Emergence of epidemic dengue and DHF in Mexico: Lessons learned towards better vector and disease control

Barry J Beaty
IOM Forum on Microbial Threats
Fort Collins, Colorado
June 19 and 20, 2007
Dengue Hemorrhagic Fever Cases in the Americas 1980-1998 and Countries Reporting Cases
American countries with *Aedes aegypti* in 1970 at the end of the mosquito eradication program and in 2002
VECTOR GENETIC DETERMINANTS OF EPIDEMIC DENGUE
Ae. aegypti altitudinal range is from sea level to ~2000 feet (Ibañes-Bernal, 1995)
Geographical groups of *Aedes aegypti* in Mexico and the U.S.
Extrinsic incubation period is the time from ingestion of an infectious blood meal until transmission capability. Alphaviruses: 4-12 days
Time course of DENV-2 Jam 1409 midgut infection after oral challenge of *Aedes aegypti*.

Salazar-Sanchez, et al., BMC, 2007
Quantification of DENV-2 in midguts of orally infected Chetumal mosquitoes.

A) qRT-PCR

B) End point titrations

C) Plaque assays
Aedes aegypti salivary glands infection by DENV-2 Jam 1409 after an oral challenge.
Temporal and spatial infection of DENV-2 Jam 1409 in Chetumal mosquitoes.

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<thead>
<tr>
<th>Days post-infectious blood meal</th>
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<td>Malpighian tubules</td>
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10-25%  26-50%  51-75%  76-95%
Infection Rates of *Aedes aegypti* Populations after *P. Oswaldoi* Infection with Dengue 2 JAM1409

![Graph showing infection rates of Aedes aegypti populations](image)
Is the barrier to gene flow between northeastern Mexico and the Yucatan epidemiologically significant?
Correlation between Dengue Seroprevalance, Vector Competence and Vector Serotype

TABASCO
- Seroprevalence: 31%
- Vector Competence: 49%

CAMPECHE
- Seroprevalence: 34%
- Vector Competence: 43%

YUCATAN
- Seroprevalence: 56%
- Vector Competence: 68%
Viral determinants of epidemic dengue and dengue hemorrhagic fever in Mexico
Correlation Between Dengue Occurrence and DENV Introductions

Introductions:
- DENV-1
- DENV-2, 4
- DENV-3
- 2 DENV-2 genotypes
- "American-Asian"

Years: 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 00, 02

DF cases ➤ DHF cases

DF cases: 0, 500, 1,000, 1,500, 2,000
DHF cases: 0, 500, 1,000, 1,500, 2,000

Legend:
- Green: DF cases
- Red: DHF cases

Graph shows the correlation between the years and the number of DF and DHF cases, with specific introductions indicated.
Southeast Asian Dengue 2 genotype viruses disseminate in *Aedes aegypti* much more efficiently than an American genotype dengue 2 virus.

![Diagram](image-url)

Salazar-Sanchez, et al.
Increased Vector Abundance & Hyperabundance

Increased Probability of DHF / SS

Increased Probability of Virulent Strain Selection

Increased Probability of Immune Enhancement

Increased Transmission Trafficking of Viruses

Increased Vector Abundance & Hyperabundance

Increased Probability of Secondary Infection

HYPERENDEMICITY
Not-so-Novel Vector-borne Disease Control:

For the foreseeable future, traditional approaches to reducing vector populations or repelling vectors will remain the first lines of defense against emerging and resurging diseases. Clearly, the development of new, environmentally acceptable pesticides and formulations will be critical to mitigate the potential for dramatic increases in such diseases.

IOM / NAS Study: *Microbial Threats to Health Emergence, Detection and Response*, 2003
Innovative Vector Control Consortium: Improved Control Of Mosquito-Borne Diseases In And Around The Home

Janet Hemingway, Barry J. Beaty, Mark Rowland, Thomas W. Scott and Brian L. Sharp
Trends in Parasitology, 2006

- Control of vectors in and around the house
- Major POC for transmission of:
  - Malaria
  - Dengue
  - Filariasis
  - Leishmaniasis
  - Chagas
- Successful in the past
Background

• Five year public private partnership programme started Nov 2005
• Funded by a US$50million award from the Bill and Melinda Gates Foundation
• Consortium Members
  1. Colorado State University
  2. Liverpool School of Tropical Medicine
  3. London School of Hygiene and Tropical Medicine
  4. Medical Research Council, South Africa
  5. University of California Davis
Need for IVCC

• No new public health chemical pesticides for vector control in DECs for 30 years

• Development of new public health insecticides demands investment. The cost of developing a single new insecticide is in the range of $70 million. The overall annual public health insecticide market – for all diseases and all developing countries - is around $151.2 million. Clearly, market size limits commercial sector investment and the pipeline of new insecticide candidates

• The IVCC can facilitate development of products with industrial partners
IVCC Major Thematic Areas

• **Objective 1.** Development of new public health products (e.g. insecticides and their formulations)

• **Objective 2.** Development of better tools and approaches to facilitate malaria and dengue vector control
AIM: To produce new insecticide based products that will improve our ability to control insect vectors of disease in the home.

• The Vision.

1. To develop a pipeline of innovative vector control products that achieve a significant advance on current vector control options.

2. To develop a pipeline of vector control products to protect and promote the sustainability of both ITN and IRS approaches to vector control.
A Portfolio Approach

- **Balanced portfolio:** The IVCC aims to support a range of vector control products that will have a major impact on malaria and dengue transmission.

- **Portfolio selection:** Similar principles to those used in industry but with the added criteria of **global access** (which will be discussed later).

- **Scope:** The exact scope of the portfolio is not fixed but will be revisited as the portfolio grows.

- **Industry:** Expected to cover some of the development costs in cash or in kind, with relative contribution agreed through consultation.

- **Global Access Plan:** All projects receiving support and funding from the IVCC will develop a GAP to maximize product uptake and impact on vector borne disease.
OBJECTIVE 1: NEW INSECTICIDES AND FORMULATIONS

- The portfolio approach
- Pipeline of products
- Industrial partners – IP worked out
- New insecticides for ITM and IRS applications will include alternative active ingredients, longer lasting formulations, and new combinations of existing insecticides
- External Scientific Advisory Boards
IVCC Critical Path for Public Health
Pesticide Product Development

IVCC Decision Support Systems

Repurposing
- Large Scale Tender
- Market Analysis
  - Individual Consumer

Discovery
- WHOPES
  - Phase I: Evaluations - Efficacy/Safety, Resist./Toxicology
  - Phase II: Small Scale Field Trials
  - Phase III: Large Scale Field Trials
  - Phase IV: Specifications, final formulations, data analysis
  - Proof of concept: Field trials in disease endemic sites

IVCC Contributions

Large Scale Tender
- Markets
  - Individual Consumer
Aim: To establish the partnership in a format that stimulates improved delivery of these products and systems.

The Vision

- To involve major employers, international organisations, Ministries of Health, DEC communities, operational control programs in the partnership from the outset to stimulate improved delivery of the products as they are developed and marketed.
OBJECTIVE 2. IMPROVED TOOLS FOR VECTOR CONTROL.

PYRETHROID QUANTIFICATION KIT
Rapid determination of pyrethroid activity in ITM/ITN/IRS in the field – enzyme based systems for field relevant testing

POPULATION MONITORING TOOLS
Molecular based rapid detection of insecticide resistance (eg, pyrethroid, temephos) in dead insects*
Other phenotypes of interest – eg, infection status

OBJECTIVE 2. IMPROVED DECISION SUPPORT TOOLS FOR VECTOR CONTROL.

• DECISION SUPPORT SYSTEMS FOR MALARIA AND DENGUE VECTOR CONTROL

• SIMULATION MODELS FOR MALARIA AND DENGUE
The Dengue Decision Support System

- A rationally designed, computer-based dengue information system (DIS) with multiple subcomponents (DMS, DWS, ESS, EIS, SDMS) that is functional at different capacity levels:

- DIS 1 – Local and regional vector control to achieve more efficient usage of resources in very resource limited environments. Basis dengue and *Aedes aegypti* information for control

- DIS 2 – In addition to DIS 1, information on insecticide resistance for operation management for vector control.

- DIS 3 – Proactive surveillance, modeling, GIS-based data analysis.
Outline of DDSS structure

DENGUE DECISION SUPPORT SYSTEM

DENGUE INFORMATION SYSTEM (for local application at capacity levels 1-3)

- Dengue Management System
  - Passive syndromic surveillance data
  - Dengue case data (incl. spatial location and date of onset)
  - Knowledge of Aedes aegypti and dengue among local population

- Dengue Warning System
  - Climate data (early warning of potential for dengue epidemics)
  - Herd immunity data (susceptibility of population to dengue serotypes)
  - Data from active syndromic surveillance in sentinel sites
  - Data from rapid confirmation of dengue diagnosis in sentinel sites

- Entomology Surveillance System
  - Surveillance methods used (incl. person-days used for surveillance)
  - Vector presence / abundance data (larvae, pupae, adults)
  - Vector abundance data (pupae) by container type (for determination of key breeding containers)
  - Insecticide resistance data

- Entomology Intervention System
  - Type of insecticide and application technique used (incl. data on person-days used for application)
  - Quantity of insecticide used
  - Spatial coverage of application
  - Temporal application scheme

- Spatial Data Management System
  - Geographical boundaries
  - Socio-economic data
  - Housing characteristics
  - Location of hospitals, health clinics, schools, cemeteries etc
  - Environmental data (climate, elevation, vegetation etc)

DATA WAREHOUSE (Access, SQL)

- SPATIAL AND TEMPORAL MODELLING
  - Dynamic query tools
  - Standardized reports, tables, graphs
  - Map outputs (e.g., spatial pattern of dengue cases, dengue incidence, spatial pattern of vector abundance, spatial distribution of vector populations resistant to insecticides

DATA WAREHOUSE (Access, SQL)

- MANAGEMENT TOOL & DATA DISSEMINATION
  - Application packages for Dengue Information System 1-3 (incl. user manuals, protocols, cost estimates)

- Other DDSS components (available from central web-server)
  - Dengue Resource Network
  - Dengue Resource Library
  - Dengue Decision Guide (incl. access to CIMSiM and DENSiM)
Spatial dengue case clustering; Merida and Chetumal, 2006
DENGUE VECTOR CONTROL

• Larviciding and source reduction
  (Temephos resistance)

• Spraying and vector control around premises to intervene in impending epidemics
  (need for early intervention)
**Syndromic surveillance**

refers to methods relying on detection of clinical case features that are discernable before laboratory confirmed diagnoses are made.

*CRF may be key for success*

*New national policy on sample collection*
Dengue Warning System components

- Epidemiological week
- Number of dengue cases

- Clinical diagnosis
- Syndromic surveillance
- Mosquito abundance
- Weather

Likelihood of introduction of serotypes with potential for causing epidemics

Vector control
Seasonality of dengue cases; Merida and Chetumal 2006

Epidemiological week

Number of dengue cases

Chetumal
Merida

Yucatan
Quintana Roo

DDSS project demonstrations - 2
DENGUE VECTOR CONTROL

TIME TO REVISIT THE ISSUE

OUTDOOR ULV SPRAYING INEFFECTIVE

FOCUS UPON THE BIOLOGY OF THE VECTOR IN TRANSMISSION

EXPLOIT NEW TECHNOLOGIES TO EXPAND THE ARMAMENTARIUM FOR *Aedes aegypti* CONTROL
DENGUE VECTOR CONTROL: ULV Indoor Spraying and Targeted Larviciding


ASTMH Annual Meeting Abstract 756
Intradomicile Intervention managed disease: 2002 Dengue Epidemic in Iquitos

- Clinical disease was reduced for ~1 year following vector intervention (Dec 2002 to Dec 2003). During 2004 clinical cases began to increase.
- DEN-3 epidemic was aborted (~30% prevalence would have increased to ~60% without vector intervention).

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<thead>
<tr>
<th>Year</th>
<th>ELISA</th>
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</table>
DENGUE VECTOR CONTROL: ITMs

The effect of Olyset net screen to control the vector of dengue fever in Vietnam.

Nguyen HT, Tien TV, Tien HC, Ninh TU, and Hoa NT.

Impact of dengue virus infection and its control.
Igarashi, A.

Permethrin-treated bamboo curtains for dengue vector control-field trial, Viet Nam.

Nam VS, Nguyen HT, Tien TV, Niem TS, Hoa NT, Thao NT, Tron TQ, Yen NT, Ninh TU, and Self LS.
### Anti-dengue IgM-ELISA on healthy school children
Hai Hung Province, Vietnam, 1994

<table>
<thead>
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<th>Area</th>
<th>Number of specimens tested</th>
<th>Number of positive specimens (%)</th>
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<td>April, before epidemic season</td>
<td>November after epidemic season</td>
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<td><strong>Study Area</strong></td>
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<td>1 (1.3)</td>
<td>5 (6.4)</td>
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<td><strong>Control Area</strong></td>
<td>78</td>
<td>4 (5.1)</td>
<td>26 (33.3)</td>
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Curtains:
Veracruz, Mexico lambda cyhalothrin treated
Trujillo, Venezuela deltamethrin (LLITM – PermaNet)

Water containers:
Veracruz, Mexico pyriproxyfen chips
Trujillo, Venezuela PermaNet covers

Outcomes at both sites:
Entomological
Dengue infection
The reason for efficacy: Endophily and Endophagy

*Aedes aegypti, Anopheles gambiae, and Anopheles funestus* (and *Culex quinquefasciatus*) seldom feed on plant sugar

*Anopheles* and *Aedes* preferential and frequent feeding on human blood

Multiple other vectors (e.g., sandflies, triatomids) feed preferentially in domicile
Regional Chagas Disease Control: Southern Cone Initiative - 1991

Controlling Chagas disease by attacking the epidemiologically significant point of contract between humans and the vector – the domicile

*Triatoma infestans* – the prototype of an endophilic vector
Enhancing Dengue Vector Control
In Latin America:
“CASA SEGURA”

Developed country housing (screens, airconditioning, etc.) provides a Casa segura

Incorporate ITMs/IRS/Repellents into existing control programs to effect a Casa segura in DECs
Benefits of “Casa Segura” approach with use of long-lasting ITMs to protect homes, schools etc from *Ae. aegypti*

- Low cost allows for near universal coverage
- Can be implemented by vector control programs as well as individual homeowners
- Potential for protection against other arthropod vectors as well as “nuisance biters”
- Integrated into MoH, SSY (state), and municipal (Merida) control programs
**LLIN Estimate:** 2 doors
3 windows
eaves

**Size estimate:** If 1 door is 7 x 3.5 ft = 24.5 sq ft, so 2 doors = 49 sq ft. If 1 window is 3 x 3 ft = 9 sq ft, so 3 windows = 27 sq ft 49 + 27 = 76 sq ft or 7 sq m + 2 sq m for eaves. Total of netting material needed = 9 sq m.

**Cost:** LLIN Max cost (from WHO report) = 6.00 USD, 150cm x 180cm x 160cm = 13.08 sq m of netting material
Approximate cost per house = 4.00-5.00 USD.
Cost effectiveness of dengue vector control by Casa segura (ITM/IRS)

- Vaccine targets only one pathogen. Ae. aegypti control targets DEN and YF as well as other pathogens transmitted in the domicile.

- Protects against many diseases that are vectored principally in the endophilic environment.

- Protects many people in one approach (e.g., separate bednet for each person not essential, etc.).

- Protects against multiple vectors (mosquitoes, eg Anopheles & Culex, sand flies, kissing bugs, etc.) and pest species (e.g., bed bugs, cockroaches) and pathogens (YF, DEN, malaria, Chagas, leishmaniasis).

- Provides economic incentives for people to purchase the product.
Major arguments against “stove-piping” of diseases and infrastructure, resources, and talents to reduce or eliminate these diseases.
<table>
<thead>
<tr>
<th>CSU-PIs</th>
<th>Dengue research</th>
<th>RNAi</th>
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<tbody>
<tr>
<td>Barry Beaty</td>
<td>Alexander Franz</td>
<td>Kimberley Keene</td>
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<td>Norma Gorrochetegui-Escalante</td>
<td>Brian Foy</td>
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<td>Carol Blair</td>
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<td>Isabel Salazar-Sanchez</td>
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<td>Scott Bernhardt</td>
<td>SSY, Merida Health, UADY</td>
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<td>Dr. Ildefonso Fernandez-Salas</td>
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<td>UAY:</td>
<td>Dr. Jose Arturo Farfan-Ale</td>
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<td>Maria Alba Lorono-Pino</td>
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FIN
• Establishment through subcontract PIs Farfan-Ale and Fernandez-Salas of collaborations with vector control and health agencies in Merida (Merida Municipal Health Program, Yucatan State Health Services, Instituto Mexicano de Seguro Social) and Chetumal (Quintana Roo State Health Services).

• Involvement of Drs. Farfan-Ale and Fernandez-Salas in ongoing revisions by the National Center for Epidemiological Surveillance and Disease Control (Drs. Pablo Kuri Morales, Carlos Alvarez Lucas, and Jorge Ricardo Esquinca) and the National Center for Diagnosis and Epidemiologic Reference (Dr. Celia Alpuche) for guidelines for vector and dengue control in Mexico: “Grupo de Expertos para la Prevencion del Dengue”.

• Development of methodology for using free mapping tools (e.g., Google Earth or MS Virtual Earth) as a minimal cost alternative to GIS-software and use of Google Earth to generate city structure data layers for Chetumal and Merida.

• Development of a Google Earth-based mock-up model for spatiotemporal spread of a dengue epidemic in Chetumal.

• Georeferencing of cases in Chetumal and Merida.

• Ongoing development of insecticide resistance database for *Ae. aegypti*. 
Gene flow in *Aedes aegypti* in Southeastern Mexico
Revisiting vector competence of Southeastern *Aedes aegypti* mosquitoes after 10 years

- Chetumal, Ciudad del Carmen, Saylula, Lerdo de Tejada, Martinez de la Torre, Moloacan, Minatitlan, Poza Rica, Alvarado.  
  Bernhardt, Scott, et al.

2005 DENV-2 JAM 1409 Vector competence