Making Dengue a Vaccine Preventable Disease

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Joint International Tropical Medicine Meeting (JITMM)
Bangkok, Thailand
October 13, 2008

Dengue Vaccines

Where are We Today ?

- No vaccine licensed
- High levels of country interest
- Low levels of awareness about dengue vaccine development by “vaccine community”
- Strong vaccine ‘pipeline’– a number of candidates
- Candidates in different stages of evaluation
- No large-scale clinical trials

Dengue Vaccines – Feasible

- Type-specific dengue virus (DENV) infection confers protection against disease
- Can produce candidate vaccines

Dengue Vaccines – Challenges

- Tetravalent formulation
  - Interference - live vaccines
- Less than ideal diagnostic tests and assays
  - acute illness
  - measure of protection / correlate of protection
- Evaluation – Efficacy and Safety
  - Protection against multiple dengue virus (DENV) types
  - Wide spectrum of ages
  - Disease occurs in both hemispheres
  - Safety - theoretical potential for immune enhanced disease (ADE / DHF)

Types of Dengue Vaccine Candidates

- Cell culture adapted, live attenuated viruses
- Infectious clones
  - chimeric viruses
  - attenuation by site directed mutagenesis
- Recombinant subunits of DENV envelope proteins
- Inactivated dengue viruses
- DNA and DNA shuffling

The PDVI Dengue Vaccine Portfolio

Vaccines in Commercial Development

Developer	Partner	Approach
	Live Attenuated	
WRAIR	GSK	Cell culture passage
Acambis	Sanofi Pasteur	Yellow fever – Dengue chimera
NIH	Biological E	Dengue 4 - dengue chimeras and gene deletion
	Butantan	
	Panacea	
CDC	InViragen/Shantha	Dengue 2- dengue chimeras
	Subunit	
HBI	Hawaii Biotech (HBI)	Envelope + NS1 recombinant

Why Multiple Candidate Vaccines ?

- No assurance that any one vaccine will be successful in a efficacy trial
- Availability of multiple vaccines is more likely to ensure:
  - An affordable vaccine
  - Sustained and sufficient availability of product

Status of Dengue Vaccines

Developer	Producer	Process Development	Evaluation		
			Phase 1	Phase 2	Phase 2b
Acambis	SanofiPasteur	→	→	→	2009 ?
WRAIR	Glaxo SmithKline	→	→	→	2009 ?
NIH		→	→	? 2009 Tetravalent	
	Biological E	→	? Late 2009		
	Butatan	→	? Late 2009		
	Panacea	→	?		
CDC	InViragen / Shantha	→	Mid -2009		
Hawaii Biotech	Hawaii Biotech	→	Mid-2009		

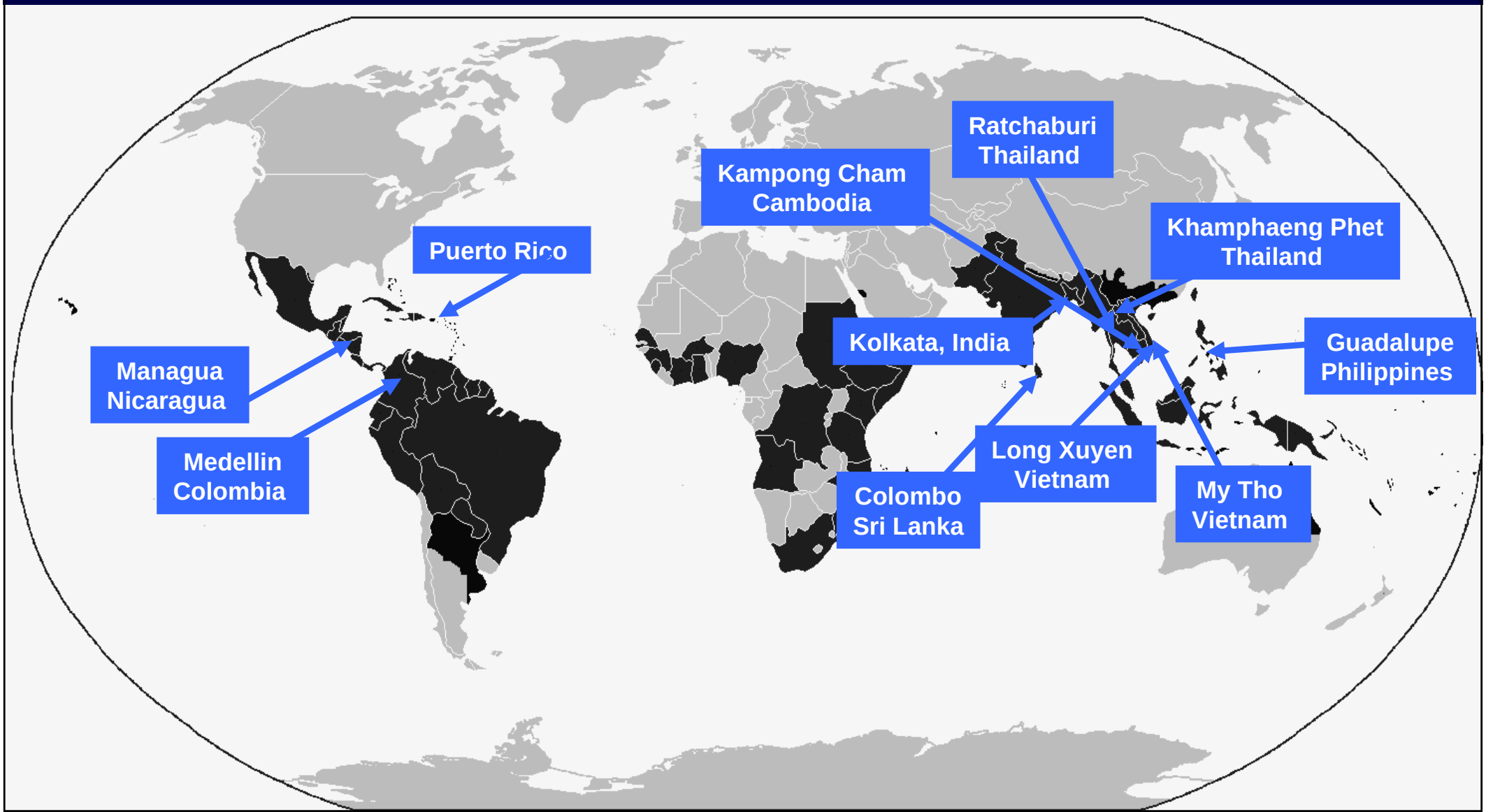
Vaccine Evaluation – Needs

- **Multiple sites** in Asia and the Americas
- Laboratory-based **dengue fever incidence** data
- Population-based, **fever surveillance** to identify cases over a wide range of ages
- **Comparable** case definitions and laboratory testing algorithms and methods
- **GCP** monitoring for surveillance
- **GLP** with internal and external quality control

PDVI Field Site Consortium

- Population-based fever surveillance
- Reliable estimates of dengue disease incidence/ disease burden
- State-of-the-art dengue diagnostics
- Comparable case definitions
- Clinical care for dengue disease
- Conducted under GCP / GLP
- Sites funded by multiple sources

Field Site Consortium, 2008



"Guidelines for Clinical Evaluation of Dengue Vaccine in Dengue Endemic Populations"

Issue	Recommendation
Disease (DF) identification	Fever surveillance
1° end-point (statistical) **2° end-points (descriptive)**	Dengue fever (fever + viremia) Severe dengue (DHF)
Correlate (s) of protection	Post-hoc analysis (PRNT ± other assays)
Protection against multiple DENV types	Statistical endpoint likely only for single DENV type in any one site.
Antibody response	Sample of participants for short and long-term follow-up (up to 5 yrs)
Safety	Cohort to remain blinded for 3-5 yrs (no crossover) + expanded trials

Dengue Diagnostics

Diagnostics: Evaluation of Vaccine Preventable Diseases

- **Diagnosis of infection / disease**
  - Clinical diagnosis / management
  - Epidemiologic studies (e.g., disease burden, natural history)
  - Clinical trials (Phase IIb, Phase III, post- Phase III)
  - Surveillance
- **Response to vaccination**
  - Clinical trials (correlates of protection)
  - Post-vaccine introduction - surveillance
  - Long-term protection (“immune memory”)

Dengue Diagnostics Initiative

To make available dengue diagnostic tests and assays so that:

- Individuals with dengue can be accurately and effectively diagnosed to receive treatment
- Public health officials will have reliable epidemiologic information on dengue
- Individuals can have access to safe, effective and affordable vaccines

Objectives

- **Create an enabling environment** to support development, evaluation, manufacture, introduction and use of improved diagnostic tests and assays

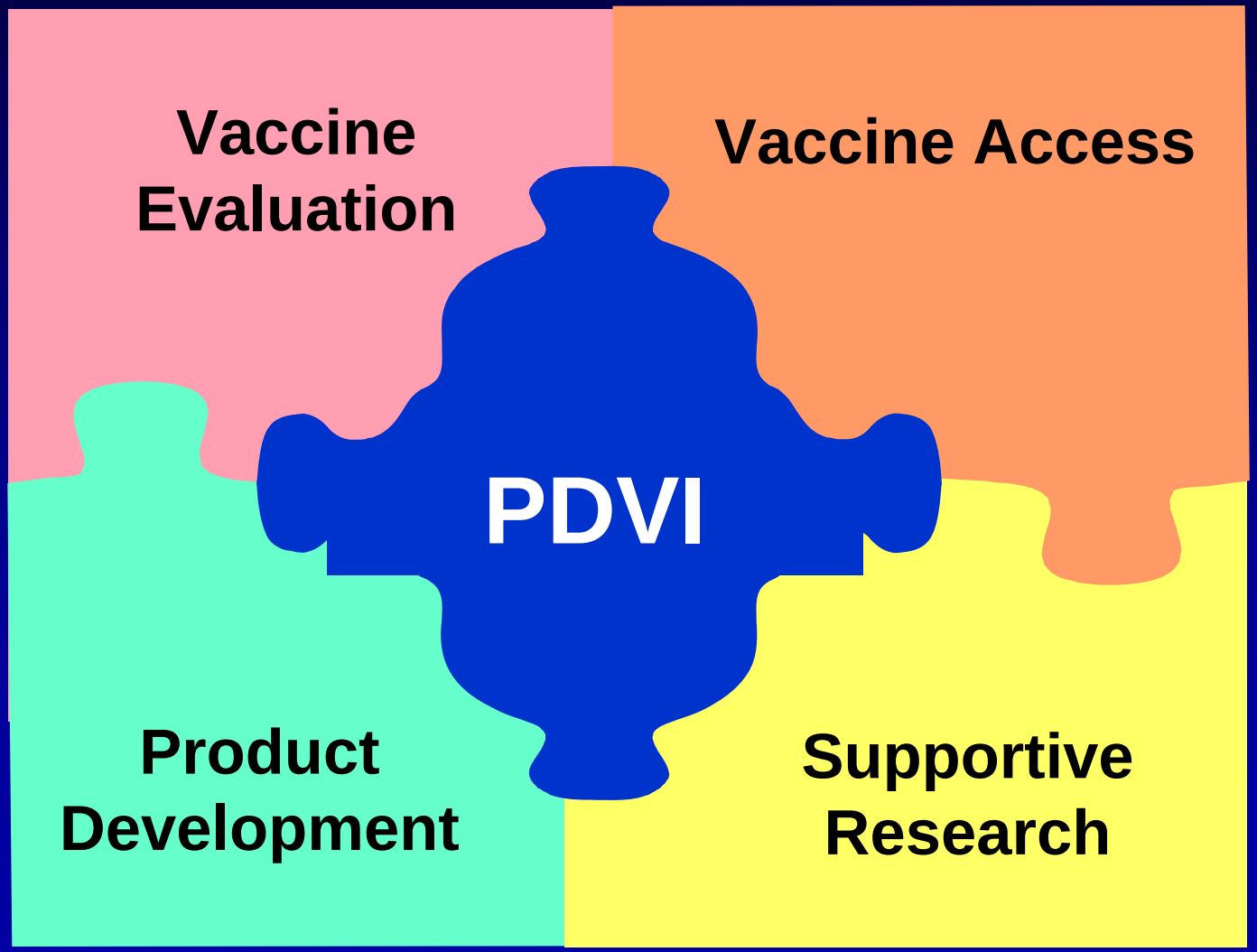
- Develop and ensure wide availability and appropriate use of affordable and accurate **diagnostic tests for acute dengue** for: 1) use in clinical and reference laboratories, 2) point-of-care (POC) settings, and 3) for evaluation of dengue vaccines

- Develop and produce standardized **assays to measure serotype-specific protective and enhancing antibody** to dengue virus (DENV) infection for dengue vaccine evaluation

What are the Needs ?

- Accurate diagnosis of dengue on a single specimen during the early phase of illness (days 1-5)
  - Minimal cross-reaction with other DENV or Flavivirus infections (e.g., JE, YF, WNV)
  - Virus detection probably best
- Accurate measure of protective DENV antibody
  - Vaccine trials and epidemiologic studies
  - Replace the plaque reduction neutralization test (PRNT)

Thank You


Vaccine Evaluation
Vaccine Access
PDVI
Product Development
Supportive Research