

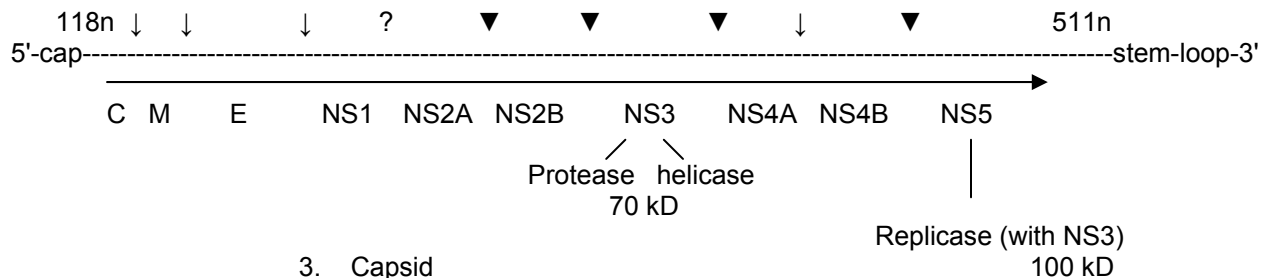
# Emerging viruses – The Flaviviruses

## Flaviridae

- I. Distinguishing Characteristics
  - A. Small, enveloped single stranded RNA virus
  - B. Structural proteins are clustered at the 5' end of the genome
  - C. Genome as mRNA makes a single polyprotein
  - D. Polyprotein is cleaved during post-translational processing
  - E. Prototype virus is yellow fever virus
  - F. Also associated with viral encephalitis and hemorrhagic fevers
  
- II. Structure (using yellow fever virus)
  - A. Size: 40-60 nm
  - B. Envelope: yes
    1. Glycoproteins:
      - Envelope protein, E - 50 kD
      - Envelope-associated, M - 8kD
    2. M protein may be found in two forms, depending upon the maturity of the virus. In immature virions a 165 amino acid, glycosylated pre-M (prM) protein forms a heterodimer with the E protein. In virion only the C-terminal region (90 amino acids) is retained in the membrane.
    3. Other proteins:
      - none
  - C. Nucleocapsid
    1. Nucleic Acid
      - Type: RNA
      - Stranded: Single
      - Polarity: +
      - Mol. Wt.: 10.5 kb
      - # Genes: approx.6-8
    2. Genetic (physical) map:
      - Yellow fever virus
      - 10,862 nucleotides

Baltimore Type: IV

↓ = Signal peptidase  
▼ = NS3 protease



3. Capsid
  - a. Symmetry: icosahedral, T=3
  - b. Capsomers: 180 C proteins - 13 kD (5x12 + 6x20 = 180)
  - c. Size: 40-60nm;
  - d. Matrix protein: M - 8 kD

### D. NS proteins are all associated with the membrane

NS1	50 kD glycoprotein	on cell surface and in medium
NS2A	21 kD	integral membrane protein
NS2B	15 kD	integral membrane - acts with NS3
NS3	70 kD	peripheral membrane protein Amino term protease C-terminal helicase (with NS5)
NS4A	15kD	integral membrane protein
NS4B	29 kD	integral membrane protein
NS5	100 kD	peripheral membrane - Replicase

III. Classification and Characteristic Members

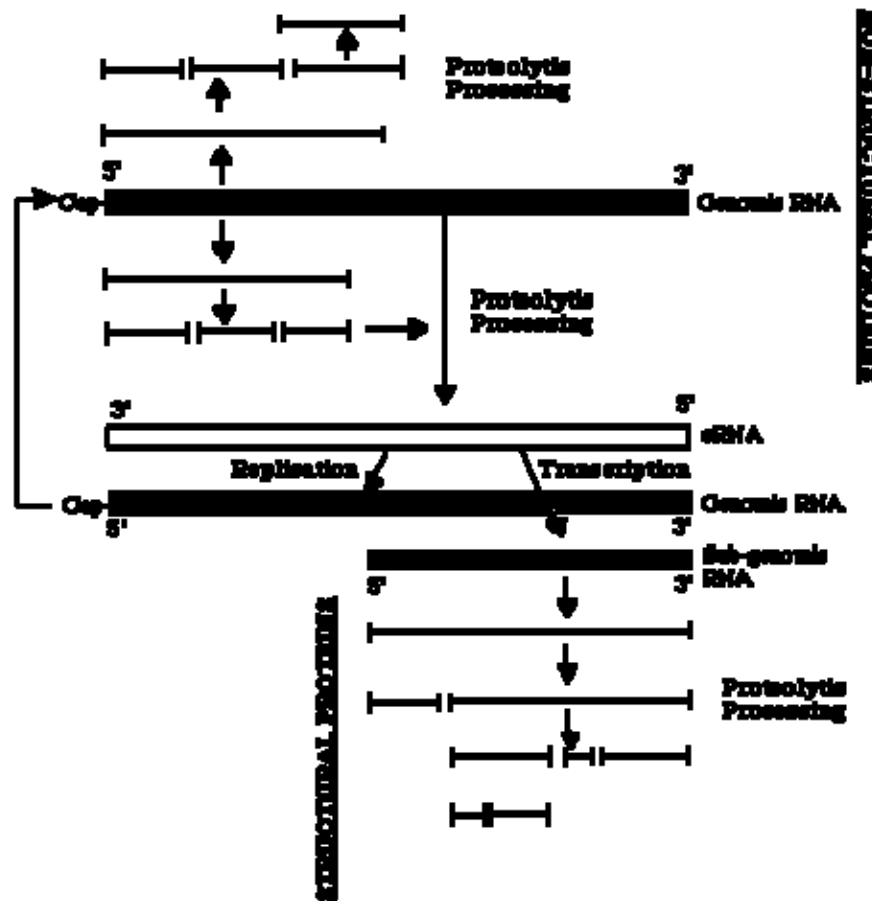
Genera	Properties	Members
Flavivirus	Many viruses, 9 serotypes, tick-borne, mosquito-borne, non-insect-borne	Yellow fever virus St Louis Encephalitis (SLE) West Nile virus Dengue virus 4 serotype
Pestivirus	Bovine viral diarrhea	2 serotypes
Hepacivirus	HCV	1 serotype (variable!)
Unclassified:	Hepatitis G virus	1 serotype

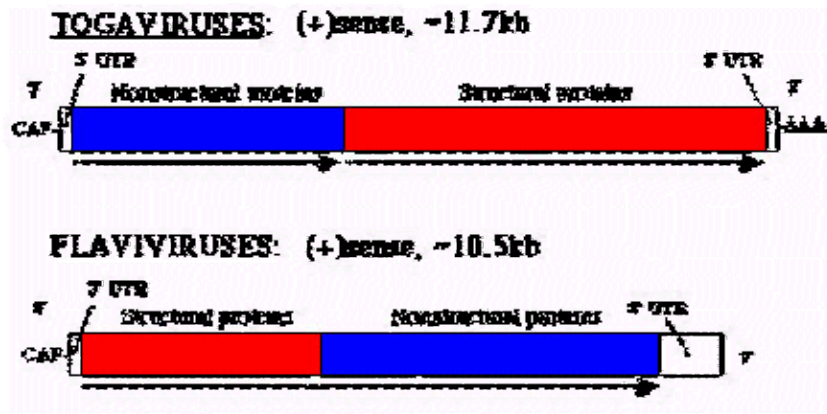
IV. Replication:

The initial stages of replication are similar to Togaviridae (occurring in cytoplasm), but there are significant differences:

1. The entire virus genome is translated as a single polyprotein, which is cleaved into the mature proteins
2. Complementary (-) strand RNA is synthesized by non-structural proteins, and is then used as a template for genomic progeny RNA synthesis.  
Assembly of the virion occurs during budding into cytoplasmic vacuoles. Release of the virion occurs at cell lysis.

The following figure gives the general mode of replication of togaviruses.





## V. Clinical Correlations

- A. Can survive for long periods in hosts such as ticks by replicating in them, and replicate in many insect and mammalian cell lines.
- B. Can produce a wide range of diseases such as fever, arthralgia, rash, hemorrhagic fever, and encephalitis.
- C. Outcome of infection is influenced by both virus and host-specific factors (age, sex, or genetic susceptibility).
- D. Yellow Fever was first recognized by Walter Reed in 1900 (Panama Canal) and is transmitted by mosquitoes.
- E. Primary multiplication is in lymph nodes; secondary multiplication occurs in liver (jaundice), spleen, kidneys, heart and bone marrow with much tissue damage. Very debilitating, mortality
- F. Vaccine: 17D - live attenuated vaccine strain is very effective and has eradicated Yellow Fever from USA.
- G. Dengue Fever is a major health problem worldwide (Asia, Africa and America). Transmitted by mosquitoes. There is no vaccine for humans.
- H. Hepatitis C fastest growing non-A/B viral hepatitis.

