1 Flaviviruses

Family: *Flaviviridae*

Single-stranded positive-sense RNA genome

'Flavi' - Yellow

Genus: 'Flavivirus'

Example Species: Zika, Dengue, Yellow Fever, West Nile

Aedes Aegypti & Aedes Albopictus

1.1 Characteristics of Flaviviruses

Linear, ssRNA positive-sense genome

~10 kb in size

Host species: Humans, mammals, insects

Transmission: vector-borne (mosquitoes)

Diseases: Hemorrhagic fever, encephalitis (brain inflammation)

Surface 'dimers' cover nearly entire virus

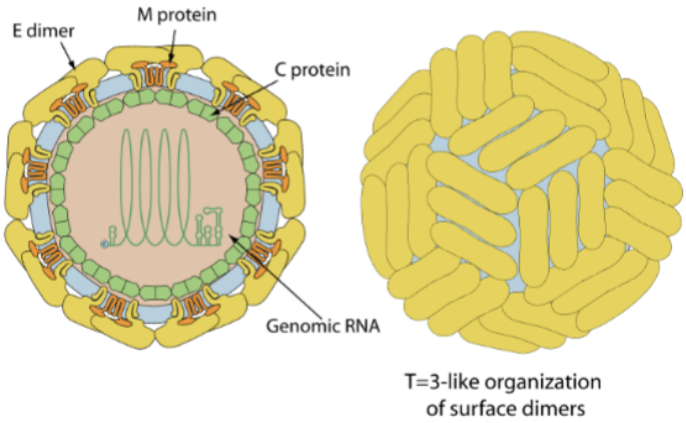

Figure 1: E protein: Target of antibody recognition

1.1.1 Genome

Long genomic polyprotein is cleaved by a viral protease (like polio)

Genomic RNA looks like host mRNA

2 Dengue Virus

2.1 Infection

Dengue infects both humans and mosquitoes

1. DENV replicates in people (4-7 day incubation) and infects mosquitoes
2. DENV replicates in the mosquito vector (8-10 day incubation period)
3. Mowquitoes transmit DENV to new people

Dengue viruses circulate in both human (urban) and primate (sylvatic) cycles

Aedes (human mosquito) sometimes transmits to monkeys

Haemagogus (primate mosquito) sometimes gets infected by humans

Virus is detected from research in mosquitos, not monkeys

2.2 Emergence

Dengue is a zoonotic spillover from infected primates

Figure 2: Primate Dengue is more closely related to human Dengue than other 3 serotypes of human Dengue

2.3 Disease Burden

~390 million total dengue infections annually

Geographical range of mosquito vectors has increased due to global connectivity and climate change

3/4 of Dengue infections are asymptomatic

Few get Dengue fever

Fewer get Dengue Hemorrhagic Fever

2.4 Pathogenesis

Dengue Disease:

High fever, nausia, vomiting, rash, aches and pains (eyes, joints, bones)

Self-limiting (most people recover without assistance)

Severe Dengue:

1:20 people get shock, internal bleeding, and death

3 Dengue Viruses: 4 Serotypes

Antibody responses to one serotype of DENV cross-react with the other serotypes

After first exposure, durable protection is provided to the particular serotype, with waning protection to other serotypes

3.1 Antibody-Dependent Enhancement

Occurs when antibodies generated during an immune response recognize and bind to a pathogen, but they are unable to prevent infection and instead enhance infection

3.1.1 Mechanism

FcGamma Receptors (FcgR) on many immune cells bind to antibodies

DENV can enter (infect) immune cells using the antibodies

DENV infection via this route may also result in aberrant cytokine secretion

3.1.2 Vaccine Development

Live attenuated DENV vaccine exists which includes all 4 DENV serotypes

Limitation: Vaccination acts as primary infection, leading to increased risk for ADE

Was, however, extremely protective in people who had already been previously infected

Vaccine does not induce cytolytic T cell responses

3.1.3 Mosquito Bacterium

Wolbachia naturally infects many mosquito species but not Aedes Aegypti

DENV transmission decreases in mosquitos with Wolbachia

4 Zika Virus

A DENV-like flavivirus that infects humans (significant immune cross-reactivity)

Typically mild (fever, rash, headaches, joint pain, etc.) or asymptomatic

Severe infections can occur in pregnant women

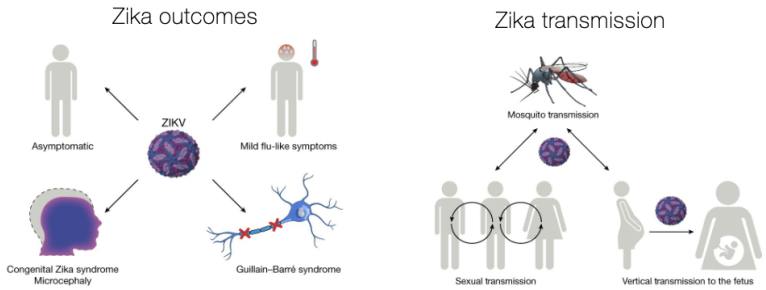

Figure 3: Sexual and vertical transmission (can infect placenta)

Zika antibodies can increase risk of DENV disease (cross-reactivity)

Many places around the globe can circulate DENV and ZIKV

However, very little Zika virus currently circulating globally