



**Dengue Vaccines**  
The Pathway

The Pediatric Dengue Vaccine Initiative  
International Vaccine Institute  
Seoul, Korea

## **The Pediatric Dengue Vaccine Initiative**

The Pediatric Dengue Vaccine Initiative is a program of the International Vaccine Institute, Seoul, Korea funded by the Bill and Melinda Gates Foundation, the Rockefeller Foundation and the government of the Republic of Korea.

The PDVI mission is to 1) accelerate evaluation of candidate dengue vaccines, 2) facilitate the introduction of new and improved diagnostics, and 3) ultimately help introduce safe and effective vaccines in dengue endemic countries.

### **PDVI Goal:**

**Introduce dengue vaccination into the national immunization program in one developing country in each endemic region**

### **Contact Information**

Dr. Harold Margolis  
Director  
Pediatric Dengue Vaccine Initiative  
International Vaccine Institute  
Seoul, Korea  
[hsmargolis@pdvi.org](mailto:hsmargolis@pdvi.org)

## TABLE OF CONTENTS

Introduction.....	1
First: About Dengue.....	1
Next: Societal and Economic Implications.....	1
So Now: Addressing the Challenges.....	2
But the Inevitable Barriers: What are they?.....	3
Getting over the Barriers: Some Goals .....	4
Finally: Join us! The PDVI is a partnership.....	5



## Introduction

The Pediatric Dengue Vaccine Initiative addresses a daunting but achievable task: to vaccinate tens of millions of susceptible children annually against the dengue virus in regions of the world where the disease is endemic – places that are poor with limited human, financial and institutional resources.

The barriers are significant. We hope to succeed.

It will take more than hope to overcome the barriers. It will take a plan, and we have one. The plan shows us how to harness the power and knowledge of scientists, medical and public health and corporate leaders, and policymakers. We could be less than a decade away from success.

Let's see how it will be done.

## First: About Dengue

Dengue fever is a mosquito-borne disease primarily affecting children. It occurs mostly in tropical and subtropical countries and is spreading to new parts of the globe each year. Dengue fever, with its threat of consequences of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), results in substantial morbidity, mortality and economic losses.

Dengue can become a vaccine preventable disease. The disease is caused by four Flaviviruses, dengue types 1 – 4. Other Flavivirus diseases – yellow fever, Japanese encephalitis and tickborne encephalitis – are controlled by effective vaccines. This leads us to believe we can succeed against dengue as well. A number of dengue vaccine candidates are in different stages of pre-clinical and early clinical evaluation. However, none has yet to enter the late-stage clinical trials needed to put a vaccine on the market.

Progress has been slow; dengue is one of the more complex vaccines presently under evaluation. A vaccine must provide durable protection against infection from the four different dengue viruses. In addition to a vaccine, we need new and improved diagnostics to better diagnose, and monitor the disease in the population and to help in evaluating the vaccine.

## Next: Societal and Economic Implications

Dengue fever affects 50-100 million people a year and threatens half the world's population. For the roughly 5% of dengue fever patients who develop dengue hemorrhagic fever and dengue shock syndrome, dengue fever can be a death sentence. Left untreated, dengue hemorrhagic fever can have mortality rates as high as 33%. A conservative estimate is that 20,000 people a year die from dengue hemorrhagic fever; these estimates suffer from the limits of accurate diagnosis and record keeping in many dengue-plagued parts of the world.



The consequences of this burden of illness are significant. In regions and countries where dengue is prevalent, its impact on health can be comparable to more well-known diseases such as TB and malaria. In fact, health workers in those countries are deeply concerned about the impact of dengue and its ability to produce large epidemics on a regular basis. Dengue causes a cyclical spike in demand on already-fragile local medical resources and places tremendous pressure on overburdened hospitals and clinics.

A few early studies have identified and measured the impact of dengue fever on the social and economic fabric of societies where it is most common. We do not know the real burden of disease globally, since all susceptible regions are not equipped to make an accurate assessment. What we do know, however, is that dengue has spread into almost all tropical and subtropical regions due to urbanization and globalization. Dengue has been documented in areas usually not thought to be afflicted, including northern Australia, the Middle East, and the states of Texas and Hawaii in the U.S. Each year, a substantial number of people traveling or working in endemic regions are afflicted as well.

Because dengue fever strikes mostly children – and they fall more seriously ill – both they and their parents suffer from the medical aspects of the disease and the cost of care, and from the time away from work and other family responsibilities.

Additionally, dengue fever is a mosquito-borne illness, but environmental management to control mosquito breeding is a very costly and never-ending job. One economic model showed that a comprehensive vaccine program would be far less expensive than environmental management approaches.

## **So Now: Addressing the Challenges**

Development of an effective vaccine against all four dengue viruses is not only possible, it is technically feasible. In fact, given the accelerating pace of progress, it is more than likely that a vaccine to prevent dengue fever will be ready several years before vaccines for other high-profile, diseases such as HIV, TB and malaria. This kind of success and the lessons learned along the way could make dengue vaccine and the PDVI as models to help guide other vaccine programs.

PDVI is supporting work to assess the prevalence of dengue fever, track its spread, and determine the impact it has on healthcare costs and family income. These data should provide further backing and motivation to governments, companies, research institutes, and public health officials trying to control this disease.

One key challenge is to demonstrate that candidate vaccines provide long term protection against dengue infection and are safe. While several candidate vaccines have demonstrated immunity in small clinical trials, there have not been the larger and much more expensive trials to show that these vaccines really work. PDVI will help organize and execute these trials. The trials will take place in Asia and the Americas, will involve upwards of several thousand participants, and they will be costly. In addition, PDVI will ensure that trial participants are monitored for many years to ensure that the vaccine provides long-lasting protection and is safe. PDVI plans to work with



leading vaccine companies and developing country governments to launch these trials before 2010.

Once there is a safe and effective vaccine, PDVI will work with the governments of dengue endemic countries to make the vaccine available to the population. In particular, PDVI will help mobilize the money to buy the vaccine and will provide assistance to countries to build systems to deliver the vaccine.

PDVI will work to encourage use in rich and poor countries. The reason is to make sure companies can get enough profit in rich countries so that the vaccine can be offered cheaply in poor countries. For example, dengue vaccines might be priced similar to other vaccines offered in developing countries like hepatitis B vaccine where the price can be around \$8 per dose while for developing countries the price is now at \$0.27 per dose. PDVI believes that there will be a substantial market among travelers, the military, and overseas workers from Europe, the United States and Australia.

PDVI is a part of a new way that companies and the public sector are working together to develop and introduce new vaccines needed by the poor. Several pharmaceutical firms have developed “no-profit, no-loss” strategies for these products. These strategies reflect the companies’ realization that we live in a global world where old walls have fallen down. The key today is to build bridges.

## **But the Inevitable Barriers: What are they?**

The PDVI has laid out its goals. We believe they are sensible and can be achieved. But as with all great undertakings, there are barriers. What are they for dengue vaccines?

### **Barrier 1: There is no safe and effective vaccine to prevent dengue.**

Simple enough but a big challenge. There is no vaccine today. Our first priority has to be to do those critical tasks that will speed up vaccine development as much as possible.

### **Barrier 2: Endemic countries lack sufficient information for establishment of national immunization programs.**

Even with a vaccine, countries have to want it and they have to know how best to use it. PDVI will have to help make sure adequate information is available on which to base wise and effective decisions.

### **Barrier 3: There is no assurance of adequate supply and procurement (market) in developing and developed countries.**

Nobody is going to make a product that no one is ready to buy. PDVI will work with developing countries to build demand and with international donors to plan for them to help countries buy the vaccine. PDVI will also help build demand in developed countries because those markets are crucial to overall success.



#### **Barrier 4: There are insufficient resources to achieve success.**

The Bill and Melinda Gates Foundation and the Rockefeller Foundation have been very generous. The companies are investing tens of millions more. Countries are ready to help. But all these sums together will not be enough. PDVI will work very hard to justify additional investments in dengue vaccines. We estimate the total bill by the end of 2015 could be around \$150 million.

These are the barrier. What are we going to do about them?

## **Getting over the Barriers: Some Goals**

PDVI has specific and achievable goals that, given a lot of help from many others, should put a dengue vaccine into use by 2015.

### **Goal 1: Strategic Partnerships**

As is clear from the foregoing, there will have to be a lot of teamwork. PDVI is working in partnership with companies, countries, universities, research institutes, and individuals. We will nurture these partnerships to make sure there is a powerful international network to achieve success.

### **Goal 2: Supportive Research and Development**

The creation of a new vaccine requires a lot of science. Several companies are working hard on developing vaccine candidates. Government agencies, particularly in the United States, are also developing vaccine candidates. PDVI will focus on the neglected area of diagnostic development. These diagnostics will be critical for testing vaccines, finding out how many people suffer from the disease, and helping hospital and clinic staff treat patients.

### **Goal 3: Vaccine Evaluation**

The PDVI will work with companies to test vaccines in clinics. These studies are necessary for gaining approval from regulatory agencies. The PDVI is also working in several developing countries to build a network of “field sites” for testing vaccines in real-life situations. These field sites are usually defined urban areas with high levels of dengue.

### **Goal 4: Vaccine Access**

It's not enough just to build partnerships, undertake R&D, and complete vaccine evaluation. There needs to be a real demand for the vaccine, there needs to be understanding of how the vaccine can help improve health, there needs to be a good supply of the vaccine based on accurate uptake estimates, and there needs to be international support for using the vaccine. PDVI is addressing each of these challenges. For example, PDVI is forming authoritative groups who will issue expert opinions on key issues concerning all these topics. These groups will be made up mostly of individuals from endemic countries.



## **Finally: Join us! The PDVI is a partnership**

PDVI is pleased to have presented you with this information about our progress and plans. We would like to thank you for your interest in taking the time to read this document, and we invite you to join our cause. We have a strong and enthusiastic group of talented and dedicated individuals working diligently to overcome the dengue fever scourge. With PDVI's vision and tools, and with your support, we are only years away from conquering a global health threat.