengue vaccine development forward, results of studies (positive and negative) funded by PDVI/IVI would usually be made public. PDVI/IVI understands the possible need to delay publication for the purpose of protecting intellectual property and ensuring that confidential information is not disclosed.

#### **2. Commitment to continued development of the vaccine**

Should PDVI/IVI enter into an agreement with Company to support development or testing of a dengue vaccine, PDVI/IVI would want a guarantee from Company of continued development of the vaccine and would want terms identified by which the technology could be transferred to other developers in the event that Company should abandon the project or fail to meet agreed milestones.

#### **3. Commitment to manufacture and supply**

If PDVI/IVI supports Company's development or testing of a dengue vaccine, PDVI/IVI would expect a commitment to have the vaccine manufactured in sufficient quantity to ensure access in dengue endemic countries without extensive delay following licensure. The Company's vaccine will satisfy the appropriate regulatory requirements necessary to supply the vaccine to dengue endemic countries. PDVI/IVI would want to identify terms by which PDVI could co-promote and co-distribute the product in dengue endemic countries, if the vaccine were not widely distributed to those in need.

#### **4. In-licensing**

If Company in-licenses new technology to develop or make the vaccine, the licenses should provide for the distribution and sale of the product in dengue endemic countries.

#### **5. Global Access Plan**

PDVI/IVI and Company will agree to a vaccine Global Access Plan for dengue endemic countries which may include milestones, deliverables, and due dates.

## 6. **Governance**

PDVI/IVI and Company will form a vaccine development Steering Committee to ensure the effective governance of the collaboration in line with industrial standards for accelerated vaccine development. The Steering Committee will oversee the implementation of the project plan, including developing protocols for preclinical and clinical trials, interpreting data, identifying and solving technical roadblocks, reviewing and amending the plan, and reviewing expenditures against the budget. Company will hold the determining vote. In the case of another PDP, the Malaria Vaccine Initiative (MVI), the Steering Committee is made up of 8 individuals with four coming from MVI and four from the partner. The rules of conduct for the Committee provide for the partner to have veto power over Committee decisions, although this issue has not arisen in practice.

7. The price for the public sector is an issue of high priority, but it is also a very difficult issue to address, especially with a product that is in early development stages.

## Appendix 5: Supportive R & D Program: Pre-Clinical Research Projects

<b>Principal Investigator</b>	<b>Recipient Institution</b>	<b>Title</b>
Carol D. Blair	Colorado State University	Understanding dengue 2 virus attachment, virus-mediated cell membrane fusion, and of virus neutralization
Alan Barrett	University of Texas Medical Branch at Galveston	Interaction of dengue virus envelope protein domain III with cell receptor(s) and neutralizing antibodies
Jacob Schlesinger	University of Rochester	The role of monocyte Fc receptors in dengue virus neutralization escape
Mary Marovich	Henry M. Jackson Foundation for the Advancement of Military Medicine	Mechanism of antibody enhancement (ADE)
Daved Fremont	Washington University	Structural analysis of dengue and West Nile virus glycoprotein
Anna Durbin	Johns Hopkins Bloomberg School of Public Health	Rhesus macaque model for dengue, DHF/DSS
Felix Rey	Centre de la Recherche Scientifique	Structural studies of Den viral envelope protein: the antigenicity and receptor binding interaction
Richard Kuhn	Purdue University	Role of antibodies in controlling dengue virus infection
Erica Ollmann Saphire	The Scripps Research Institute	Comparative structural analysis of dengue 1-4 E proteins
Siamon Gordon	University of Oxford	Receptors for dengue virus on primary human macrophages
Aravinda de Silva	University of North Carolina at Chapel Hill	Antibody dependent neutralization and enhancement of dengue serotype 3, associated with severe and mild diseases
Ted Pierson	National Institutes of Health	Mechanisms of antibody neutralization and enhancement of dengue virus infection
Eva Harris	University of California, Berkeley	A Murine Model for Dengue Virus Infection and Disease
Ramesh Akkina	Colorado State University	Dengue pathogenesis and immune enhancement in SCID-hu mouse
Xia Jin	University of Rochester	Leukapheresis for Studying Pathogenesis of Dengue Virus Infection

## Appendix 6: Vaccine Access Program: Dengue Cost of Illness Studies

Country	Principal Investigator	Recipient Institution	Title
Brazil	João Bosco Siqueira Jr.	The Institute of Tropical Pathology and Public Health, Federal University of Goiás, Brazil.	Economic impact of Dengue Fever/Dengue Haemorrhagic Fever in the City of Goiânia, Goiás State, Brazil
Cambodia	Ngan Chantha	National Dengue Control Program, Ministry of Health of the Kingdom of Cambodia	A hospital-based study on the dengue disease burden. Takeo Provincial Hospital, Kingdom of Cambodia
El Salvador	Dr. Romeo Montoya Acevedo	Ministry of Health and Social Assistance of El Salvador	Estimating burden of dengue in B. Bloom Pediatric Hospital and Unicentro Health Center, San Salvador, El Salvador
Guatemala	Dr. Leticia del Carmen Castillo Signor	Laboratory of the Ministry of Health and Social Assistance of Guatemala	Clinical, epidemiological and socio-economic Characterization of Dengue in Three Health Units of Guatemala City
Malaysia	Prof. Lucy Lum Chai See	University of Malaya Medical Center	Economic impact of dengue in the Klang Valley, Malaysia
Panama	Dr. Blas Armien	Instituto Conmemorativo Gorgas de Estudios de la Salud, del Ministerio de Salud de Panamá	Burden of illness for dengue in Panama
Thailand	Dr. Sukhontha Kongsin	Faculty of Public Health, Mahidol University, Thailand	Measurement of the Dengue Burden in Thailand: Impact on Household of Dengue Hospitalized Episode
Venezuela	Dr. Fátima Garrido Urdaneta	Ministry of Health and Social Development of Venezuela	Burden of dengue in Falcón State, Venezuela