

Pediatric Dengue Vaccine Initiative In the Americas

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Where are We Today ?

- No vaccine licensed
- High levels of country interest
- Low levels of awareness about dengue vaccine development by “vaccine community”
- A number of candidates - strong ‘pipeline’
- Candidates in different stages of evaluation
- No clinical trials of efficacy



Dengue Vaccines – Feasible

- Type-specific dengue virus (DENV) infection confers protection against disease (?infection) with that serotype
- Can produce vaccine candidates
 - Immunogenic
 - Excellent safety profiles



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)

Dengue Vaccine Use – Challenges

- **Tetravalent formulation**
 - More than one dose required
- **Vaccine delivery**
 - early childhood (EPI) – 2nd year of life
 - catch-up immunization
- **A crowded immunization schedule**

Dengue Vaccines











Types of Dengue Vaccine Candidates

- **Present Generation** (commercial development)
 - Cell culture adapted, live attenuated viruses
 - Infectious clones
 - chimeric viruses
 - attenuation by site directed mutagenesis
 - Recombinant subunits of DENV envelope proteins
- **Next Generation** (in development)
 - Inactivated dengue viruses
 - DNA
 - DNA shuffling
 - Viral vectored subunits

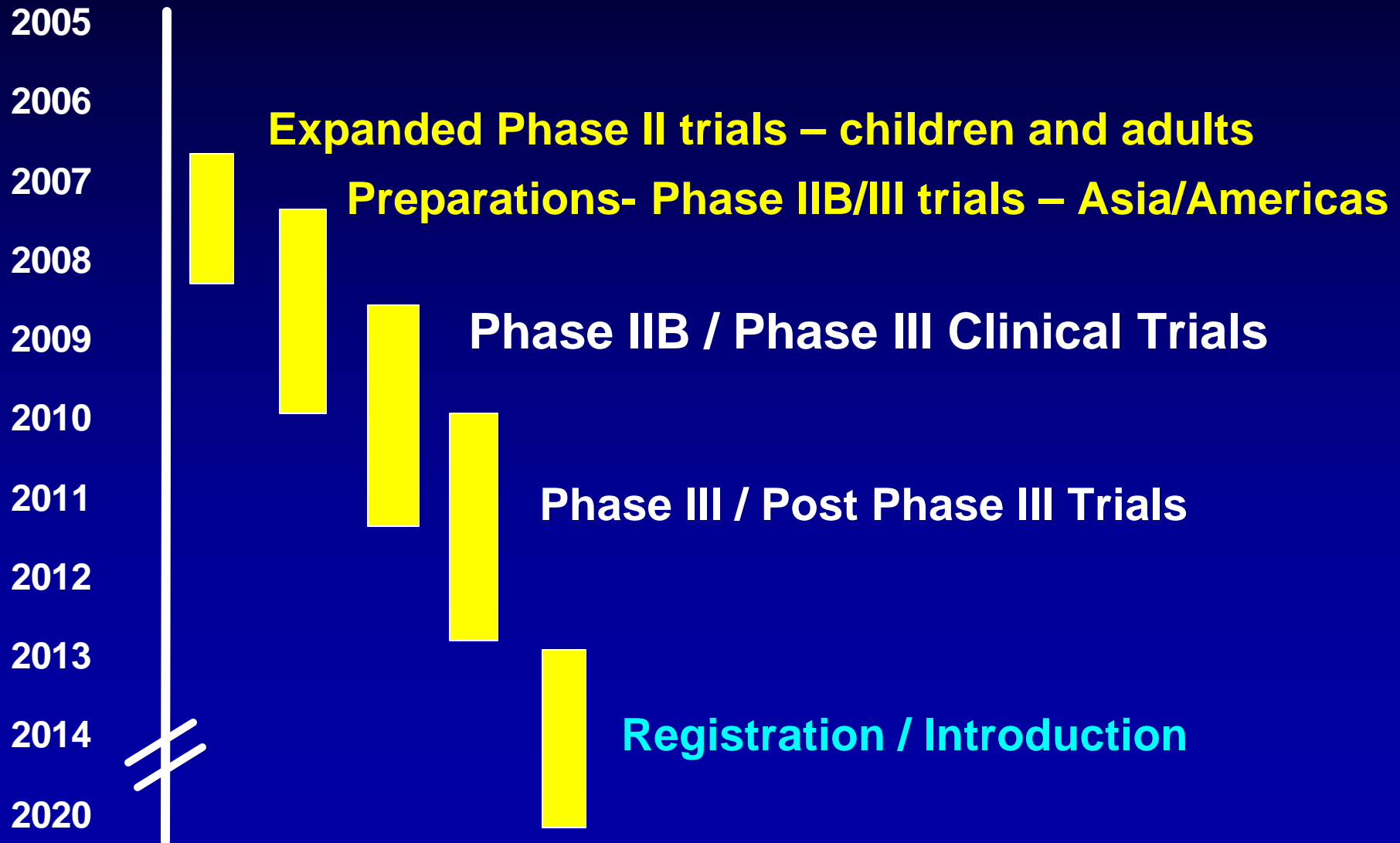
Dengue Vaccines in Commercial Development

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

Status of Dengue Vaccines

Developer	Producer	Process Development	Evaluation		
			Phase I	Phase II	Phase IIb
Acambis	SanofiPasteur				Late 2008
WRAIR	Glaxo SmithKline				2009
				? 2009 Tetravalent	
NIH	Biological E		? Early 2010		
	Butantan		? early 2010		
	Panacea		?		
CDC	InViragen / Shantha		Mid -2009		
Hawaii Biotech	Hawaii Biotech		Mid-2009		

Projected Dengue Vaccine Timeline Lead Candidates



Addressing the Challenges



The Pediatric Dengue Vaccine Initiative (PDVI)

- **Founded Dec 2001 - Ho Chi Minh City, Vietnam**
- **A product development partnership (PDP)**
- **Funding**
 - **2001-2006: Rockefeller Foundation**
 - **2003-2010: Bill and Melinda Gates Foundation**
- **Program of International Vaccine Institute (IVI)**

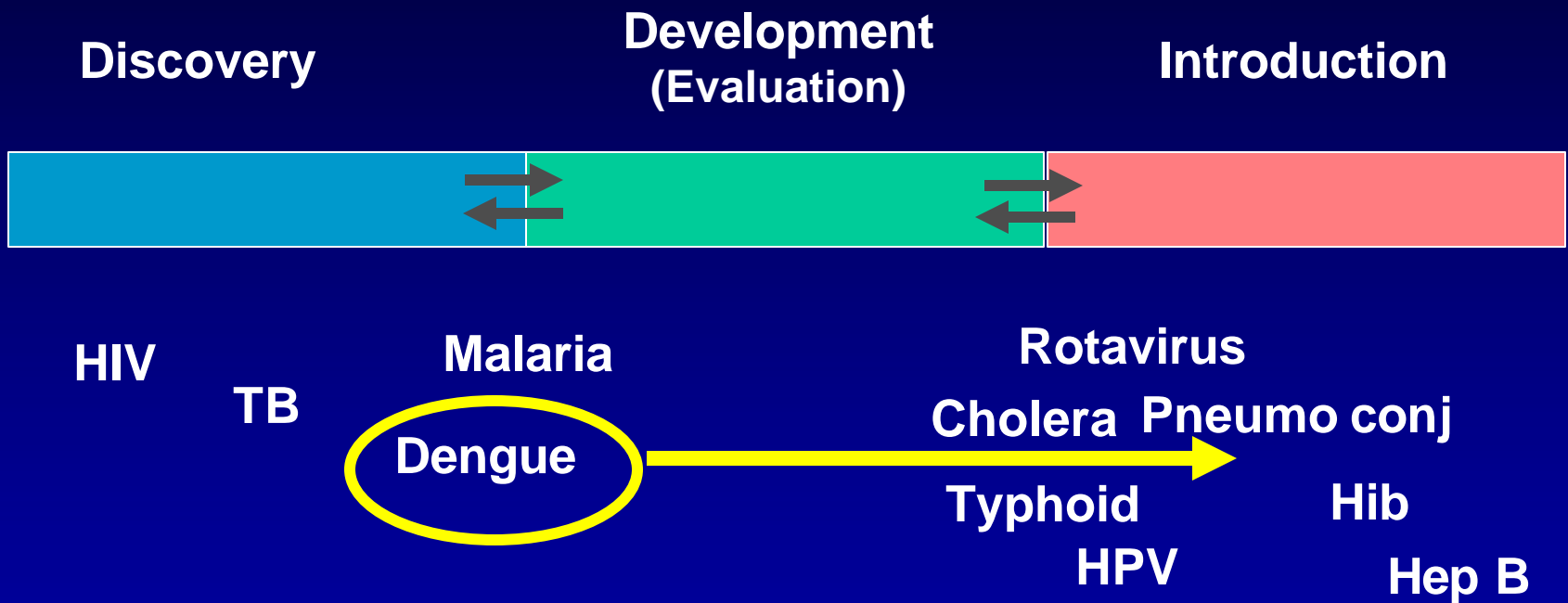


PDVI Goals

- To **accelerate** development, evaluation and introduction of dengue vaccines
- To make safe and effective dengue vaccines available to populations in dengue endemic countries to **reduce disease incidence**



Dengue in the Vaccine Pipeline

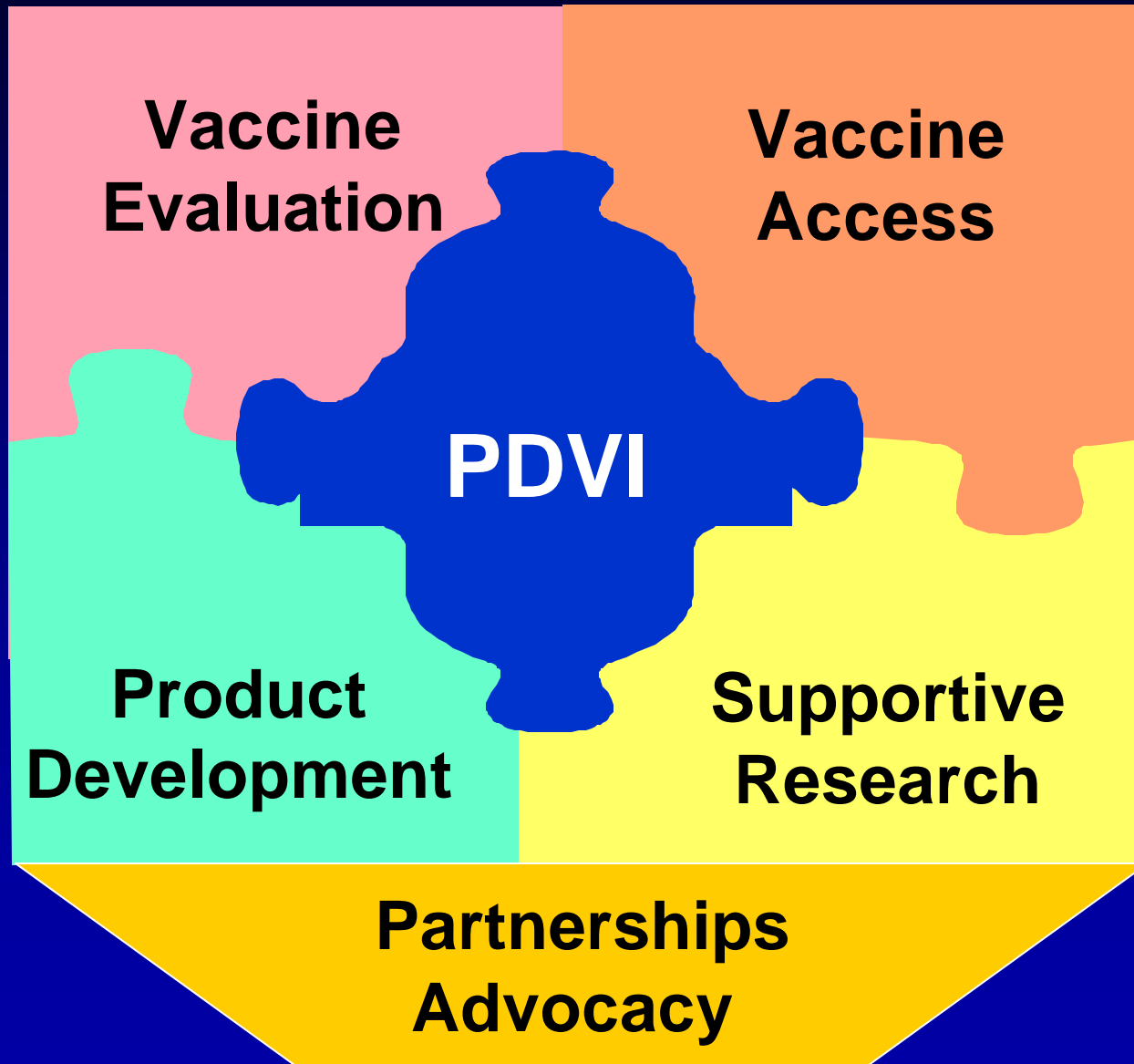


The PDVI Strategy

- To ensure introduction of safe and effective dengue vaccines in dengue endemic countries to lower disease incidence
- Need to address
 - Product development to achieve licensure
 - Public health issues to ensure timely introduction and appropriate use



PDVI Program Areas



Product Development

- **Support a portfolio of vaccines to ensure**
 - **licensure of several safe and effective vaccines**
 - **availability of multiple vaccines to ensure:**
 - **An affordable vaccine**
 - **Sustained and sufficient availability of product**



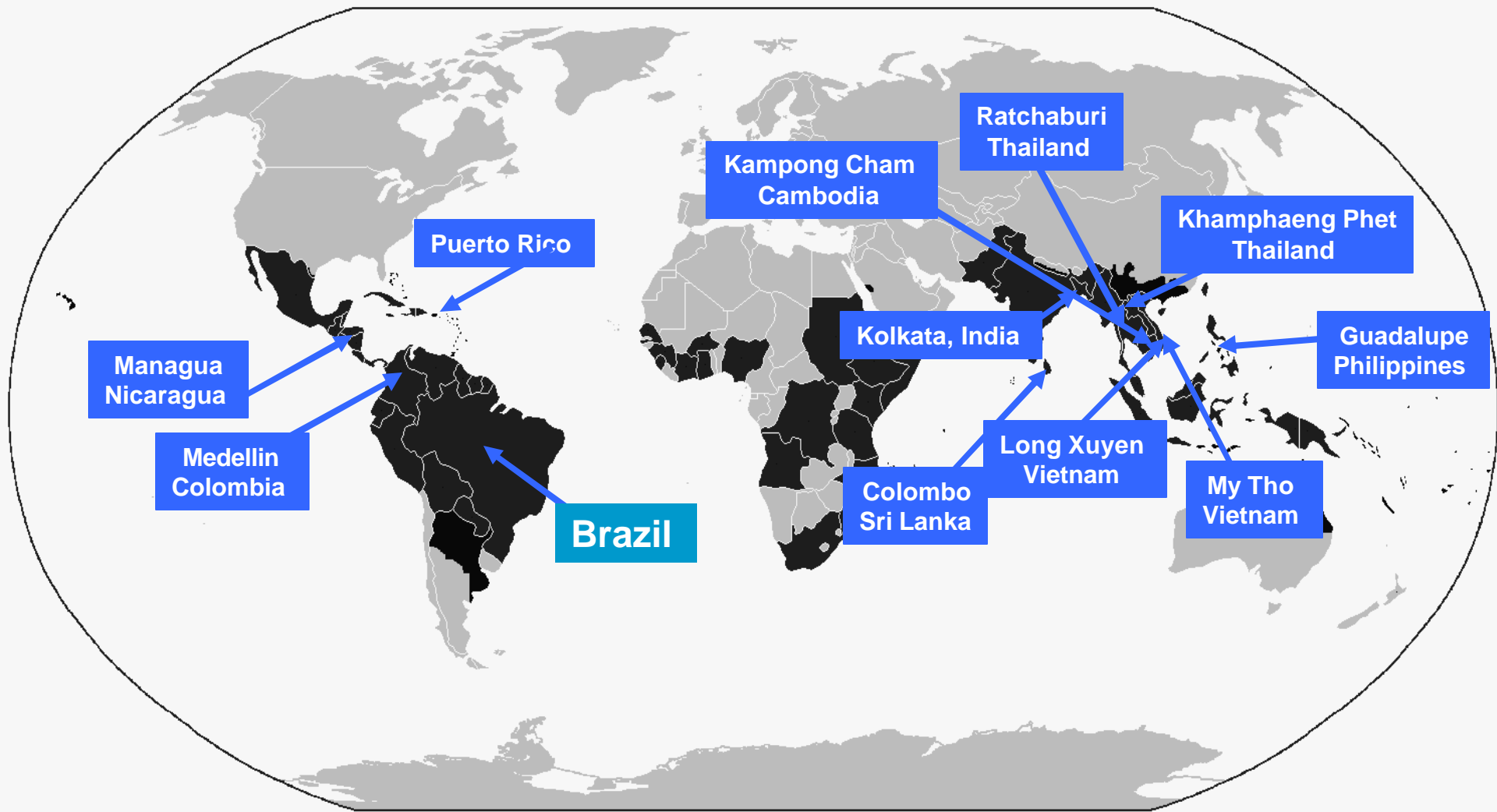
Vaccine Evaluation – Needs

- **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

- **Sites in both hemispheres**
- **Funded by multiple sources**
- **Core support activities – epidemiology, clinical trials preparation, laboratory proficiency**
- **Provides:**
 - **Reliable estimates of dengue disease incidence/ disease burden**
 - **State-of-the-art dengue diagnostics**
 - **Comparable case definitions**
 - **Clinical care for dengue disease**
 - **Platform to conduct studies of diagnostics, DENV outcomes, vaccines**

Field Site Consortium, 2008-2009



“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 \pm 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

Vaccine Access



Vaccine Access

- **Better information**
 - Improve epidemiologic and surveillance information
 - Determine costs of dengue and vector control
 - Conduct comparative economic studies
 - Estimate burden of illness and effects of vaccination strategies
- **Prepare for vaccine introduction**
 - Advocacy - regional networks of experts (“dengue prevention boards”)
 - Strengthen Regulatory Pathways – DCVRN
 - Mechanisms to sustain vaccine access

Vaccine Access

- **Working with Developing Country Vaccine Regulatory Network (DCVRN)**
 - Educational meeting and statement on dengue vaccines - May 2007
 - DCVRN and manufacturers meeting – Nov 2007
 - Country-level consultations to review clinical trial protocols – 2008
 - Development of product registration guidelines – 2008 - 2009
- **Development of regional Dengue Prevention Boards**
 - actions to improve prevention and control of dengue as a vaccine preventable disease – surveillance, diagnosis, case management, vaccine action plan
- **Provisional Dengue Vaccine Investment Case – 2008**



Dengue Vaccination Strategies (Proposed)

Dengue Endemicity	Vaccination Strategies
Low	Travelers, overseas workers and military traveling to high endemic areas
High	Early childhood (probably 2 nd year of life) Catch-up (? What ages) Epidemic control



Dengue Diagnostics



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)**



Dengue Diagnostics Initiative

- **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



Thank You

