Dengue Vaccines: Introduction

World Health Organisation
Strategic Advisory Group of Experts (SAGE)
on Immunization

Jeremy Farrar
E: j.farrar@wellcome.ac.uk
T: @jeremyfarrar

Conflicts of interest None

Dengue Overview

- Dengue Viral Infection
- Epidemiology and Distribution
- Clinical features, pathogenesis, treatment
- Vector control

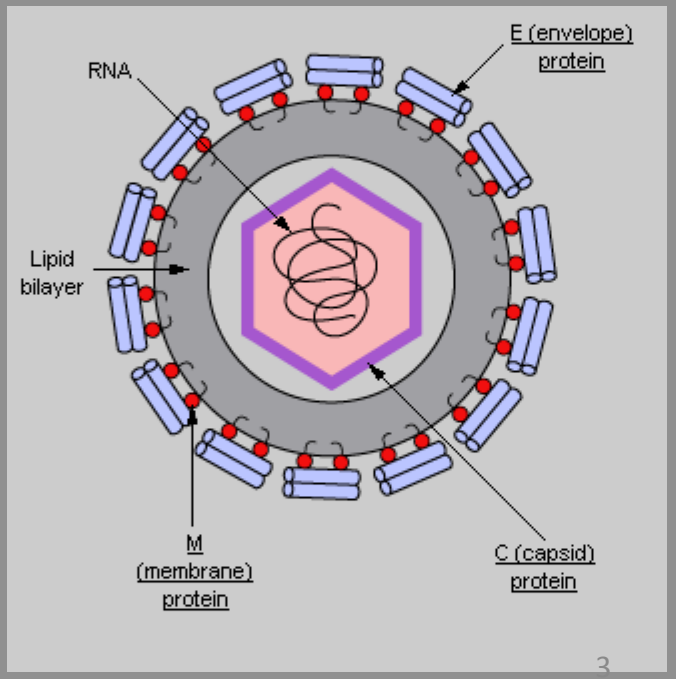
Dengue virus

Dengue virus belongs to the *Flavivirus* genus of the *Flaviviridae* family

Other flaviviruses include: Yellow Fever, JE, West Nile Virus & Zika

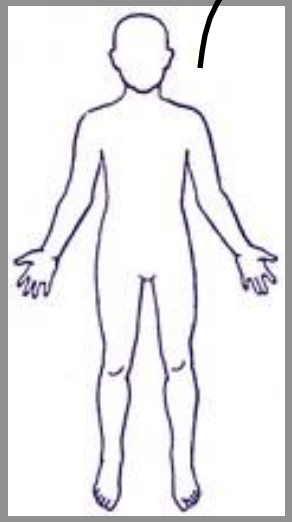
Vectors are species of *Aedes* mosquito

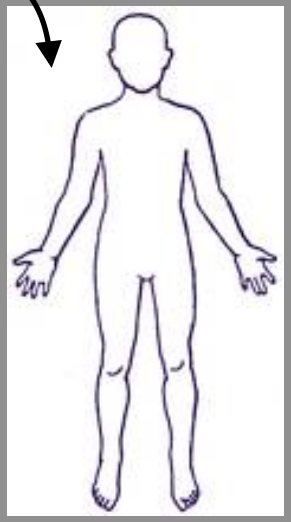
- Four antigenically distinct serotypes (DENV-1, DENV-2, DENV-3, DENV-4)
- Enveloped virus
- 10.7kb ssRNA genome
- Three structural proteins (E, C, M)



Source: Henchal EA, Putnak JR (1990) *Clin Microbiol Rev*

Transmission cycle





- Dengue is an acute arboviral disease
- Vectors are species of *Aedes* mosquito
- Major host is humans
- Dengue virus transmitted by the bite of an infective female *Aedes* mosquito

Source: Wellcome Trust Topics in International Health: Dengue 2001

Dengue

Dengue is an (emerging) infectious disease of tropical and sub-tropical regions

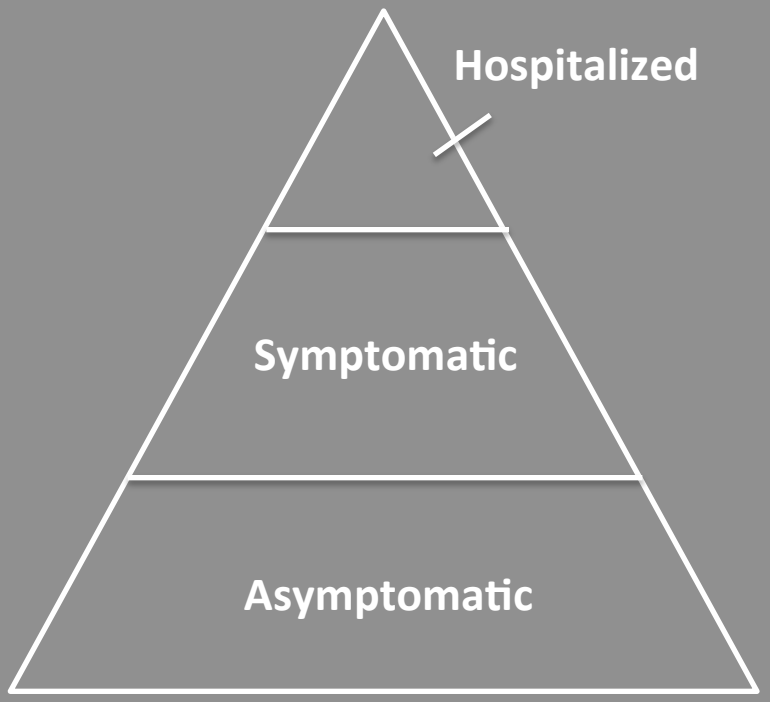
Transmitted by *Aedes* mosquitoes

Clinically apparent infections present as a spectrum:

- Dengue
- Severe dengue

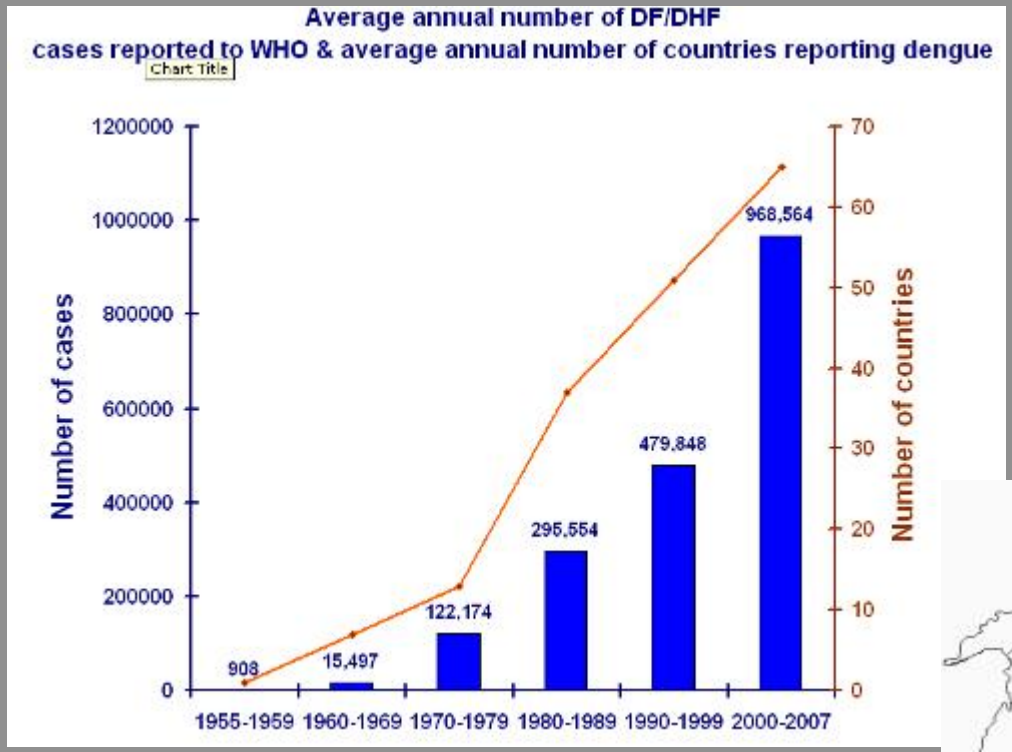
Estimated annual global burden:

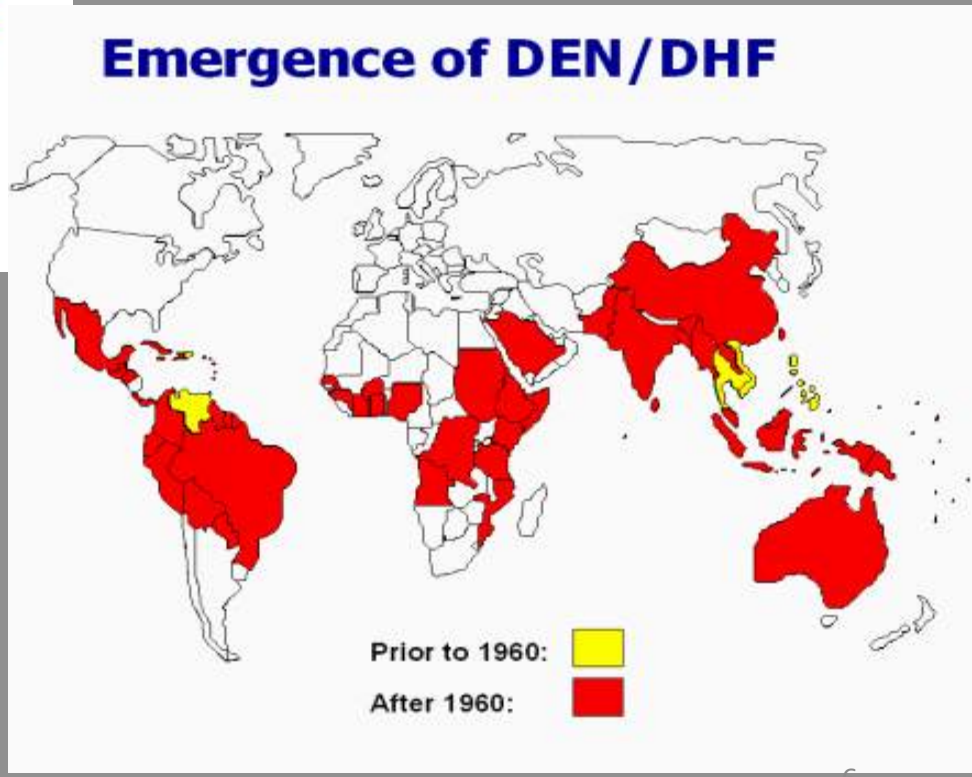
- 390 million infections (285M – 525M)
- 96 million clinical infections
- 2 million severe dengue cases
- 20,000 deaths



Can be epidemic and/or endemic

Dengue
1960 - 2010





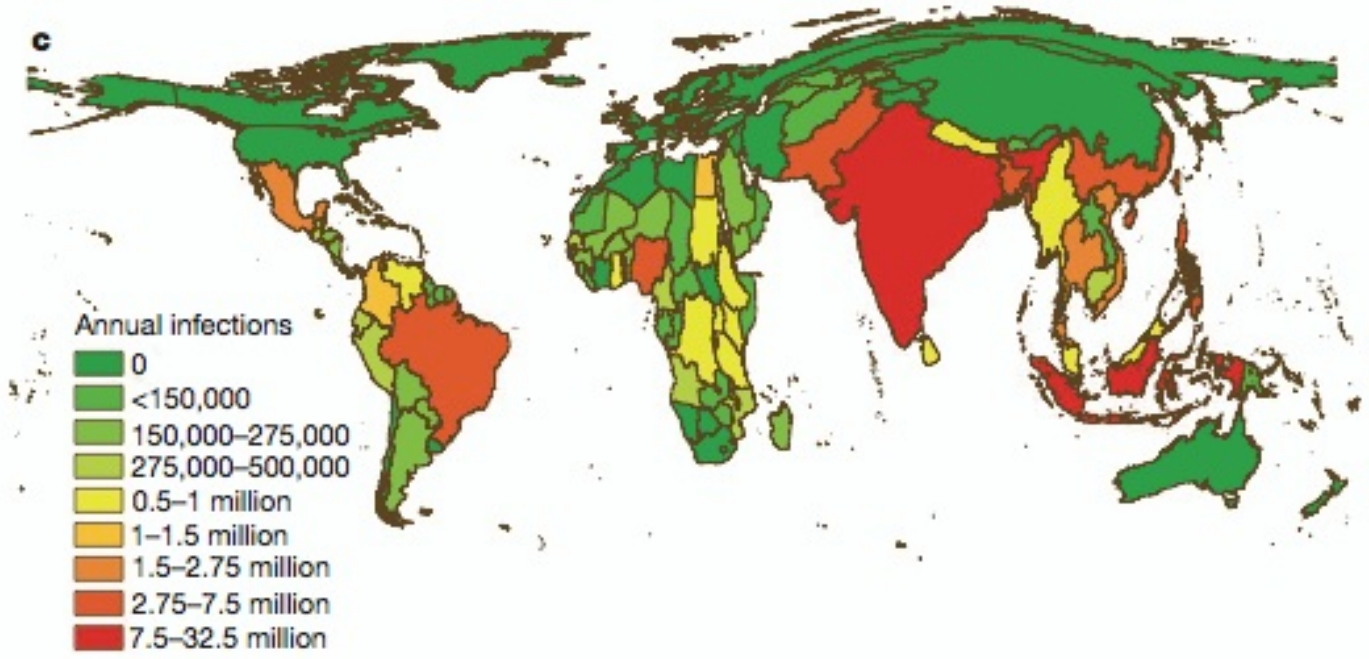
: http://www.who.int/csr/disease/dengue/impact/en/

LETTER

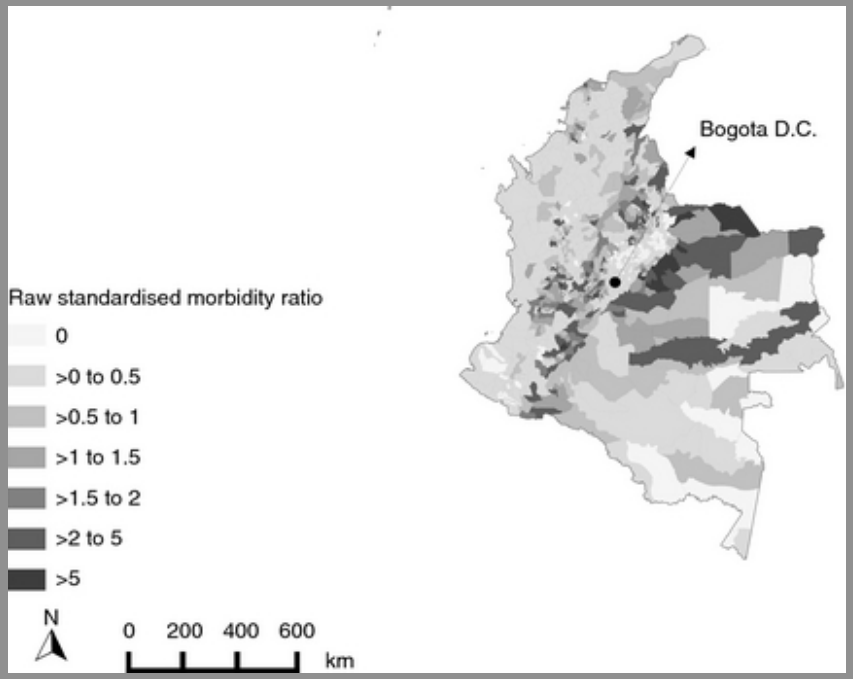
doi:10.1038/nature12060

The global distribution and burden of dengue

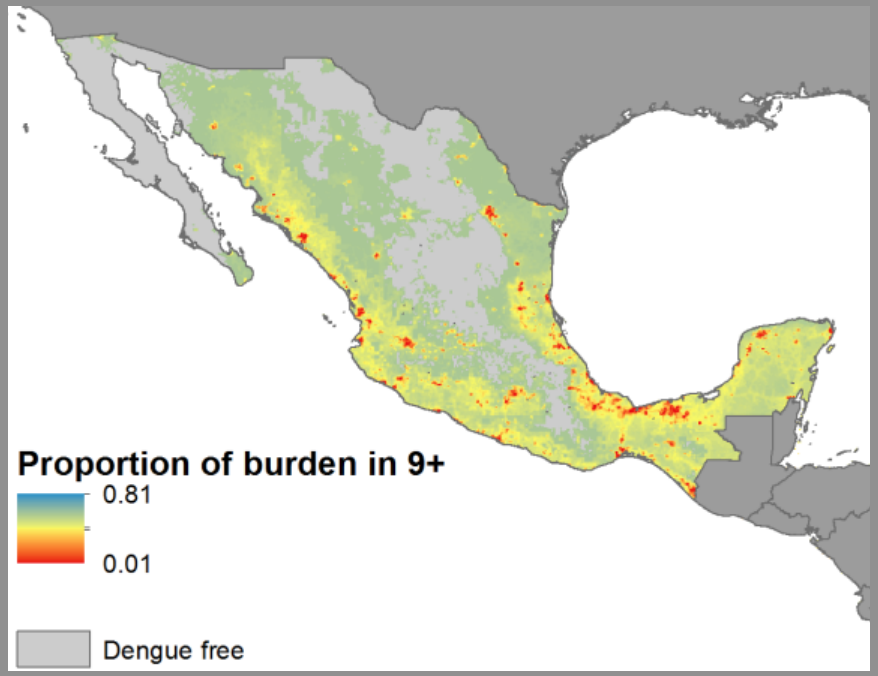
Samir Bhatt[1], Peter W. Gething[1], Oliver J. Brady[1,2], Jane P. Messina[1], Andrew W. Farlow[1], Catherine L. Moyes[1], John M. Drake[1,3], John S. Brownstein[4], Anne G. Hoen[5], Osman Sankoh[6,7,8], Monica F. Myers[1], Dylan B. George[9], Thomas Jaenisch[10], G. R. William Wint[1,11], Cameron P. Simmons[12,13], Thomas W. Scott[9,14], Jeremy J. Farrar[12,13,15] & Simon I. Hay[1,9]



Nature **496**, 504–507 (25 April 2013) doi:10.1038/nature12060



Spatial and temporal heterogeneity in disease transmission



Restrepo AC, Baker P, Clements AC. National spatial and temporal patterns of notified dengue cases, Colombia 2007-2010. Trop Med Int Health. 2014;19:863-71, and Courtesy of Oliver Brady (Oxford University).

Burden to individuals, communities & health systems

Risk factors for severe dengue

The really important clinical feature of dengue

Vascular permeability leading to dengue shock syndrome

Risk Factors

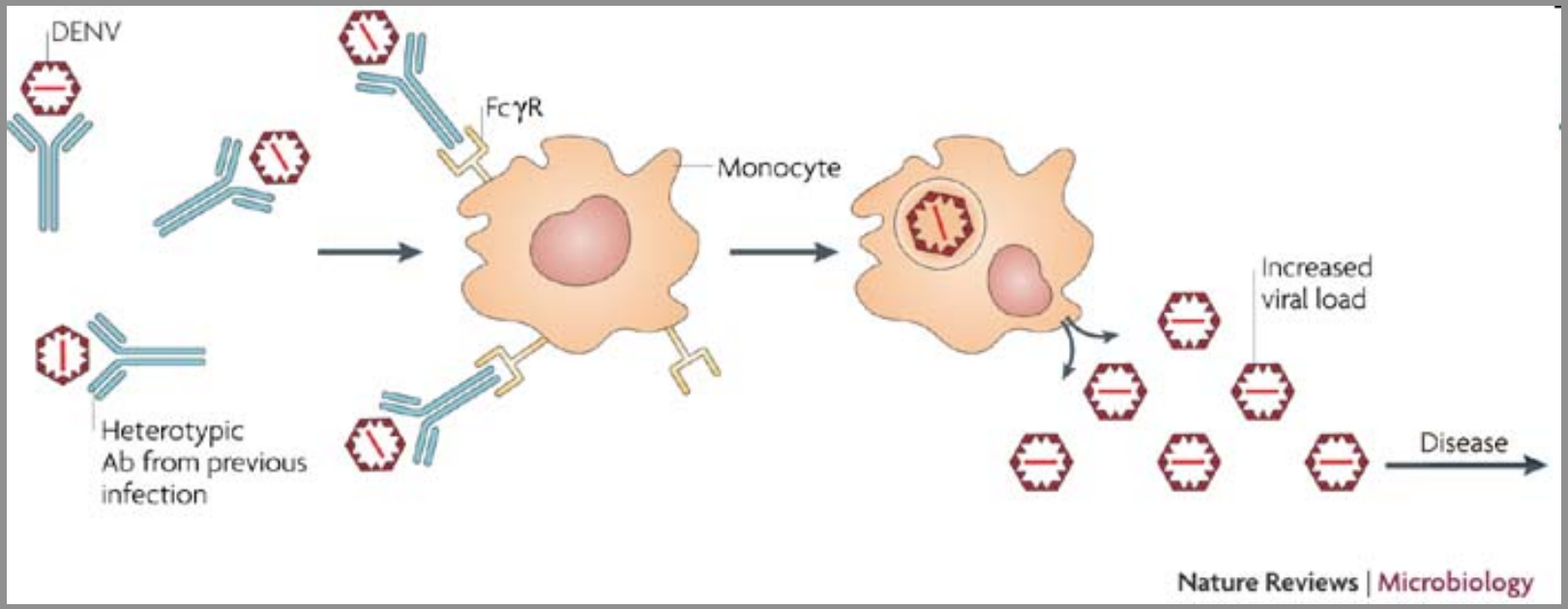
- Secondary infection
- Young age[1]
- Female gender[1]
- BMI: obesity
- Virus strain (?)
- Host genetics
- Co-morbidities

[1] Anders et al, Emerg Infect Dis. 2013 Jun;19(6):945-53.

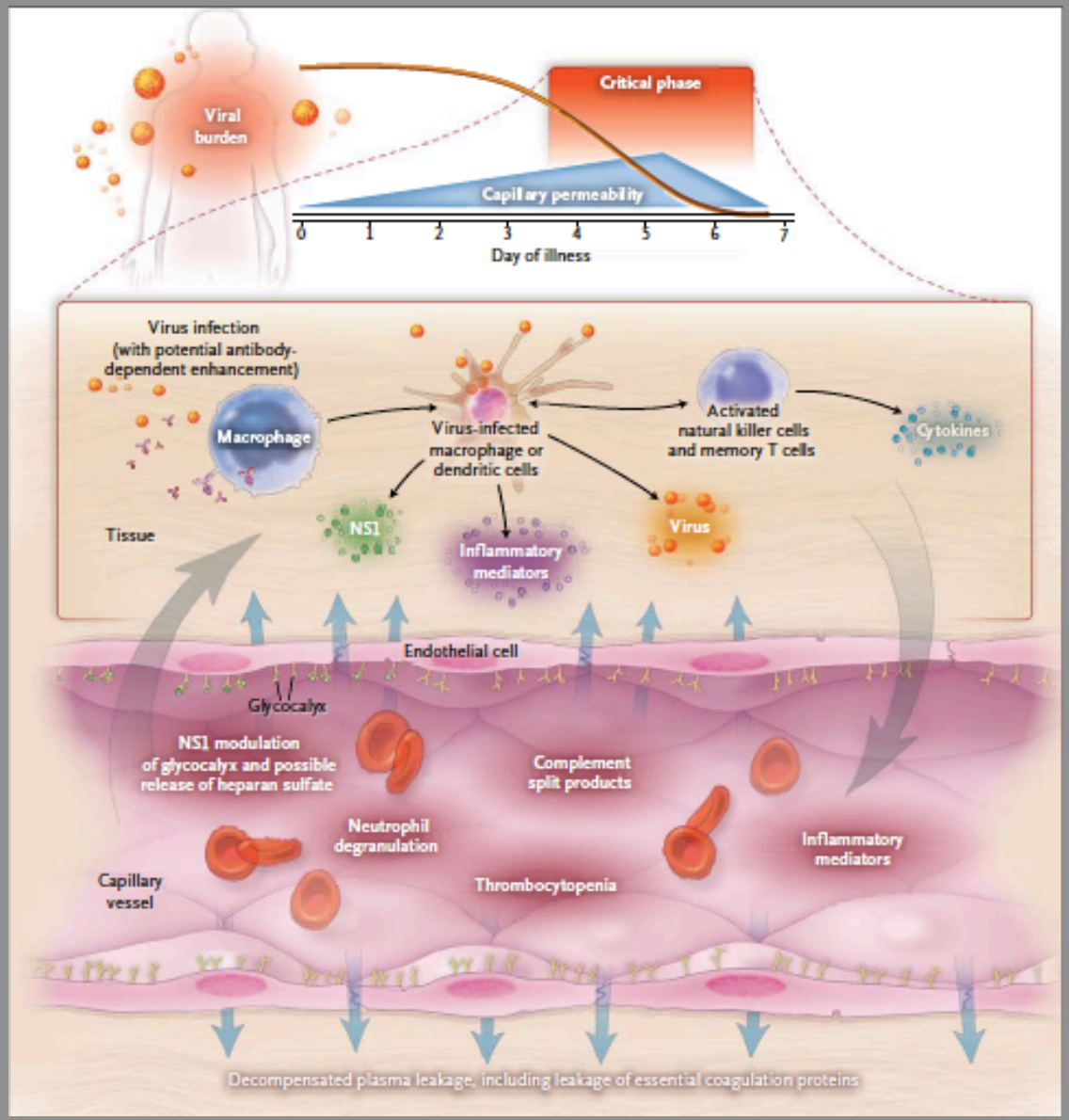
Dengue

Antibody dependent enhancement (ADE)

- pre-existing antibodies bind to heterologous serotype but fail to neutralise it. Can occur in;
  - Secondary infection
  - Primary infection in infants born to immune mothers
- Experimentally results in altered cellular tropism and higher virus burden



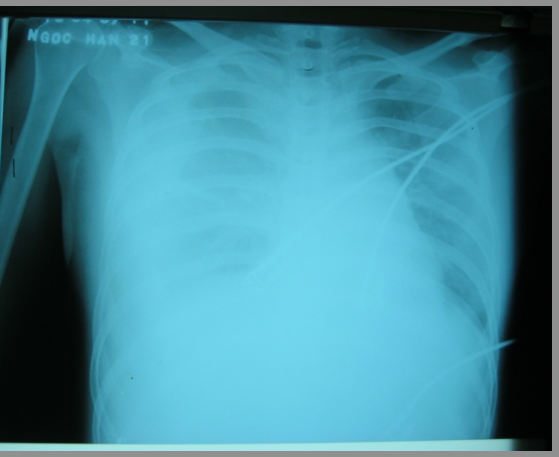
Dengue pathogenesis



- Antibody- dependent enhancement is thought to increase viral burden
  - linked to the presence of non-neutralizing antibodies
- Elevated concentrations of inflammatory mediators, cytokines, and chemokines
  - adding to inflammation
- Immunologic response is thought to promote capillary permeability when the viral burden is in decline.
  - exact mechanisms are unclear
- Loss of essential coagulation proteins probably plays a major role in the development of the typical coagulopathy

Simmons et al, N Engl J Med. (2012) 366:1423-32.

Clinical Spectrum of Dengue



Severe Dengue

Severe dengue – shock, haemorrhage or severe organ impairment

Shock: Systemic vascular permeability leading to vascular hypovolemia and Dengue Shock Syndrome

Haemorrhage: bleeding manifestations due to the combined effects of:-

- Thrombocytopenia
- Deranged haemostasis

Severe organ impairment:-

- Encephalitis, Hepatitis, Other

Treatment and Control

Supportive care

IV fluids + careful resuscitation

Anti-pyretics

Early stage development of specific therapeutics

Prevention: Classic Vector Control

Dengue vectors

- *Aedes aegypti*: most important vector in endemic countries
  - Preference for laying eggs in artificial containers around human dwellings
  - Adults tend to rest on clothing and surfaces inside homes
  - Daytime-biting, and biting preference for humans
  - Multiple feedings within one reproductive cycle
  - Once infected, the mosquito is infective for life

➔ Fully domesticated vector with behaviour that is efficient for DENV transmission

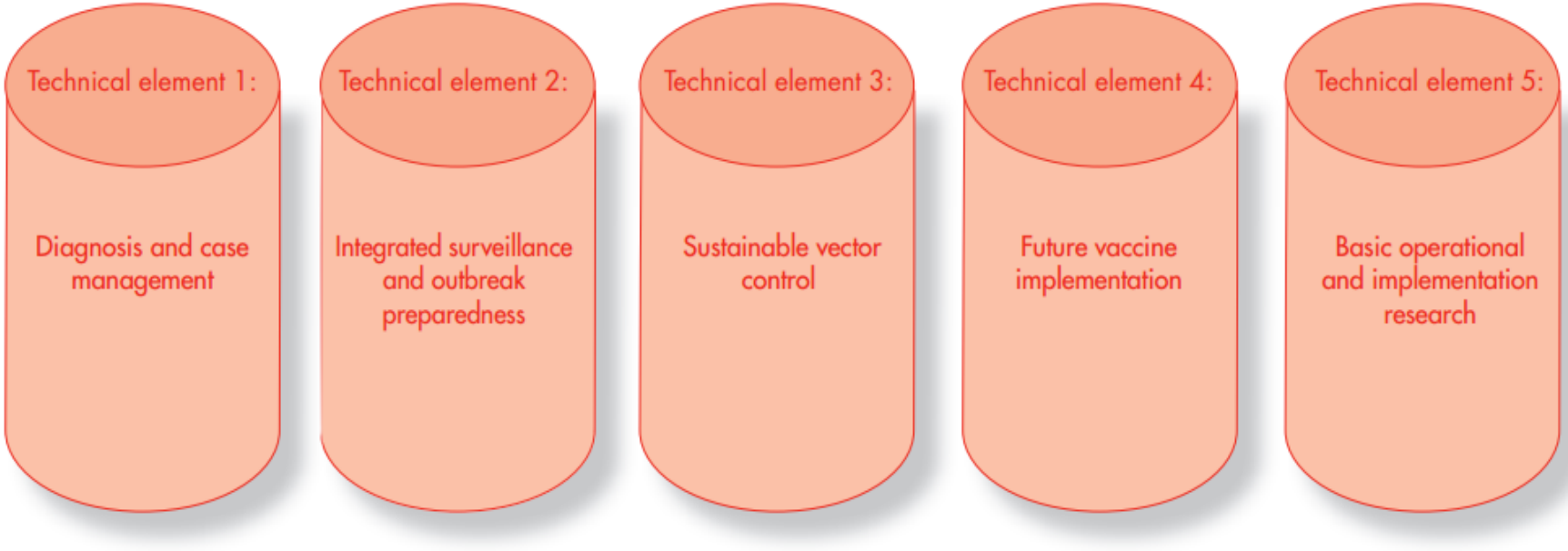

CÀ PHÊ
CHỢ LỚN
55K 67 02

WHO Global Strategy for Dengue Prevention and Control 2012-2020

OBJECTIVES:

- To reduce dengue mortality by at least 50% by 2020*
- To reduce dengue morbidity by at least 25% by 2020*
- To estimate the true burden of the disease by 2015

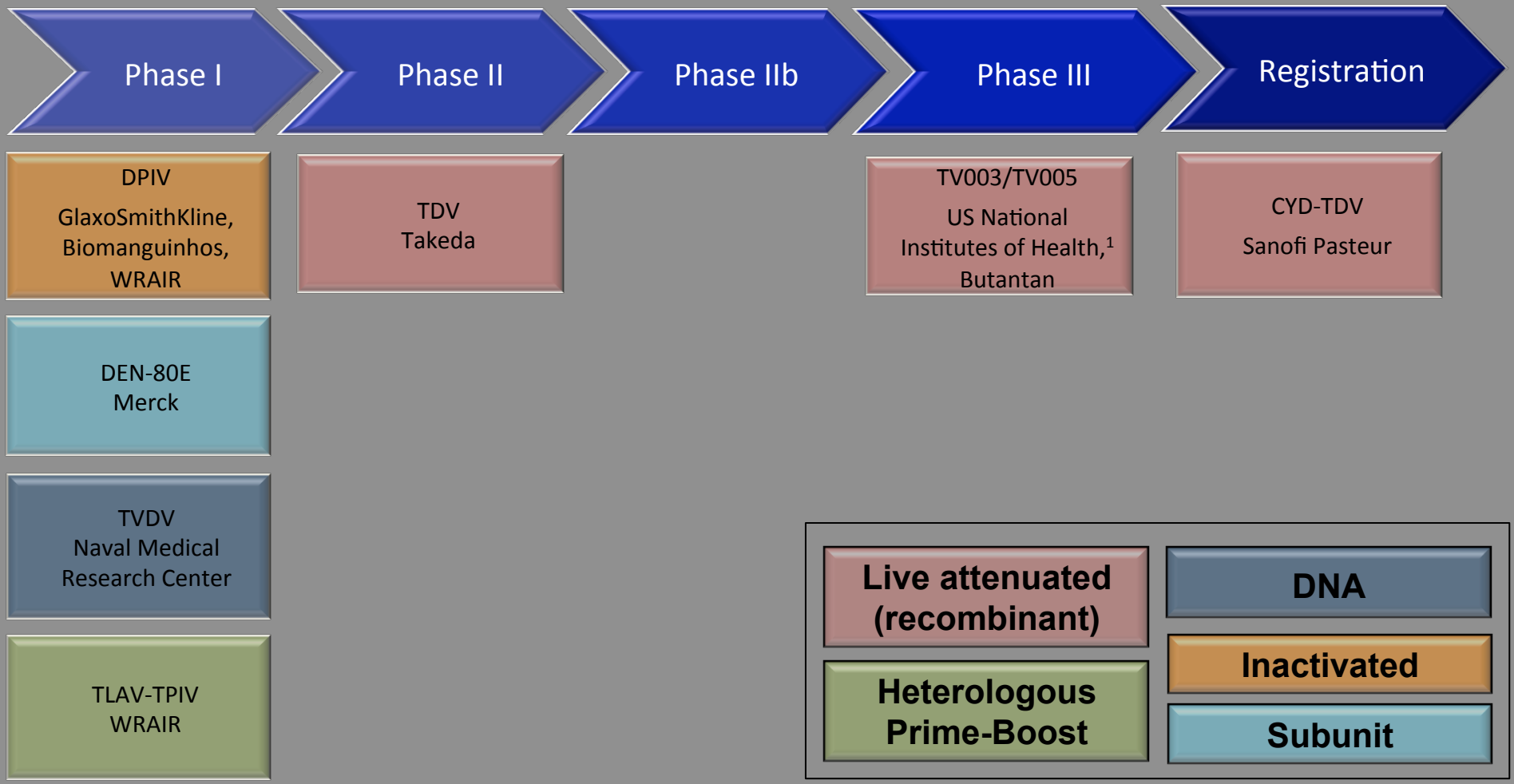
* The year 2010 is used as the baseline.



ENABLING FACTORS FOR EFFECTIVE IMPLEMENTATION OF THE GLOBAL STRATEGY:

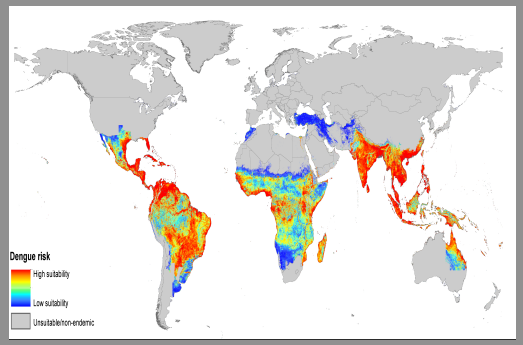
- advocacy and resource mobilization
- partnership, coordination and collaboration
- communication to achieve behavioural outcomes
- capacity-building
- monitoring and evaluation

Dengue Vaccine Pipeline



[1]Licensing agreements also with Merck, Panacea, SII, Vabiotech

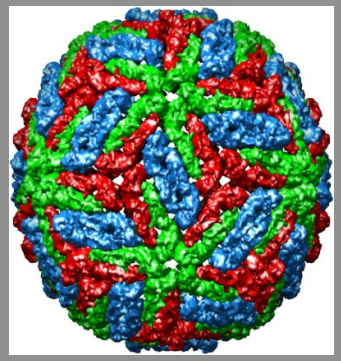
Dengue - Summary



Increasing global burden - number of cases and distribution.

Spread by Aedes which are urban living and day biting.

A vaccine licensed, no prophylaxis or therapeutic drugs



Classic vector control, Wolbachia and genetically-modified mosquito studies in trials

Clinical spectrum of illness

Very careful clinical management – Fluid replacement