

## About the Collaborators

Many people supported the work described in this book. Children, parents, teachers, principals, community health workers, community leaders, provincial leaders, public health officials, hospital directors, doctors, nurses, laboratory technicians, scientists, statisticians, data entry personnel, drivers, Thai national public health leaders, Thai political leaders, US military leaders, laboratory commanders, research and development managers, and many others contributed to these efforts.

All of the collaborators are delighted that their work may have contributed to the betterment of health of large numbers of citizens of Thailand and the United States.

## 30 Years of Thai US Collaboration

30 Years of Thai US Collaboration



## 30 Years of Thai US Collaboration

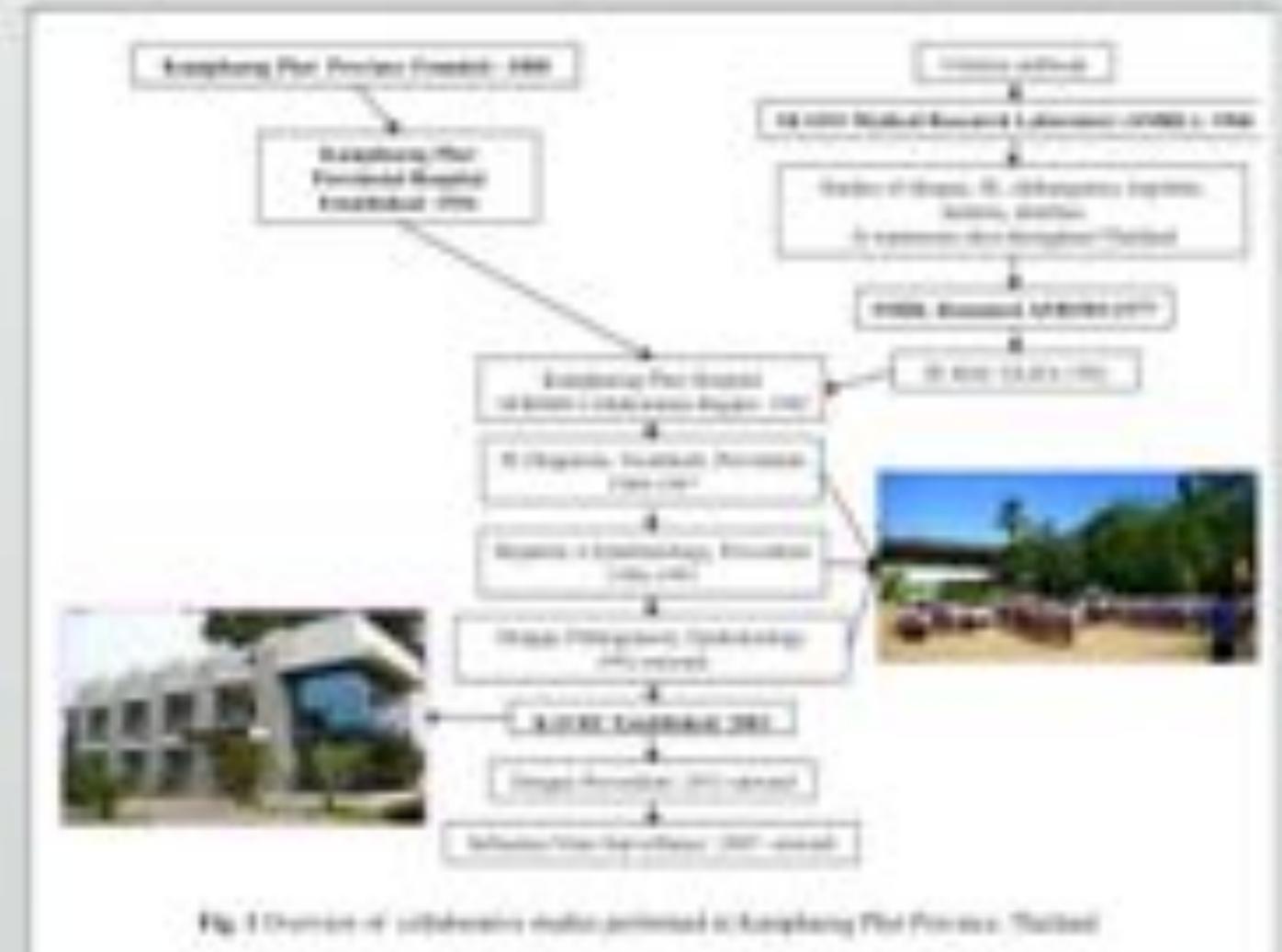
Charles H. Hoke, Jr., MD

## About this book

This book is based on a presentation made at the 17th annual meeting on vaccine research hosted by the National Foundation for Infectious Diseases. The presentation was based in turn on a paper published in the journal, Vaccine. This paper described a long and fruitful collaboration between Thai and US Army investigators that allowed them to study diseases of common interest, evaluate diagnostic and preventive strategies, and apply the results to improve the health of both Thai and US citizens. Each of the contributors either served at the Armed Forces Research Institute of Medical Sciences (AFRIMS), the Kamphaeng Phet Provincial Hospital or at the KPP Army Virology Research Unit (KAVRU).

# 30 Years of Thai US Collaboration

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Charles H. Hoke, Jr., MD

Abstract Submitted to the 17 Annual Conference on Vaccine Research, April 30, 2014

**A Model International Partnership for Community-Based Research on Vaccine-Preventable Diseases: The Kamphaeng Phet-AFRIMS Virology Research Unit (KAVRU).**

R.V. Gibbons, A. Nisalak, I. Yoon, D. Tannitisupawong, K. Rungsimunpaiboon, D. W. Vaughn, T. Endy, B. Innis, D.S. Burke, M. Mammen, Jr, R. McNair Scott, S. Thomas, and C. H. Hoke, Jr (presenter).

**Background:** An international collaboration was formed to carry out studies that contributed to the understanding of pathogenesis, diagnosis, treatment, and prevention of several febrile syndromes, including encephalitis, hepatitis, hemorrhagic fever, and influenza-like illnesses.

**Methods:** Since 1982, the Kamphaeng Phet Provincial Hospital, the Thai Ministry of Public Health, and the US Army Component of the Armed Forces Research Institute of Medical Sciences, along with vaccine manufacturers and universities, collaborated on studies that evaluated and capitalized on improved diagnostic capabilities and preventive strategies for infections caused by Japanese encephalitis, hepatitis A, dengue, and influenza viruses.

**Results:** The collaboration clarified clinical and epidemiological features of these infections and, in large clinical trials, demonstrated that vaccines against Japanese encephalitis and hepatitis A viruses were over 90% efficacious, supporting licensure of both vaccines. With the introduction of Japanese encephalitis vaccines in Thailand's Expanded Program on Immunization, reported encephalitis rates dropped substantially. Similarly, in the US, particularly in the military populations, rates of hepatitis A disease have dropped with the use of hepatitis A vaccine. Studies of the pathogenesis and epidemiology of dengue infections set the stage for studies of dengue vaccines. Approximately 80 publications resulted from this collaboration, and experience gained contributed to clinical trials of hepatitis E and HIV vaccines, conducted elsewhere. To support continuing studies, The Kamphaeng Phet-AFRIMS Virology Research Unit (KAVRU) was established.

**Conclusions:** Collaborations established to answer specific questions may expand over time to move from identification of general syndromes to demonstration of specific etiology, to population-based epidemiological studies, evaluation of interventions, particularly vaccines, and finally to implementation of control strategies. Substantial dividends may be gained in terms of knowledge gained and disease prevented.

# Overview

This is the story of a 30 year Thai-US collaboration that resulted in improved diagnostic tests, regulatory approval of two vaccines in two countries, reductions in disease incidence, many published studies, and a new laboratory for future studies.

Opinions are those of the authors.

Dr. Innis and Dr. Vaughn currently work for GSK. They worked for the US Army when this work was done.

# A model international partnership for community-based research on vaccine-preventable diseases: The Kamphaeng Phet-AFRIMS Virology Research Unit (KAVRU)

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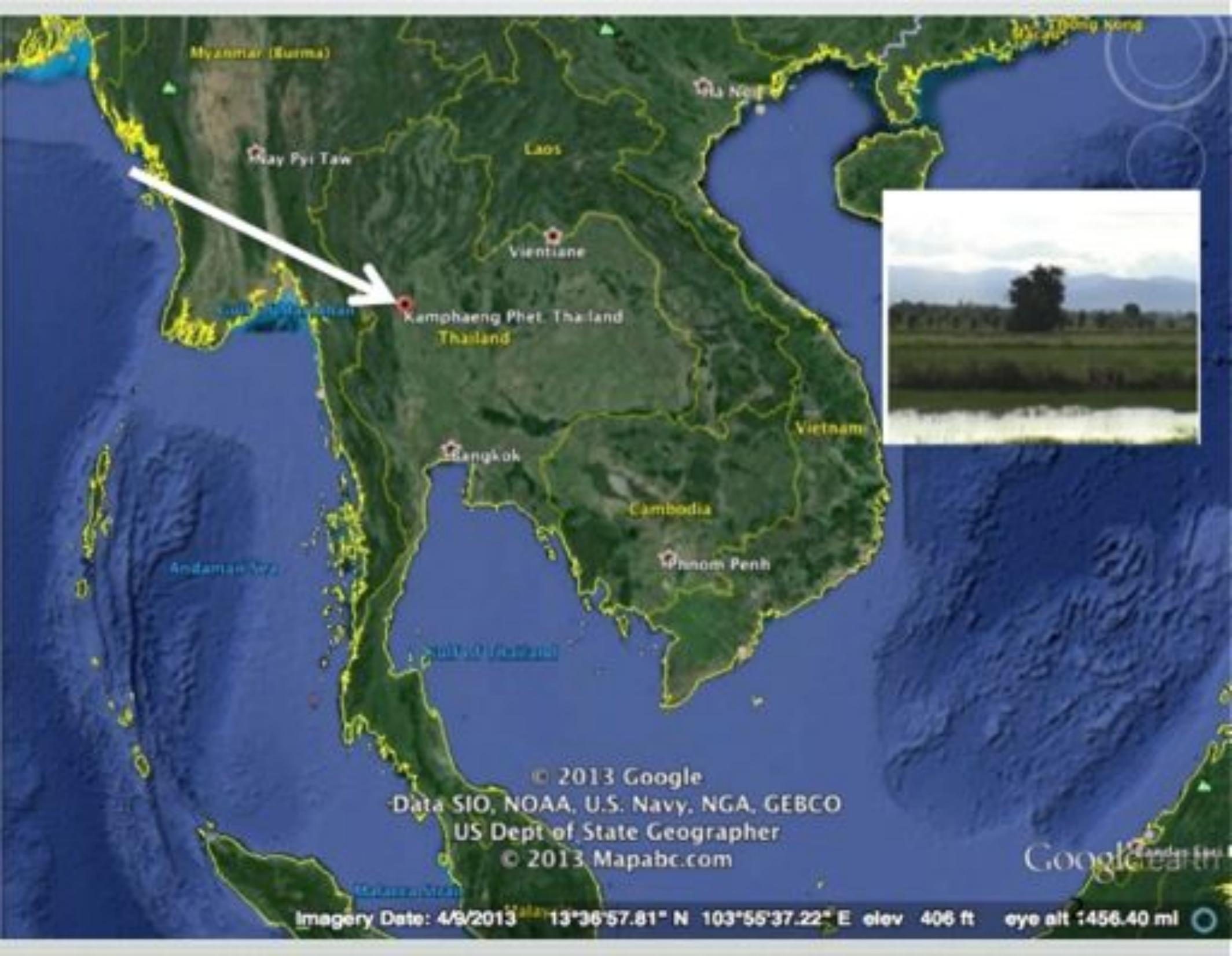
National  
Foundation for  
Infectious  
Diseases

Opinions expressed in this presentation are solely those of the authors.

\* Dr. Innis and Dr. Vaughn are employees of Glaxosmithkline.

# Location

The collaboration took place in Kamphaeng Phet Province in north central Thailand, a province with extensive rice agriculture, conducive to transmission of Japanese encephalitis, and about 700,000 people.



Myanmar (Burma)

May Pyi Taw

Laos

Vientiane

Kamphaeng Phet, Thailand  
Thailand

Bangkok

Cambodia

Phnom Penh

Vietnam

Andaman Sea

Gulf of Thailand

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Data SIO, NOAA, U.S. Navy, NGA, GEBCO

US Dept of State Geographer

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Google Earth

Imagery Date: 4/9/2013 13°36'57.81" N 103°55'37.22" E elev 406 ft eye alt 1456.40 mi

# Organizations, Missions, Goals

Three organizations with different missions found common interests as the basis of this collaboration. The Kamphaeng Phet Provincial Hospital has a mission to provide care to the people of the province. The Ministry of Public Health (MOPH) of Thailand has a mission to protect the health of Thai people. The Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, a part of the Walter Reed Army Institute of Research, has a mission to find ways to keep US Forces healthy. Populations served by all three organizations had been affected by encephalitis, hepatitis, hemorrhagic fever, and influenza like illness, illustrating that immunologically naïve US military personnel may be at risk of the same conditions that affect children and providing a basis for a productive collaboration.

AFRIMS mission:  
Protect US Forces

MOPH Mission:  
Protect Thai People



- Encephalitis
- Hepatitis
- Hemorrhagic Fever

Kamphaeng Provincial Hospital Mission:  
Provide Diagnosis and Care/Prevent Disease

# Japanese Encephalitis

The collaboration began in 1982, and it's important to realize the state of JE control at that time.

- JE virus had been identified as the cause of seasonal encephalitis in Asia.
  - In WWII, a JE vaccine had been made by Albert Sabin and used in US forces.
  - After WWII, JE vaccine was used in Japan with reduced numbers of cases.
  - Diagnosis of JE was based on the hemagglutination inhibition test.
  - Thai disease surveillance showed that sharp annual outbreaks of encephalitis occurred in certain provinces.
  - Leaders of the Thai CDC and NIH were hopeful that use of the vaccine might benefit Thai children, but data supporting vaccine efficacy outside of Japan was lacking, so JE vaccine had not been adopted for use in Thailand.
- In addition in the US, Public Health authorities had been criticized for not making JE vaccine available for travelers, and they were receptive to receiving a Biologics License Application from an appropriate manufacturer.
- At this point, to paraphrase the NEJM CPCs, “a diagnostic test was received”. Drs Burke, Nisalak and Ussery at AFRIMS had invented a new test for for diagnosis of Japanese encephalitis that would revolutionize JE control efforts.

# Control of Japanese Encephalitis 1982 Status

- JE Virus causes summer encephalitis '30s
- WWII: JE Vaccine used in US Forces
- JE vaccine reduced incidence in Japan '50s
- Dr. Halstead had identified JE in Northern Thailand
  - Ecological studies done in northern Thailand '60s
  - JE antibody detected by hemagglutination inhibition
- Thai MOPH surveillance documents provinces with encephalitis
- JE Vaccine efficacy in Thailand uncertain
- US PHS criticized for not making JE vaccine available.
  
- In 1986, a diagnostic test was received!

# A New Diagnostic Test

The new test was an IgM antibody capture ELISA. Anti IgM antibody captured IgM in the specimen. JE virus is added and, if anti-JE IgM is present, virus binds and is detected by an enzyme labeled anti-JE monoclonal antibody. A site was needed to validate the assay, but few encephalitis cases occurred in Bangkok.

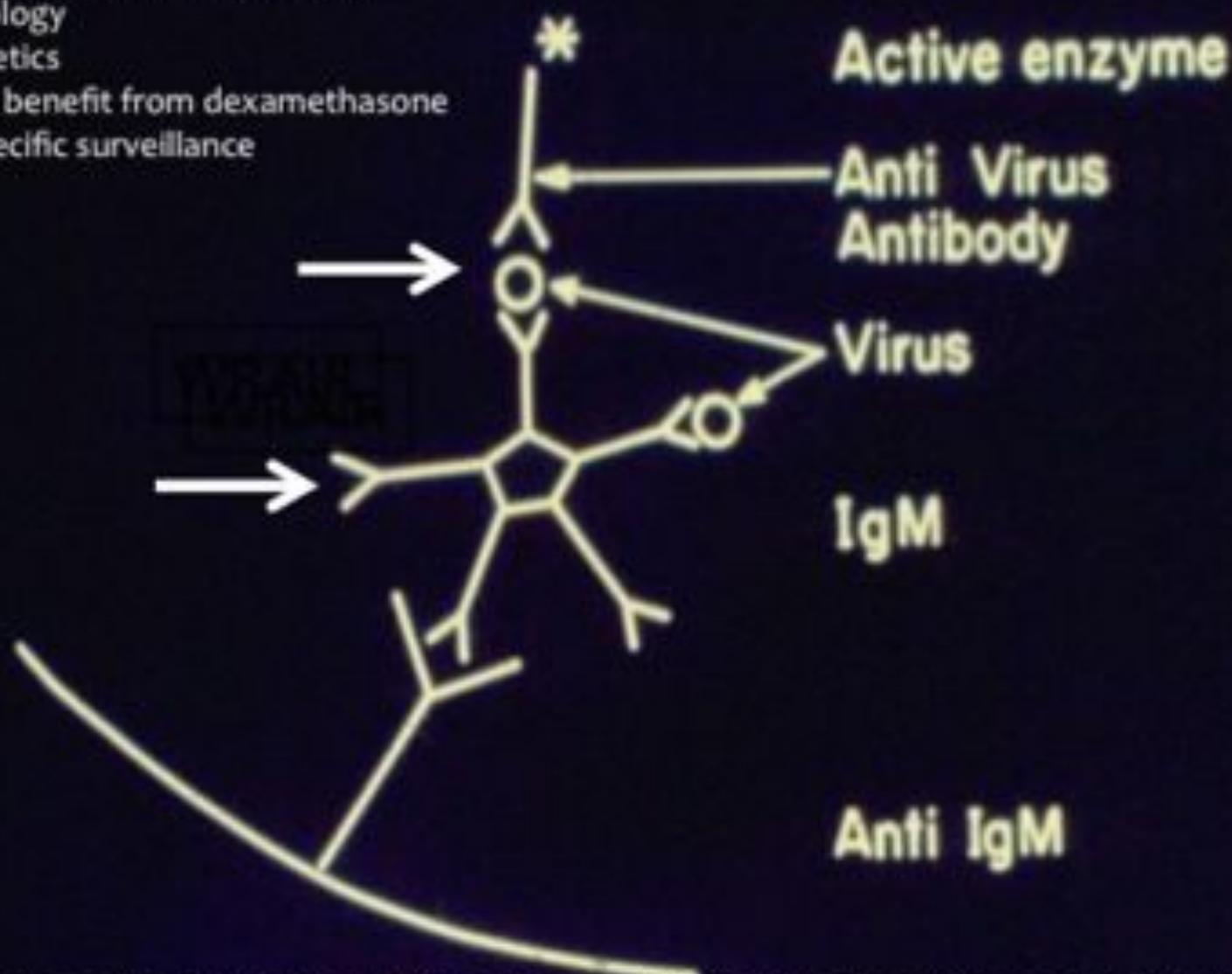
The Kamphaeng Phet Provincial Hospital admitted many children with encephalitis each summer, and the hospital director invited the AFRIMS team to evaluate their test.

The JEMAC ELISA test allowed observations on etiology, time course of antibody appearance, lack of benefit of dexamethasone and improved surveillance by testing of many specimens at once.

# JE IgM Capture ELISA

Test allowed determination of:

- Etiology
- Kinetics
- No benefit from dexamethasone
- Specific surveillance



Burke et al J Clin Microbiol. 1982;15:353-61 and 16:1034-42.

# Anatomy of an Idea

With this new tool for surveillance, the idea of conducting a vaccine efficacy trial emerged. The test vaccine would be the BIKEN mouse brain-derived inactivated Japanese encephalitis vaccine used in Japan.

Discussions with Thai MOPH leadership, the vaccine manufacturer, leaders of KPP hospital, and the US Army indicated their support for such a trial. Protocols were approved by Thai and US Army IRBs. Thai physicians in the CDC sponsored Field Epidemiology Training Program led immunization teams. With parental consent, about 60,000 children were enrolled. Two doses a week apart were administered. JE cases were defined as those individuals with fever, depressed mental status, and a positive JE MAC ELISA in serum or CSF.

The attack rate in JE vaccine recipients was 5/100,000, and in control recipients, 50/100,000, for an efficacy of 91%.

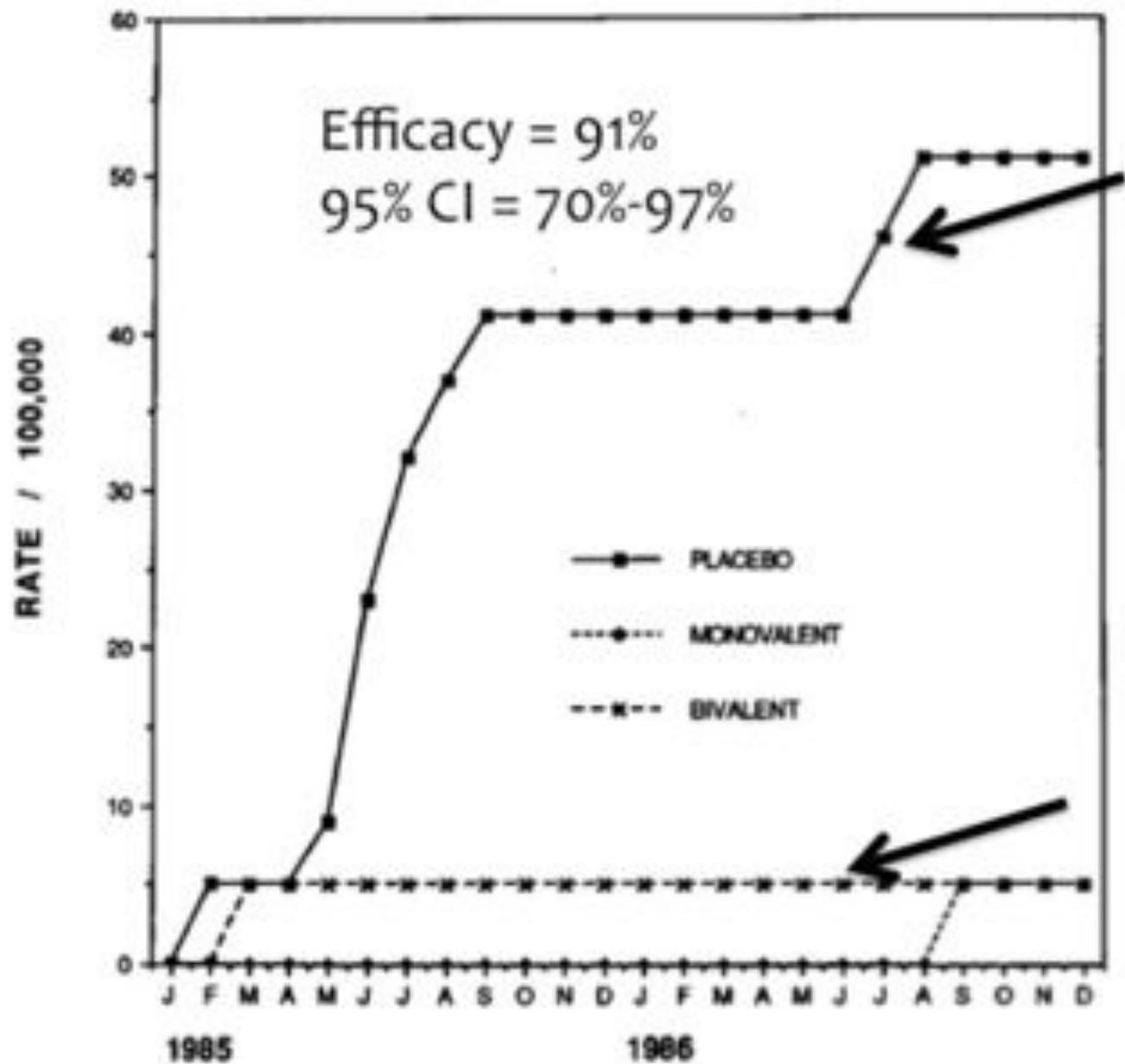


Figure 3. Cumulative Attack Rate for Encephalitis Due to Japanese Encephalitis Virus.

# Joint Publication

Representatives of the Provincial Hospital, the Thai Ministry of Public Health, the manufacturer, and the US Army jointly published the results of this trial in the New England Journal of Medicine.

**PROTECTION AGAINST JAPANESE ENCEPHALITIS BY INACTIVATED VACCINES**

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Ministry of Public Health Of Thailand  
Manufacturer  
AFRIMS and WRAIR

## Results Applied in Thailand

The efficacy trial led to palpable results in Thailand. The Thai Ministry of Public Health concluded that JE vaccine would be cost effective. Vaccine was introduced to the Extended Program on Immunizations in increasing numbers of provinces, and the numbers of cases of JE fell.

# Thai MOPH introduces JE vaccine with support of Japanese manufacturer: Cases decrease

Siraprapasiri T, et al. Cost benefit analysis of Japanese encephalitis vaccination program in Thailand. Southeast Asian J Trop Med Public Health. 1997;28:143-8.

Following US Army studies, the Japanese company built a plant, and the Thai government began using the vaccine to immunize children, with a great reduction in the number of cases.

JE Cases

US Army Field Trial

EPI-based

Number of provinces

Catch-up

Vector control and personal protection

Outbreak response and social mobilization

JE vaccine phased into routine immunization

1970

1980

1990

1997

2000

Year

## Results Applied in the US

In the US as well, important results followed the vaccine efficacy trial: Dr. Walt Brandt of the Army organized a meeting at the USFDA. The Japanese manufacturer teamed with a company with vaccine marketing experience in the US. Attendees discussed requirements for submission of a Biologics License Application.

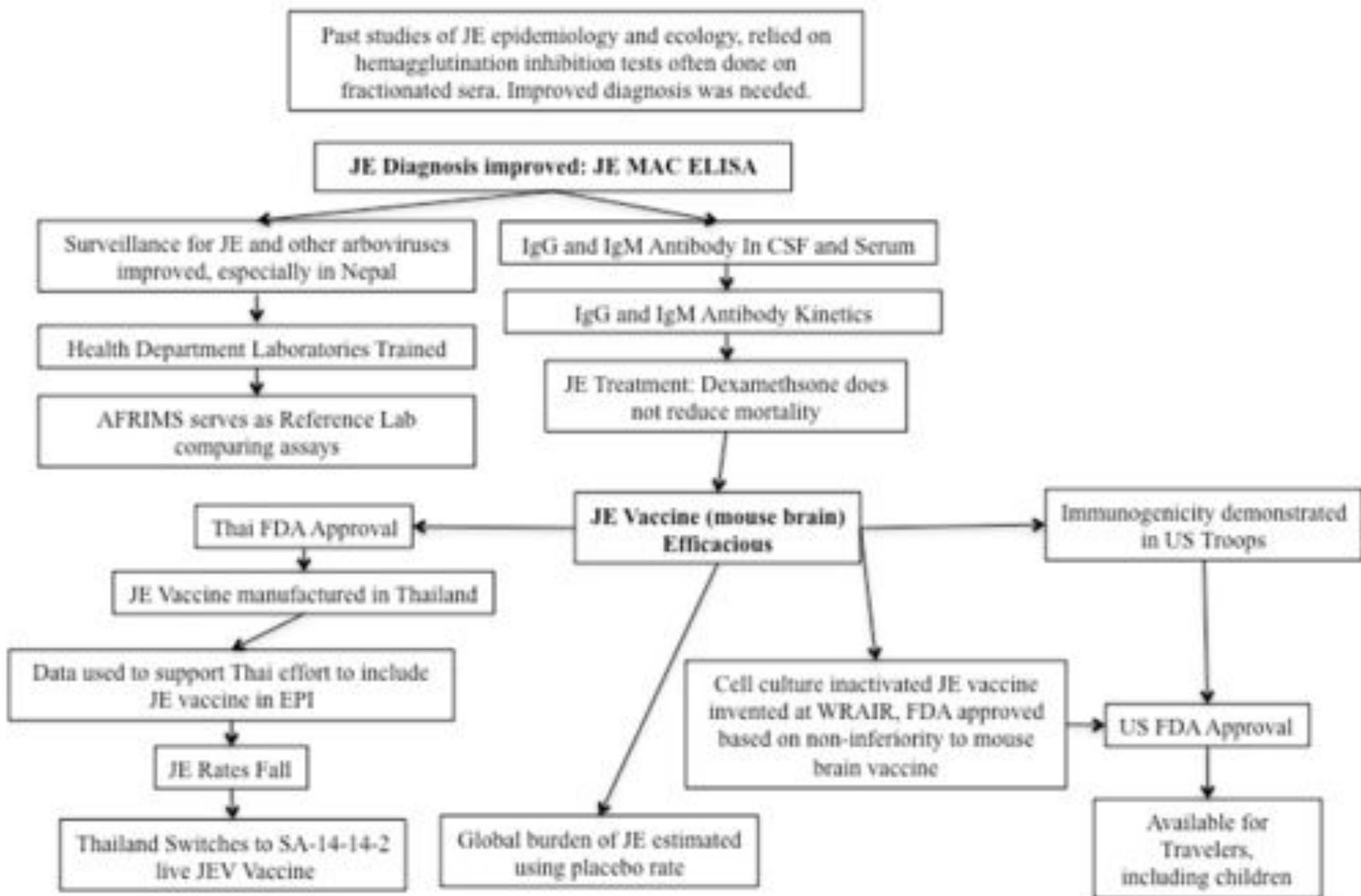
The FDA requested a further safety and immunogenicity study determining neutralizing antibody at three labs. MAJ Robert DeFraités conducted the study in US troops in Hawaii, The vaccine proved to be 100% immunogenic and safe. The company submitted a BLA, and the FDA approved the application, making the vaccine available for US travelers to Asia. And the JE MAC ELISA technology was adapted by many labs for diagnosis of JE and other forms of viral encephalitis.

## Benefits of Collaborative JE Studies in the US

- Army organized FDA meeting with manufacturer to review efficacy data.
- FDA requested safety and Immunogenicity study in US Military Personnel
  - Defraites RF, et al. Japanese encephalitis vaccine (inactivated, BIKEN) in U.S. soldiers: immunogenicity and safety of vaccine administered in two dosing regimens. *Am J Trop Med Hyg.* 1999;61:288-93.)
- BLA Filed
- US FDA approves BLA of BIKEN JE Vaccine
  - Vaccine available for immunization of travelers
- JE MAC ELISA adopted for diagnosis

## One Study Leads to Another

The chart shows how the JE MAC ELISA test improved surveillance, revealing JE in Nepal and, as laboratory personnel around Asia were trained, other countries. The test allowed the time course of IgG and IgM antibody formation to be charted and allowed studies of the treatment of JE. In particular, dexamethasone treatment was shown not to increase survival. The efficacy of the BIKEN vaccine could be determined and, eventually, become licensed in the US and Thailand. Later, a vaccine using attenuated SA-14-14-2 JE virus, produced in cell culture (instead of mouse brain) and inactivated with formalin would be invented by a team working at WRAIR, patented, and licensed to a manufacturer for distribution in the United States.



**Fig. 2** Japanese encephalitis studies performed in Kamphaeng Phet Province by Thai Ministry of Public Health and US Army and the impact of those studies on Japanese encephalitis in Thai children and in US travelers

# Hepatitis A Vaccine

In 1986, attention turned to Hepatitis A vaccine.. At that time:

- HAV passive prophylaxis had been accomplished by highly unpopular repeated doses of immune serum globulin.
- An IgM antibody test and a neutralizing antibody assays had been developed.
- Dr. Binn at WRAIR invented the first inactivated, cell-culture HAV vaccine, and
- 8/8 volunteer recipients at WRAIR developed neutralizing antibody following 4 doses.
- The US Army advertised for a commercial partner, and WRAIR scientists transferred technology to GSK.
- As lots of the new HAV vaccine were being produced and tested in safety and immunogenicity studies, Dr. Innis proposed from AFRIMS that the pivotal efficacy trial be performed in Kamphang Phet Province, and the manufacturer accepted this proposal.

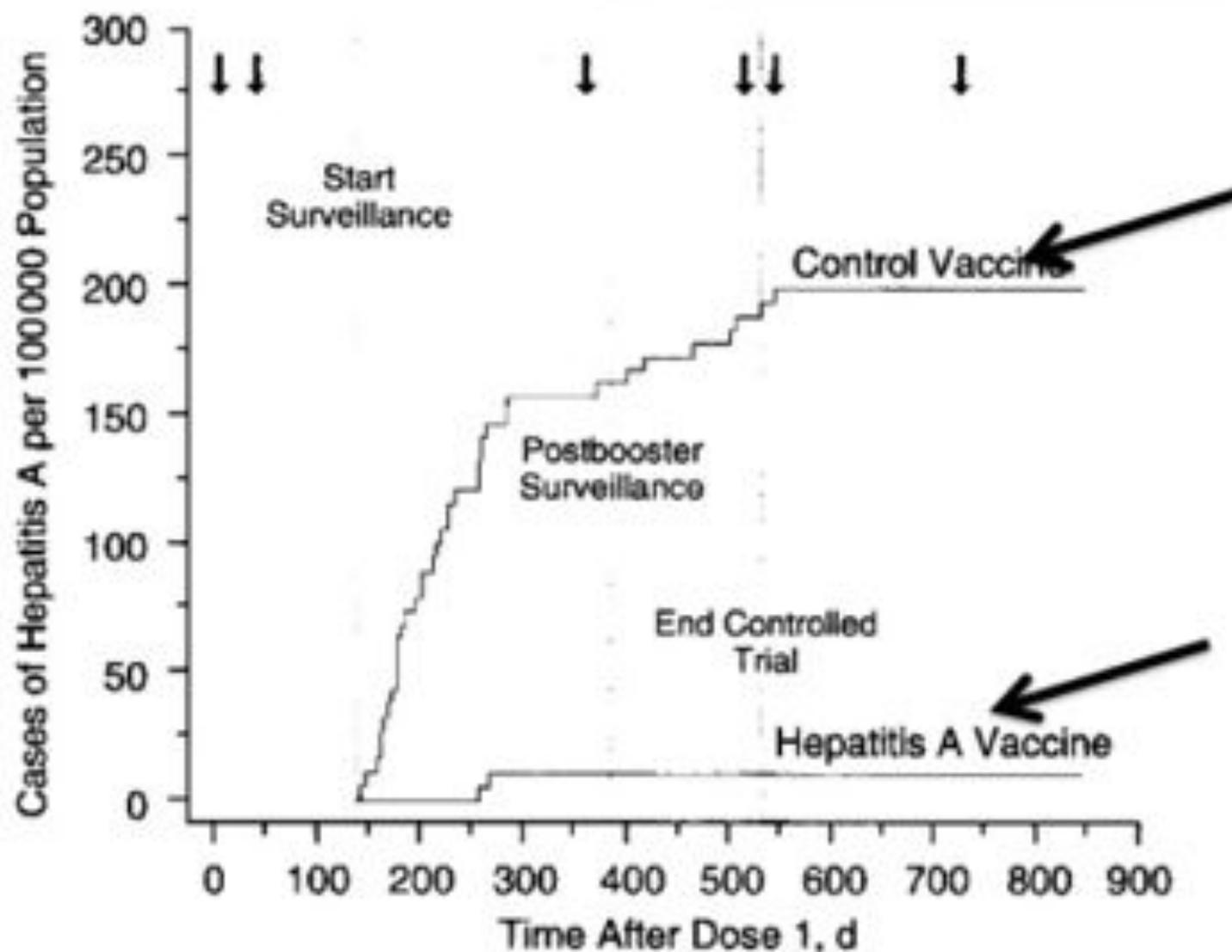
The stage was again set for an important collaborative vaccine efficacy trial in Kamphaeng Phet Province.

# Hepatitis A Status in 1986

- ISG prophylaxis '44
- IgM assay '79
- Neutralizing antibody '83
  - Lemon SM, Binn LN. Serum neutralizing antibody response to hepatitis A virus. *J Infect Dis.* 1983;148:1033-9.
- Inactivated cell-culture vaccine: WRAIR '86
  - Binn LN et al, *J Infect Dis.* 1986;153:749-56.
- First clinical trial in 8 subjects '88
  - Sjogren MH, et al. Safety and immunogenicity of an inactivated hepatitis A vaccine. In Zuckerman AJ, ed, Viral Hepatitis and Liver Disease, pages 94-96, 1988 Alan R. Liss, NY.
- Technology transfer from WRAIR to manufacturer.
- Safety and immunogenicity trials promising.
- AFRIMS proposes efficacy trial in Kamphaeng Phet.

## Another Successful Vaccine Efficacy Study

A collaborative trial of HAV vaccine was conducted in 40,000 children. Cases were children who missed school, had elevated liver enzymes and a positive serum HAVAB-M test. The attack rate in the vaccine group was 10/100,000 vs 200/100,000 in the control group, giving an efficacy of 94%.



Symptomatic  
HAV in  
Hepatitis A  
Vaccine and  
Control Vaccine  
recipients

Fig 3.—Cumulative rates of symptomatic infection with hepatitis A virus in the hepatitis A vaccine and control groups. Arrows represent timing of vaccine dose administration. Vertical lines denote when surveillance began, when booster vaccine doses were administered, and when the controlled trial was terminated at crossover, although surveillance was continued.

# Joint Publication of Hepatitis A Vaccine Efficacy Results

The Provincial Hospital, the Ministry of Public Health of Thailand, the manufacturer, and the US Army, jointly published the results.

# Protection Against Hepatitis A by an Inactivated Vaccine

Bruce L. Innis, MD; Rapin Snitbhan, MD; Prayura Kunasol, MD; Thanom Laorakpongse, MD†;  
Weera Poopatanakool, MD; Christine A. Kozik, MPH; Saroj Suntayakorn, MD; Tithinun Suknuntapong, MA;  
Assad Safary, MD; Douglas B. Tang, PhD; John W. Boslego, MD

Kamphaeng Phet Provincial Hosp  
Ministry of Public Health Of Thailand  
Manufacturer  
AFRIMS and WRAIR

JAMA 271: 1328-1334, 1994.

# Results Applied in Thailand and the US

The Thai MOPH concluded that widespread HAV vaccine use would not be cost-effective, but approved the vaccine for use in outbreaks and in special circumstances.

In the US, following FDA approval, the military began immunizing with a dramatic reduction in the rate of hospitalizations for HAV. Reductions in HAV incidence in civilian populations also occurred as vaccine was introduced.

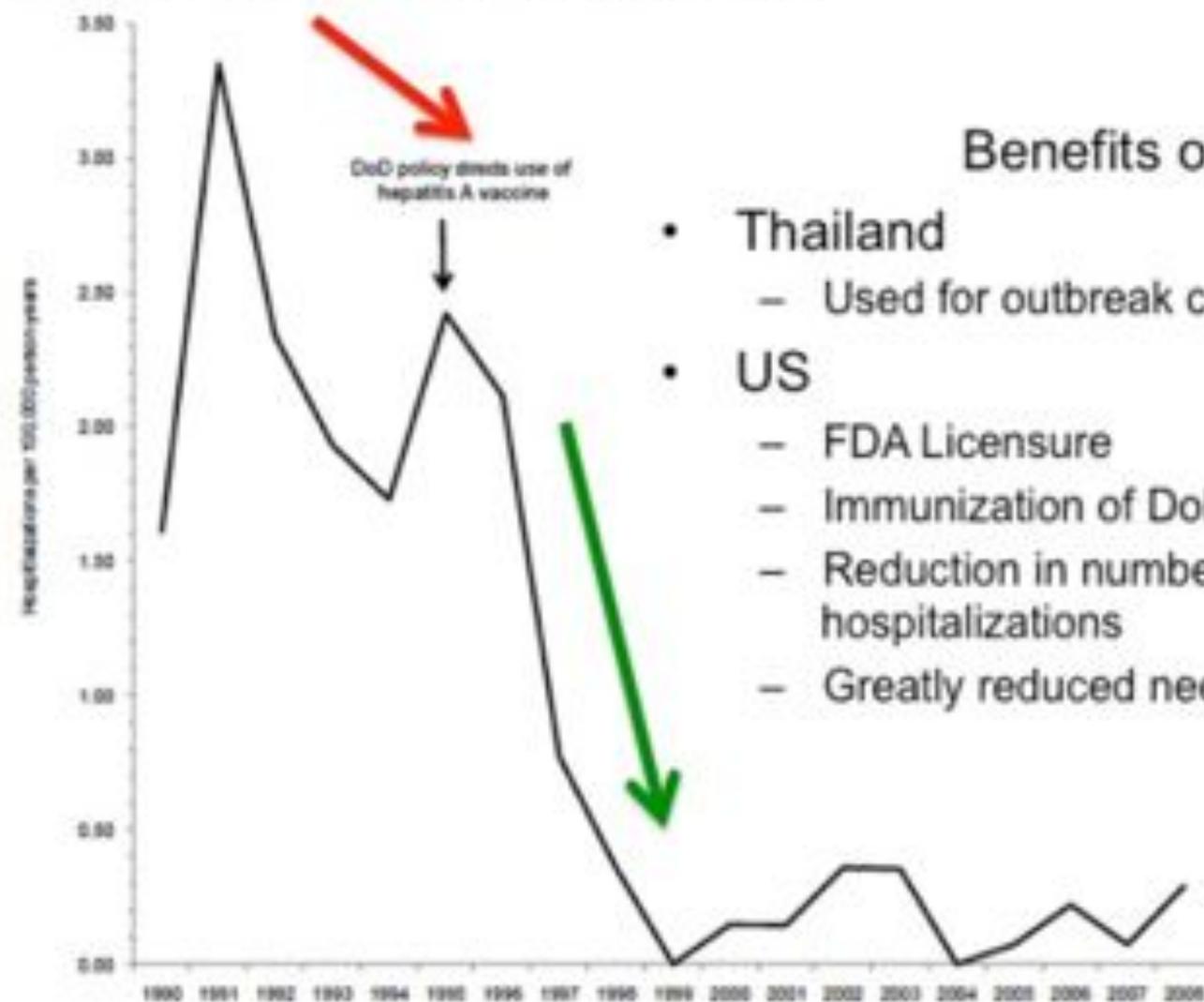
# Hospitalizations due to Hepatitis A in US Army: 1990-2007

Source: Armed Forces Health Surveillance Center, MSMR.

OCTOBER 2009

## SURVEILLANCE SNAPSHOT: Hospitalizations for hepatitis A

Trend of hospitalizations for hepatitis A, active component, U.S. Armed Forces, 1990-2008



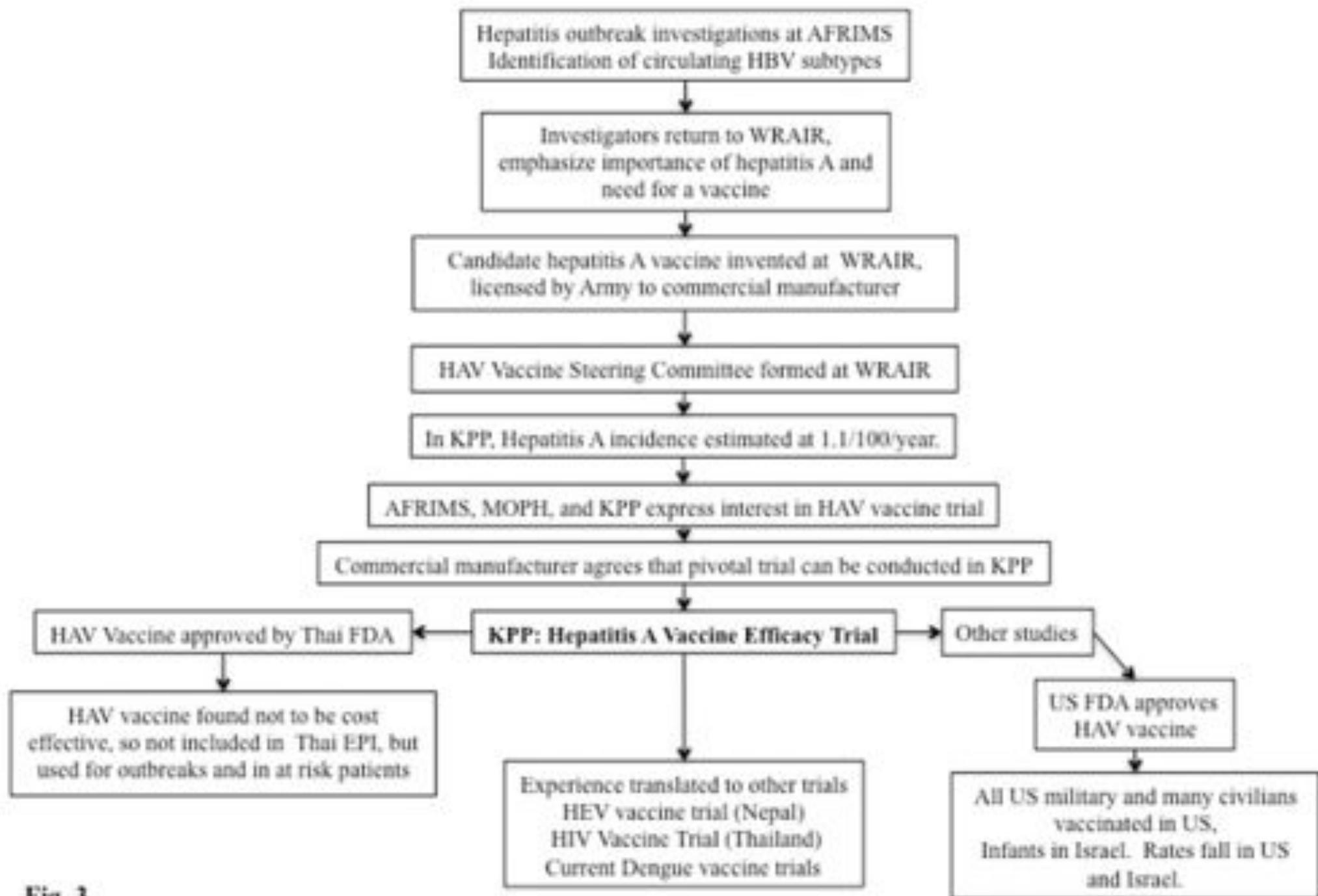
## Benefits of Collaboration

- Thailand
  - Used for outbreak control
- US
  - FDA Licensure
  - Immunization of DoD and civilian personnel
  - Reduction in numbers of HAV cases and hospitalizations
  - Greatly reduced need for ISG

Source: DMED, 2 Nov 2009

## Hepatitis A: One Study Leads to Another

AFRIMS was well-positioned to engage with the Thai ministry of Public Health in cooperative studies of hepatitis A infection. In Thailand, many outbreaks of hepatitis A had been investigated. In the US, hepatitis virus had been identified, cultivated, and adapted to cell culture appropriate for vaccine manufacture. Assays of hepatitis A antibody response were developed before commercial assays were available. In particular, a neutralizing antibody test was developed. Hepatitis A virus was inactivated with formalin and prototype killed vaccine had been produced at WRAIR (FI-1). This vaccine proved immunogenic in 8 senior members of WRAIR's staff, and a major manufacturer expressed interest in manufacturing the vaccine for commercial distribution. Studies of that vaccine were conducted at many sites, including several military posts. When a field efficacy study was needed, AFRIMS, the MOPH, and Kamphaeng Phet Province provided the perfect study site. The vaccine proved highly efficacious and the vaccine was approved by the US FDA and made available to US troops and civilian personnel. In Thailand, studies suggested the vaccine would not be cost effective, so widespread use was not implemented. However the institutional expertise gained from the efficacy study was used in Nepal to conduct a study of the efficacy of a hepatitis E vaccine and in other provinces in Thailand to conduct a study of the efficacy of a candidate HIV vaccine.



**Fig. 3** Hepatitis A studies performed in US and Thailand, particularly in Kamphaeng Province, leading to approved HAV vaccine.

# KAVRU

In 2003, the Kamphaeng Phet-AFRIMS Virus Research Unit (KAVRU) was opened as a Center for the collaborative study of viral infections. The Permanent Secretary of the Thai Ministry of Public Health and the US Ambassador to Thailand officiated at the ceremony.

# Kamphaeng Phet-AFRIMS Virus Research Unit (KAVRU)



# Dengue and Influenza

As with JE and hepatitis A, dengue had been a problem for both Thai Children and US military personnel. An IgM antibody capture ELISA for diagnosis of dengue, based on the JE MAC ELISA, had been well-characterized and standardized at AFRIMS. Clinical data collection and computer systems were upgraded by Dr. Vaughn and others.

Several US NIH grants supported studies of dengue pathogenesis, epidemiology, and virus transmission. (NIH Grants involved Dr. Ennis and his team at the Univ. of Massachusetts.) A phase III dengue vaccine trial is currently in progress.

With respect to Influenza surveillance, family transmission studies, and virus characterization are also in progress.

# Dengue and Influenza at KAVRU

- Dengue
  - Thai children and US military
  - IgM ELISA for dengue standardized at AFRIMS
  - Pathogenesis and epidemiological studies (326 hosp)
  - Phase III dengue vaccine trial (585 subjects from KPP)
  
- Influenza
  - Sentinel human surveillance since 2007.
  - Isolates provided to WHO.
  - Human-animal virus transmission since 2008.

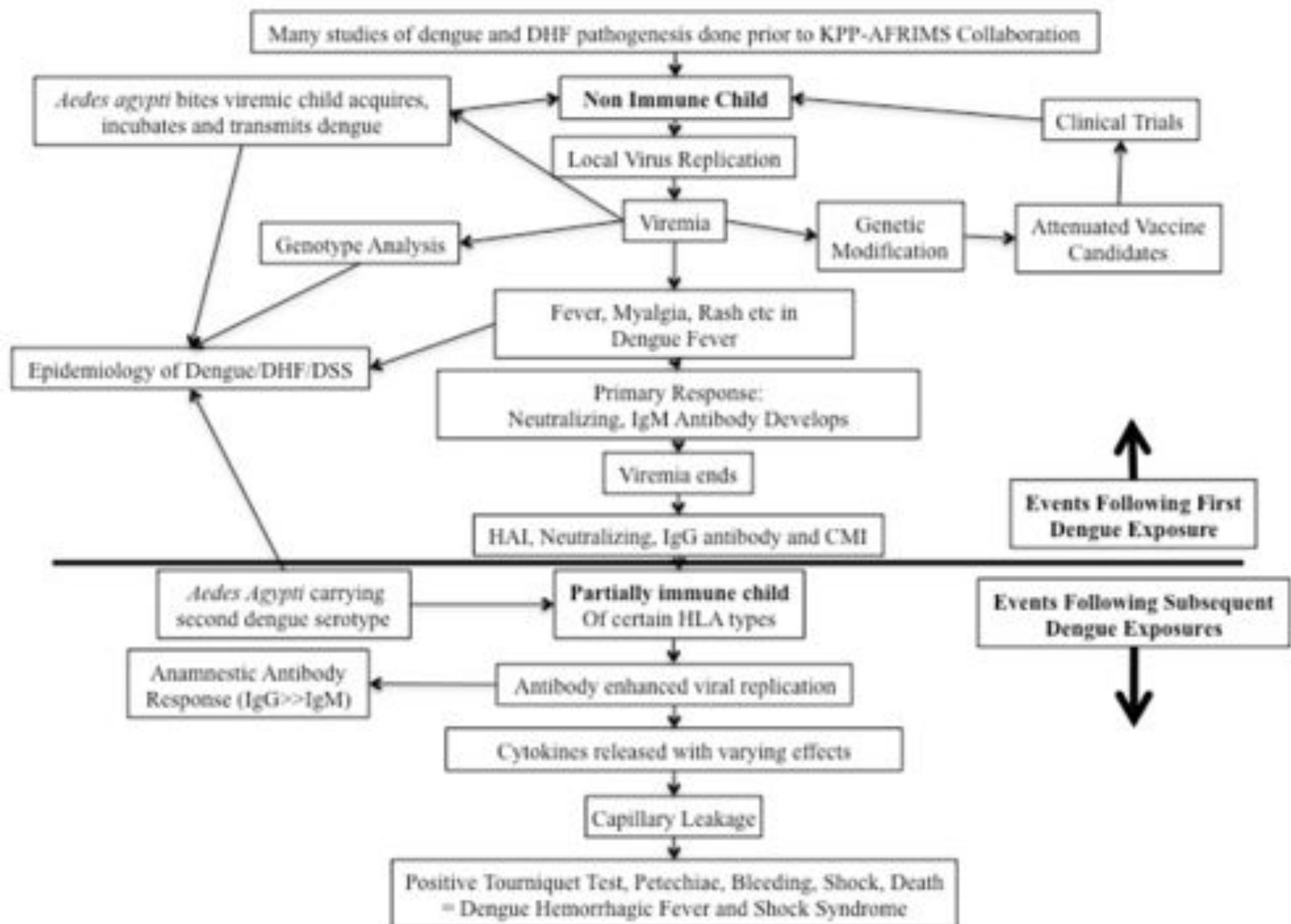


Fig. 4 Recent studies of dengue transmission, pathogenesis, diagnosis, and genetics conducted in Kamphaeng Phet Province

# Win-Win-Win-Win

In Summary, this 30 year collaboration between the Kamphaeng Phet Provincial Hospital, the MOPH, AFRIMS, and relevant vaccine manufacturers allowed all cooperating agencies to address shared concerns and fulfill their missions through improved diagnosis and prevention of JE and hepatitis A and to lay groundwork for testing vaccines for dengue and influenza. The success of the vaccine trials also illustrates the value of careful site selection and development as a foundation for large scale vaccine efficacy studies.

This Collaboration represents a win-win-win-win accomplishment that satisfies the guidance of MG Phil Russell, formerly of AFRIMS, that “Excellence in Research is Not Enough”. Real solutions to health problems must be found in the laboratory and applied in the real world.

AFRIMS Mission:  
Protect US Forces

MOPH Mission  
Protect Thai People



**Shared Concerns**

- JE
- Hepatitis A
- Dengue
- Influenza

Vaccine  
manufacturers

KPP Hospital Mission:  
Provide Diagnosis and Care/Prevent Disease

Russell PK. Excellence in research is not enough.  
Am J Trop Med Hyg. 1984;33:319-24.



## For more information:

Authors from Kamphaeng Provincial Hospital, KAVRU, and AFRIMS have jointly published a more detailed description of the collaboration described in this presentation which you can read in “Vaccine”.

# Publication

A model international partnership for community-based research on vaccine-preventable diseases: the Kamphaeng Phet-AFRIMS Virology Research Unit(KAVRU).

Vaccine. 2013;31:4487-500.

- Gibbons RV
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