



Satellite Symposium on Japanese encephalitis and Dengue Vaccine

3 December 2006, GFVR

JE: key messages

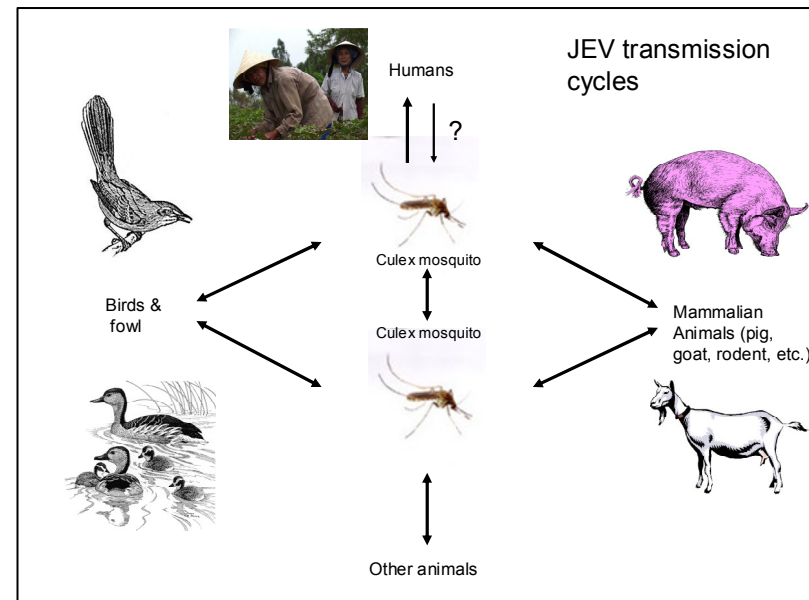
- Considerable public health concern in the regions, JE control need strong political will, disease of the poor;
- JE transmission is complex and disease burden not fully established, strong variability;
- New vaccines progressively replacing MB vaccine (and advanced candidates in the pipeline);
- Country-driven vaccine introduction, highly successful campaigns in India;
- Integration into routine immunization to be mastered;
- Open research agenda on flavivirus interaction;
- Vaccine prequalification remains an objective.



JE epidemiology (1)

By Dr Zhi-Yi-Xu
IVI, Seoul

- JE is a mosquito-borne viral disease (culex); vector propagation closely linked to agricultural practice and climate; strong seasonality
- Pigs are key amplifying hosts, humans dead end; transmission cycles are complex involving mosquitoes and different species of intermediate hosts

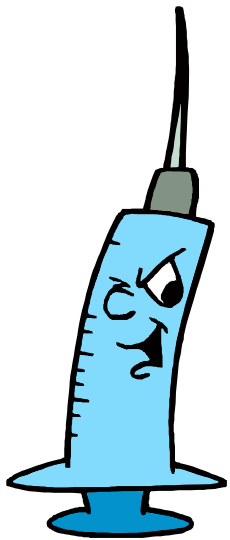


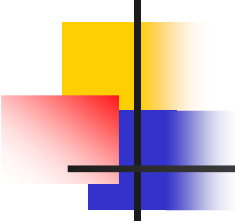
- Traditionally, JE considered the disease of temperate & subtropical climates
- Alleged low risk of JE in tropical climates may be due to insufficient surveillance and the absence of seasonality

JE epidemiology (2)



- Secondary cases appear very rare – limited use of emergency vaccination campaigns
- Vector-control has proven ineffective or only of short-term impact
- In contrast, experience with JE vaccine (mostly MB) shows profound reduction of acute encephalitis cases
- Cost-effectiveness of JE vaccination has been demonstrated in even low-incidence regions, cost-saving possible
- Co-circulating flavivirus immunity should be considered when introducing vaccine





Measuring JE associated morbidity

By Dr Tom Solomon
Liverpool, UK

- JE disease is characterised by high mortality and high frequency of neurological sequelae
- Uniform tool to improve patient management and measurement of morbidity
- Score system "Liverpool score" to be used by non-specialists
- Predict dependency reliably, high sensitivity, specificity and consistency
- Further research needed for discrimination between JE and other neurological sequelae



LA JE vaccine SA 14-14-2: key facts and new data (1)

- Extensive experience from vaccine utilization since 1988
- Neuro-attenuation well established; corroborated by new toxicity data from India
- Effectiveness data from Nepal (case-control) suggest at least 5 year protection after single dose administration – persisting titres
- New data on vaccine co-administration (JE/measles) show no interference in relation to safety and immunogenicity

By Mansour Yaich

PATH



LA JE vaccine SA 14-14-2: key facts and new data (2)

- PMS data from Korea and new data from India suggest excellent safety, low reactogenicity
- Additional studies planned on co-administration and immunization against flavivirus immunity, vireamia
- Target product profile of single dose vaccine, to be co-administered with measles first dose.
- Highly competitive public sector price
- Await product prequalification

JE vaccination in India (1)

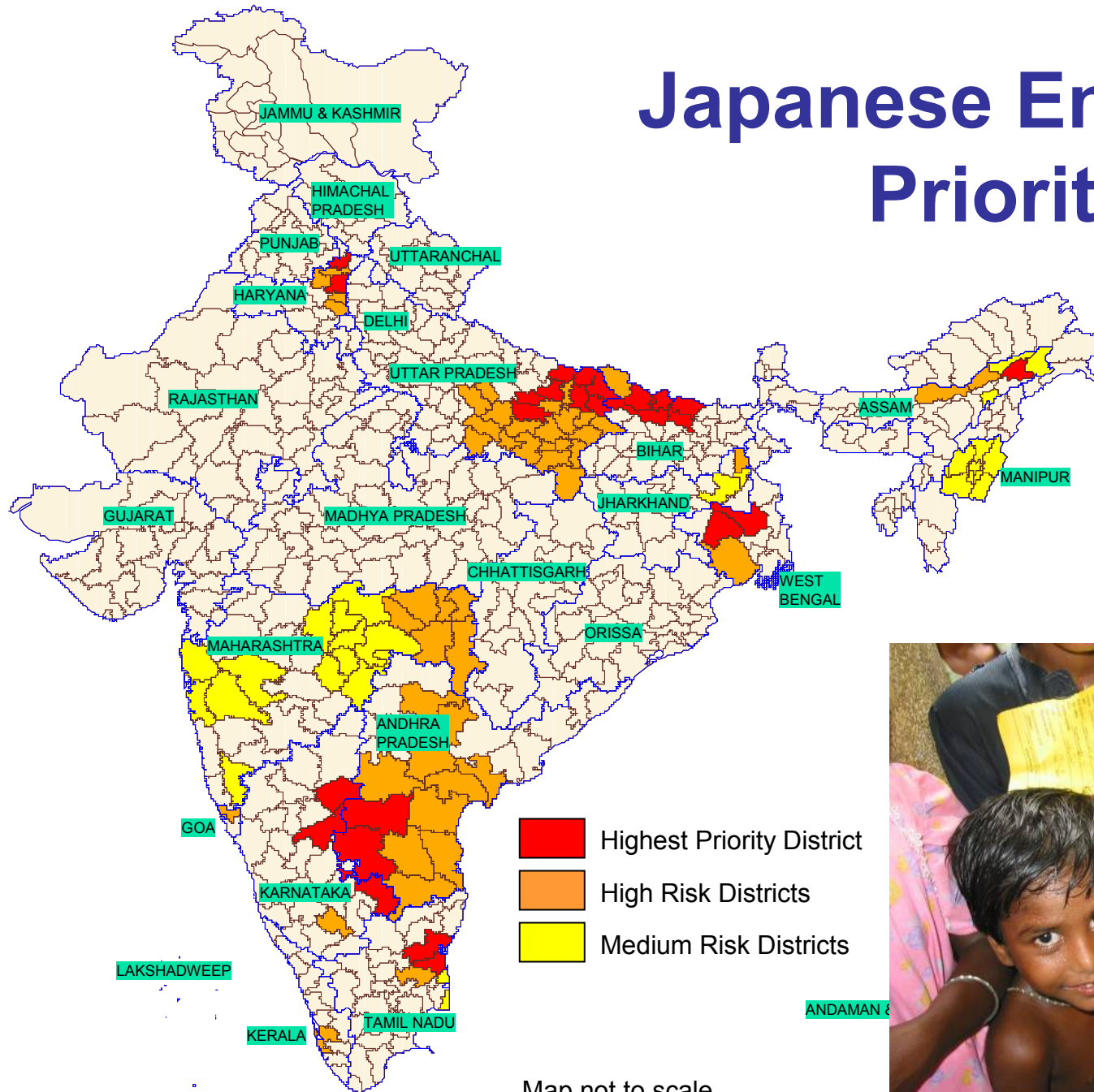
By Julie Jacobson

PATH

- Previously limited JE vaccination in certain States/district, using local MB vaccine
- Authorities response to JE epidemics in 2005, strong political will to expand immunization
- New vaccine needed at large volume and competitive price: special license for SA 14-14-2
- Starting in May 2006, India vaccinated 9.3 million children age 1-15y in 11 districts scattered in 4 states where JE is highly endemic
- The experience and the infrastructure of polio eradication in India clearly contributed to the success of the JE vaccine mass campaigns



Japanese Encephalitis Priority Districts



Map not to scale





JE vaccination in India (2)

■ **Safety:**

- Over 504 AE cases reported, 65 SAE, 22 deaths
- Central investigation of SAE's using hospital records concluded that none was associated with vaccine
- Campaign will continue in 2007 and routine immunization introduced thereafter

■ **Key lessons & challenges:**

- Risk communication to be managed nationally and internationally, have data at hand
- Exceptional coverage through campaigns, now translate to routine immunization
- Improve syndromic surveillance and case investigation/confirmation in areas where vaccine has been introduced



Interplay between JE vaccination and dengue?

By Sutee Yoksan
CVD, Mahidol

- Questions: does pre-existing immunity to flaviviruses interfere with vaccine induced protection? Does vaccine immunity interfere with other flavivirus disease?
 - **PRNT studies do not suggest DEN cross-reactivity following JE immunization (in contrast to observational studies)**
 - **No boosting of DEN titres following JE immunization**
 - **Specificity of JE titres broadens with time**
- More research needed to corroborate findings



Dengue: key messages

- Major public health concern to the region, high cost of illness;
- Dengue immunology and pathophysiology remain a major research area;
- Nevertheless, vaccine pipeline is progressing well, and trials are being used to assess open research questions;
- Need for harmonization of methods and assays;
- Continued interest in discovery & preclinical research into new candidates;
- Major investments by countries and partners into preparing the ground for multicentric clinical trials.



Immunology and immunopathology (1)

By Prida Malasit
Siriraj, Mahidol

- **Some key questions:**
 - Mechanisms leading to severe disease not well understood
 - Predictors of severe disease outcome to be clarified
 - Uncertainty on disease classification (ongoing study)
 - Relationship between virus genotype and virulence poorly understood
 - Fine characterization of antibodies, in particular in relation to disease enhancement, not accomplished



Immunology and immunopathology (2)

- **Prospects for answers:**

- Predictors for severe disease being investigated (NS1 & complement)
- Human monoclonal technology should help to elucidate antibody specificities in relation to protection/enhancement
- Systematic analysis of CMI responses ongoing
- Genomics strategies to characterize early host responses to infection
- Renewed interest in dengue, increased research and linkage between clinics and laboratory research



Vaccine pipeline (1)

By Alan Barrett
Univ.Texas, USA

- **The challenges of developing a dengue vaccine:**
 - 4 viruses, tetravalent formulation difficult
 - No suitable animal model for disease
 - Incomplete understanding of immune correlates
 - Virulence factors poorly understood
 - Immune enhancement phenomena
 - Complex disease epidemiology



Vaccine pipeline (2)

- **The advances and opportunities**
 - Flaviviruses vaccines "work"
 - Much experience with live vaccines gained
 - Increasing confidence into safety of vaccines
 - A large pipeline with divergent vaccine technologies, new vaccine developers entering the field
 - Solid preparations for population-based trials in several countries

Vaccine candidates in Clinical Trials

Approach	Developer	DEN genes/antigens	Status
Live, attenuated, produced in PDK cells	Mahidol/Sanofi Pasteur	Entire genome	Phase 2 tetravalent (long-term follow up data up to 8 years)
Live attenuated, produced in Vero cells	Sanofi Pasteur	Entire genome	Phase 1
Live, attenuated, produced in FRhL cells	WRAIR/GSK Biologicals	Entire genome	Phase 2b tetravalent
Live, rationally attenuated with 3' deletion mutation	US NIAID & Johns Hopkins Univ. (Partners: Biological E & Butantan)	Entire genome	Phase 1-2 monovalent
Live, 3' deletion mutation, DEN/DEN chimeric	US NIAID & Johns Hopkins Univ. (Partners: Biological E & Butantan)	8 DEN4 + 2 chimeric	Phase 1-2 monovalent
DNA vaccine	US Navy/WRAIR	2 (prM/E)	Phase 1 monovalent
Live, attenuated YF17D vector, YF/DEN chimeric	Acambis/Sanofi Pasteur	8 YF genes + 2 chimeric DEN genes (prM/E)	Phase 2b tetravalent

Discovery research for new dengue vaccines in Thailand (1)



- Strong collaborative networks between Chiangmai Univ. and different academic centres including the Mahidol centre for Vaccine Development (CVD)
- Competitive international funding
- Hypothesis: mutations of the polyprotein cleavage sites may yield viral mutants with diverse phenotypes, some of which may be suitable to be used as vaccine candidates
- Several candidates at preclinical stage at CVD

By N. Sittisombut
Chiangmai Univ.



Discovery research for new dengue vaccines in Thailand (2)

- **On-going work:**
 - Generation and screening of mutants of the NS1-NS2A and NS2B-NS3 junctions
 - Generation of prME chimeric viruses with prME coding sequences from recent DENV 1-4
 - Testing an influence of the prE203A mutation on the immunogenicity in mice

PDVI: Establishing dengue field sites

By Hal Margolis, PDVI, IVI, Seoul

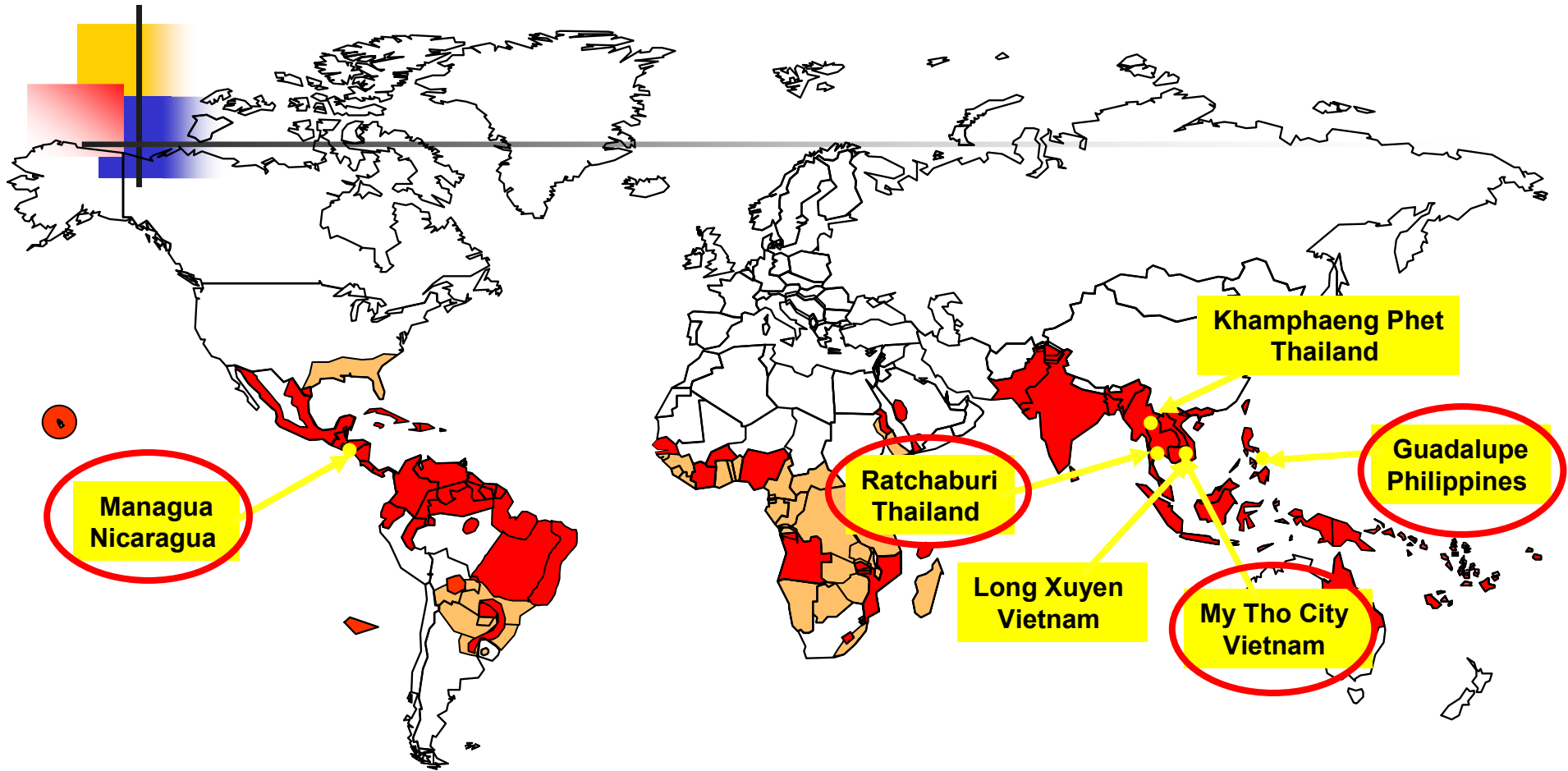
Programs

- **Epidemiologic studies**
 - natural history of dengue virus infection
 - risk factors for severe consequences of infection
- **Laboratory studies**
 - evaluation of new assays for protective immunity and ADE
 - evaluation of diagnostic tests for acute den. virus infection
- **Other population-based studies**
 - economic

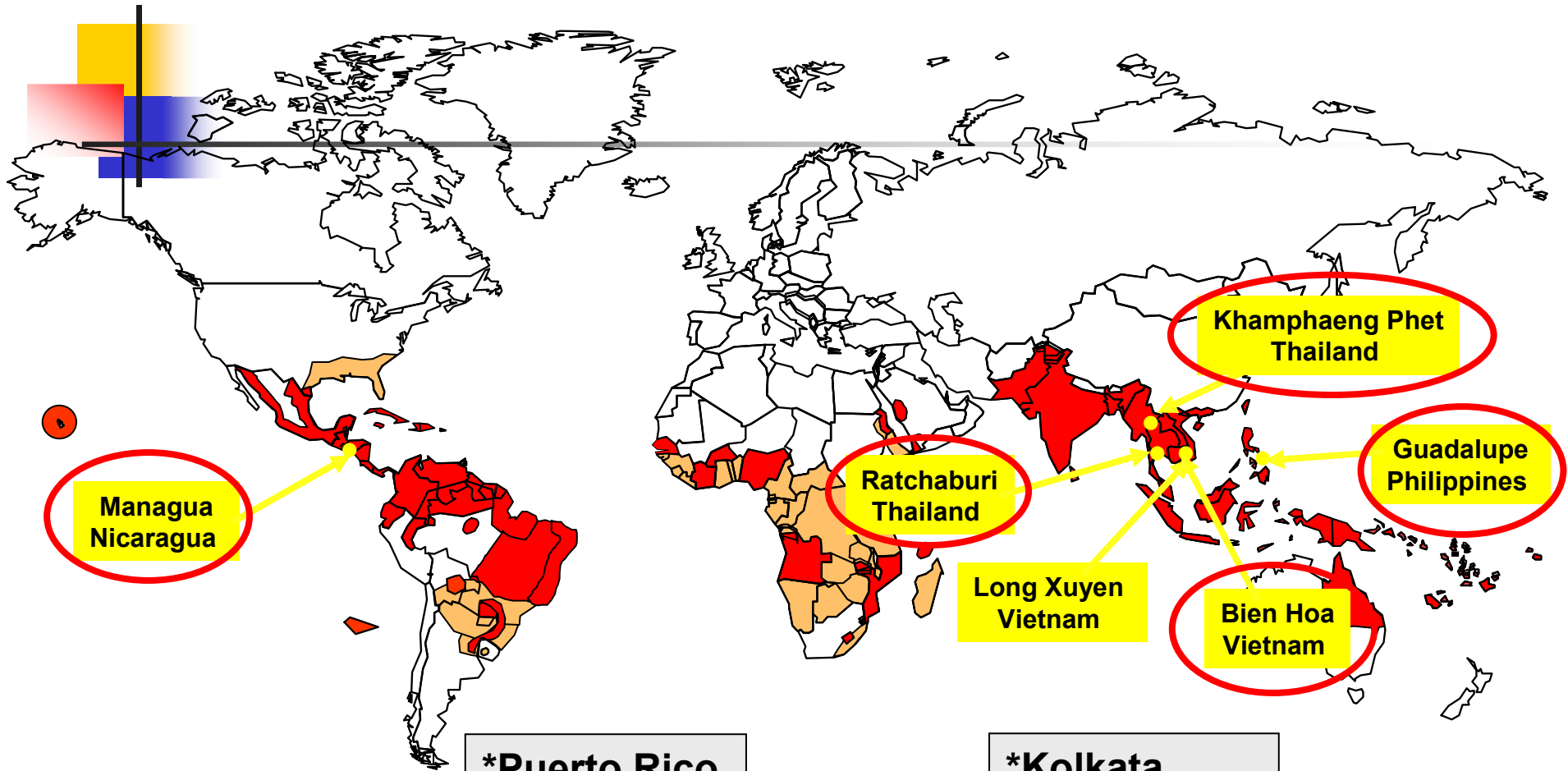
strategic emphasis:

- Strategic partnerships
- Supportive R&D
- Vaccine evaluation - build capacity for large-scale trials
- Vaccine access

Field Site Consortium, 2006



Field Site Consortium, 2007



Dengue Research Platform at Mahidol

By Dr Arunee Subcharoen, TropMed, Mahidol

- Established at Fac.Trop Med, since 1998
- Mission: To conduct research that lead to effective dengue control in Thailand, in collaboration with MOPH and other partners
- Conducted clinical evaluation of Mahidol-Aventis tetravalent live attenuated dengue vaccine in adults and children during 1998 - 1999, with long-term follow-up till 2006.
- Developing a population cohort for efficacy trial of dengue vaccine in Ratchaburi Province; partnering with MOPH, AFRIMS, CVD; with support of PDVI, Sanofi Pasteur; currently establishing epidemiologic baseline of dengue infection