

# Dengue epidemiology

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# Global burden of dengue virus (DENV)

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Half of the world's population is at risk of infection

~ 100 million symptomatic cases annually

Economic burden on low-income countries

Defined by *Aedes aegypti* and *Aedes albopictus* mosquitoes

Increasing trends in dengue cases

Surveillance is patchy

# Transmission cycle of dengue virus

## Urban cycle

1. Mosquito takes a blood meal (~2  $\mu$ L) from a person acutely infected with dengue virus
2. Virus replicates in the mosquito and disseminates to the salivary gland (8-10 days)
3. Mosquito takes secondary blood meal and sheds virus in saliva upon biting
4. Replication in exposed human and symptom onset (4-7 days after exposure)

## Sylvatic cycle

Transmission between NHPs and arboreal mosquito species

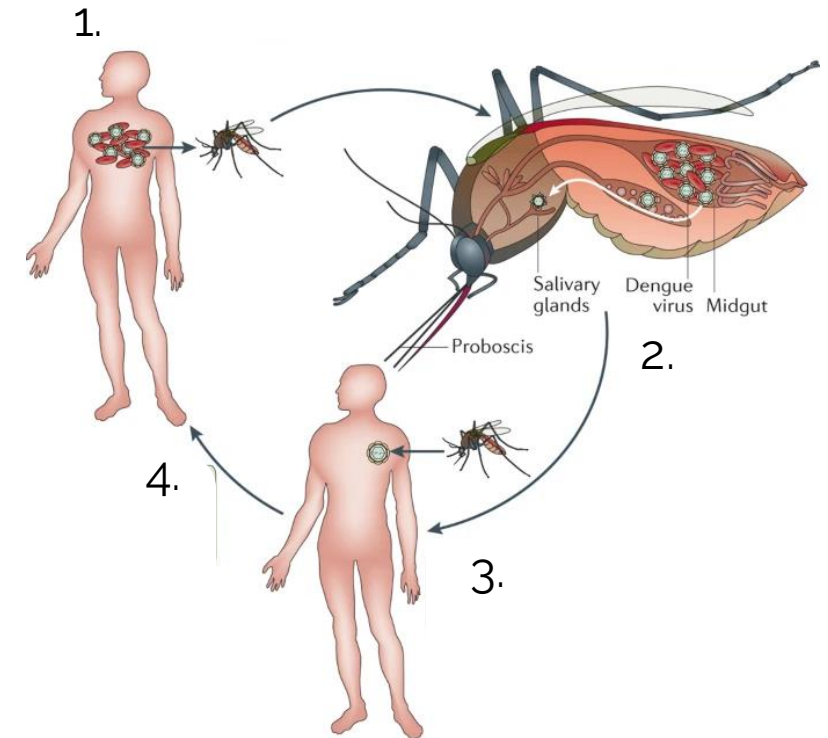
## Other methods of spread

### Humans

- Perinatal transmission from mother to baby
- Sexual contact

### Mosquitoes

- Transovarial transmission and survival





# Clinical features

Self-limiting febrile disease in the majority of cases

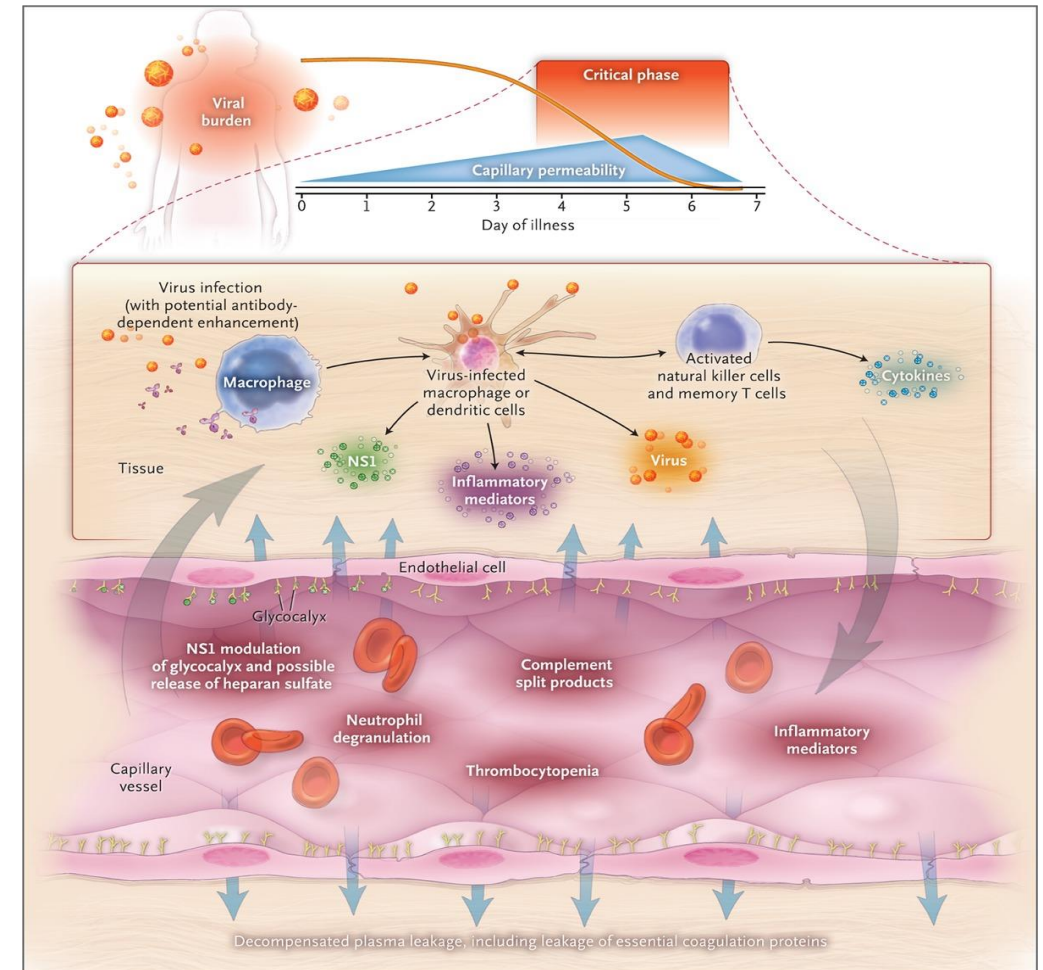
- Headache, vomiting, myalgia, joint pain and rash

Severe dengue develops in a minority of patients (< 1 %)

- Plasma leakage, dengue shock, severe bleeding and organ failure
- Increased risk of developing severe dengue on secondary infection

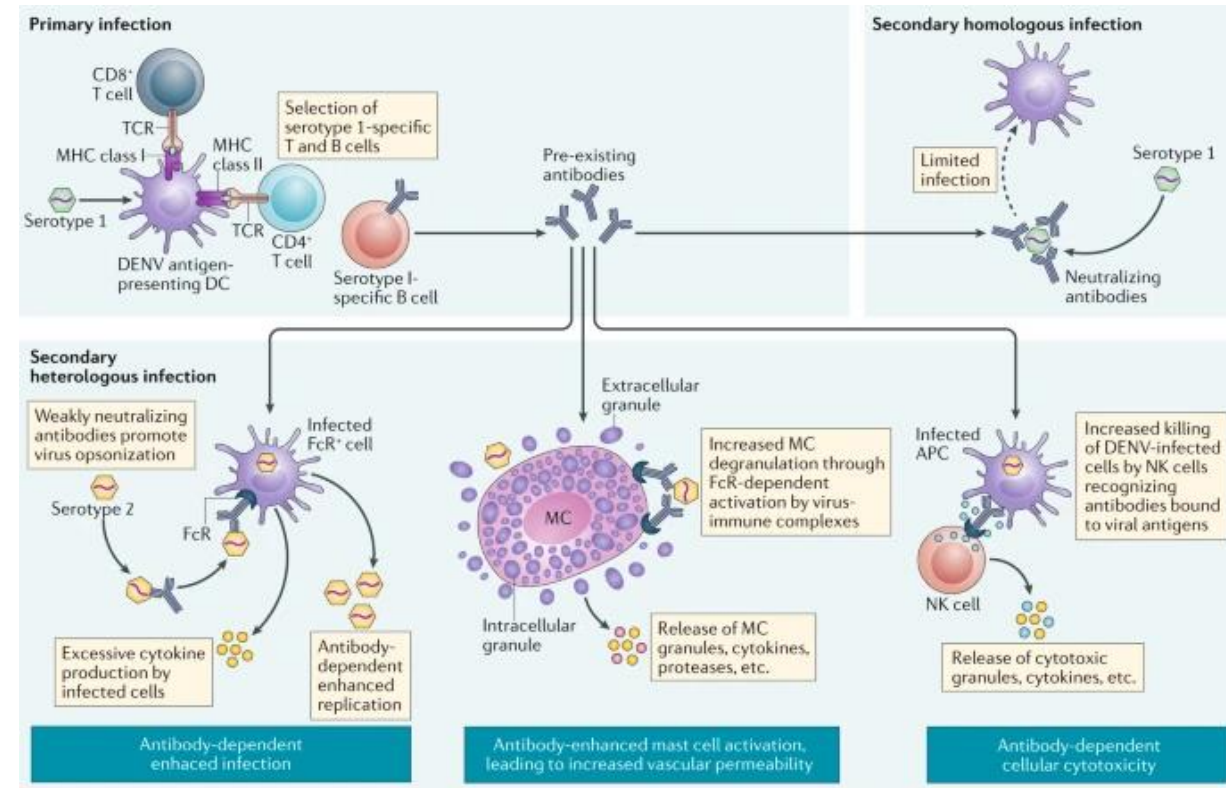
Treatment involves careful management of patients with signs of severe dengue in hospital

- by restoring plasma volume with fluid therapy
- costly for health-care systems



# Heterosubtypic infection and increased disease risk

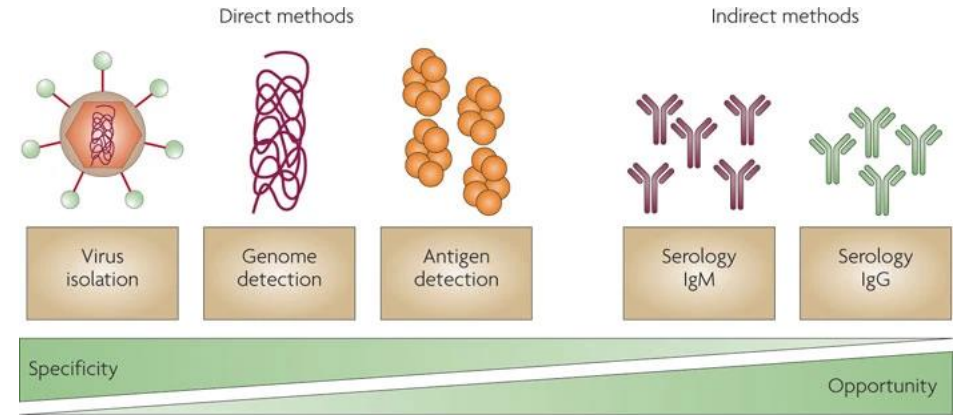
- There are four antigenically distinct types (serotypes) of dengue virus (DENV-1-4)
- Primary infection can induce lifelong immunity to the same dengue type
  - Antibodies (IgM and IgG) and T cells
- Primary infection or vaccination (if naïve - Dengvaxia) can induce cross-reactive antibodies that enhance disease upon sequential dengue infection with a different type
- Highlights the significance of serotype replacement



# Laboratory diagnosis

Serum, plasma or whole blood samples collected for laboratory diagnosis via:

- Direct methods – virus
  - Limited to viremic phase (within 10 days post symptom onset)
  - Genome detection – typing assays
- Indirect methods – serology
  - Cannot determine type – too much cross-reactivity
  - Paired sera ideal for diagnosis as IgM/IgG might indicate prior infection



- Genomics relevance:** PCR assay used can have implications for the sequencing pipeline used.
- Typing assay, then a type-specific amplicon panel and reference mapping is possible
  - Non-typing assay, then a pan-serotype method can be used for all sequences and reads mapped to several references (DengueSeq)

# Dengue virus particle

## Size

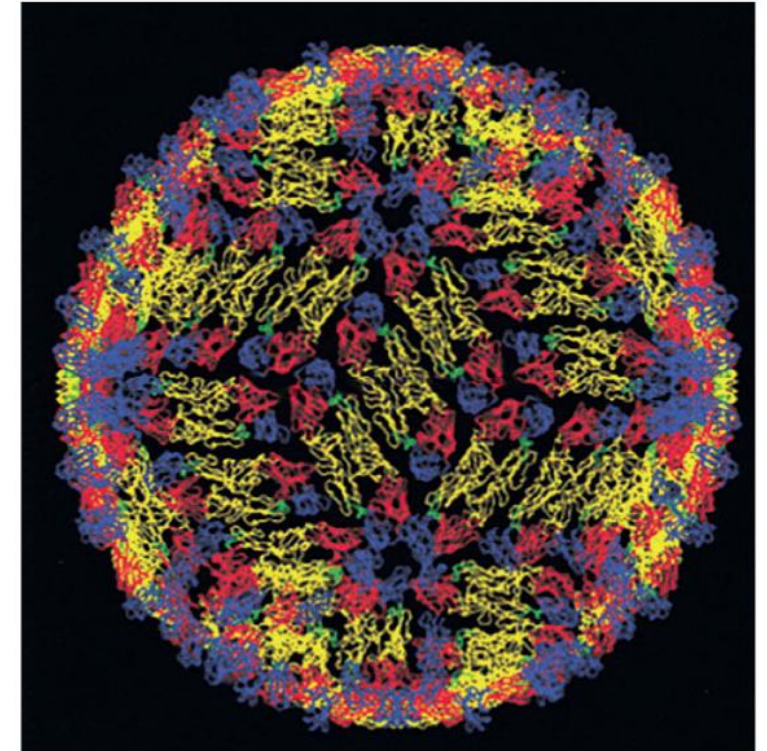
- 40-60nm

## Structural proteins

- Envelope (E)  
Attachment and uncoating
- Membrane (M)  
Virion maturation
- Capsid (C)  
Associated with viral RNA in the core

## Gen epi relevance:

E is the most commonly sequenced part of the genome and has been widely used to map the global footprint of dengue genotypes



Mature particle at neutral pH



# Genome organisation

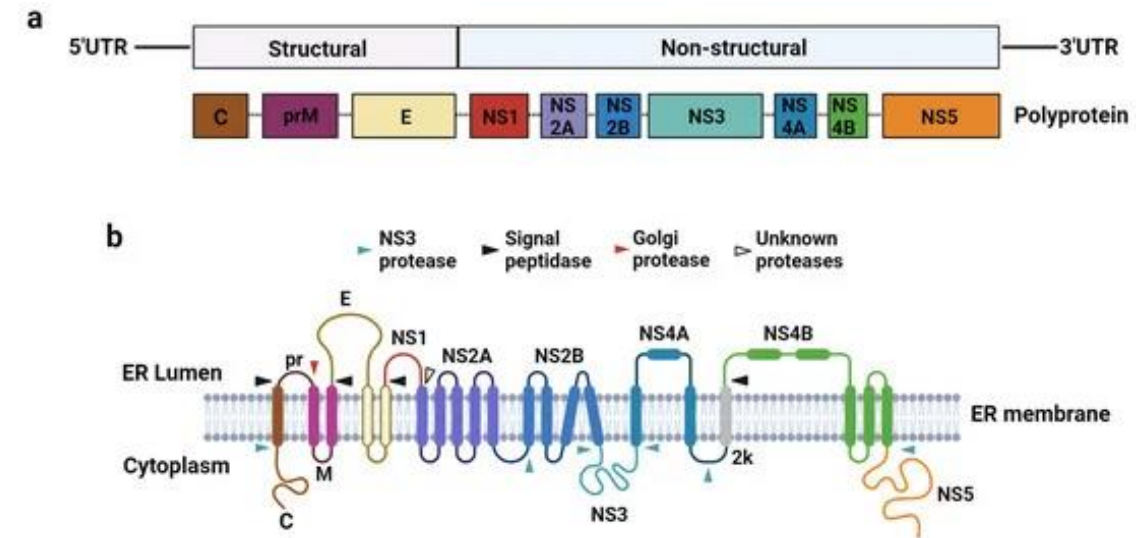
## *Flaviviridae*, orthoflavivirus

### +ssRNA genome (~11kb)

- m7GpppN (5') cap
- UTR – most diagnostic PCRs target the 3'UTR

### Genome encodes:

- 3 structural proteins (C, M, E)
- 7 non-structural proteins (NS1, NS2A+B, NS3, NS4A+B, NS5)
- Genome consists of a single ORF from which a long polyprotein is produced
- Polyprotein is cleaved after translation in the ER by viral and host proteases



**Gen epi relevance:** for communication purposes these are not technically genes i.e. not the E gene but sequence encoding the E protein.



# Genome classification and diversity



## Lineage classification system

Based on the PANGO nomenclature system for SARS-CoV-2

### Serotypes (1-4)

Serotype-specific differences in clinical manifestation

### Genotypes (I - VII)

Regional distribution

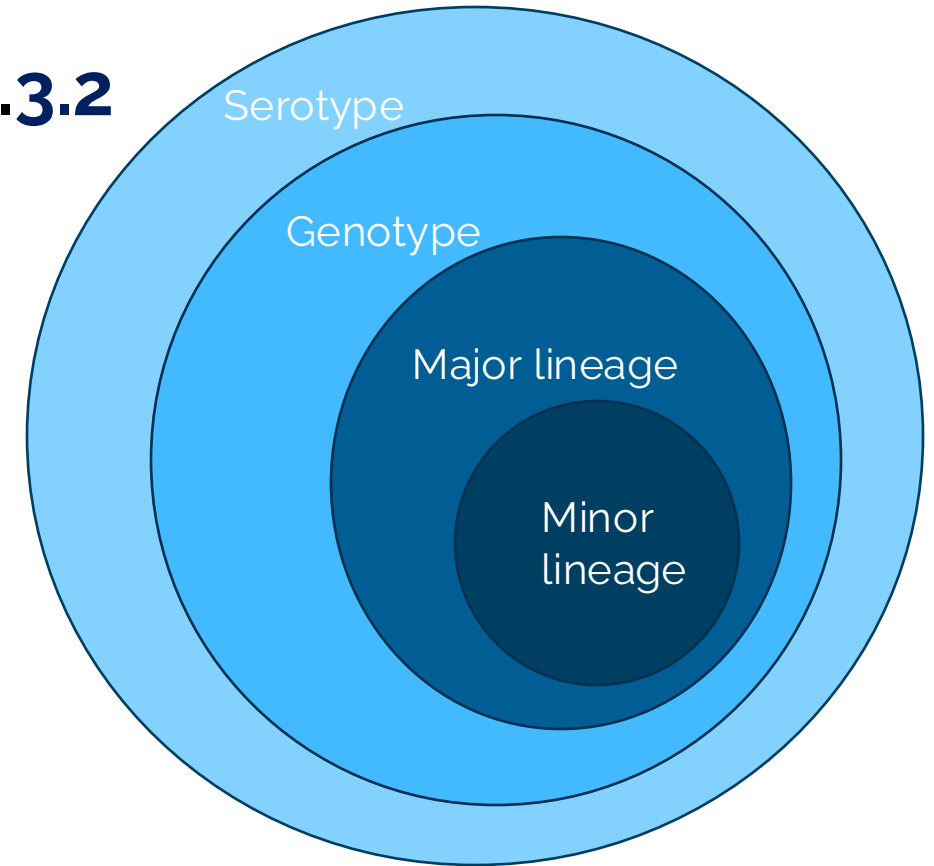
### Major lineages

Characterise regional and country-level trends in transmission dynamics

### Minor lineages

Characterise fine-scale trends in transmission dynamics

e.g. 3III\_B.3.2



**Gen epi relevance:** Having a structured classification system to describe genomic diversity enables characterization at different levels, for different epidemiological purposes and is an invaluable tool to interpret epidemiological signals using equitable terms

# Overview of steps in genome classification

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