

## Hemorrhagic Fever and Encephalitis and Rubella Viruses (Togaviridae and Flaviviridae)

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapters 33 and 72.

I. **Overview/Classification.** This group of Positive-Strand RNA viruses includes etiologic agents of rubella, encephalitis, hemorrhagic fever and hepatitis. Many of the viruses in these two families (*Togoviridae* and *Flaviviridae*) are arboviruses and spread by arthropod vectors.

A. *Togaviridae*. This family's name is derived from *toga* (cloak) referring to their enveloped virions. The viruses in this group include a number of agents of arthropod-borne encephalitis, as well as the agent that cause rubella (not arthropod borne). This family is subdivided into two genera:

1. *Alphavirus*

- a) Sindbis
- b) Semliki Forest
- c) Venezuelan equine encephalitis
- d) Eastern equine encephalitis
- e) Western equine encephalitis
- f) Chikungunya

2. *Rubivirus*

- a) Rubella virus (German Measles)

B. *Flaviviridae*. Viruses in this family cause diseases ranging from febrile illnesses, to life-threatening hemorrhagic fever, encephalitis and hepatitis. This family is subdivided into two genera:

1. *Flavivirus* includes mostly arthropod-borne viruses

- a) Dengue
- b) Yellow fever
- c) Japanese encephalitis
- d) West Nile encephalitis
- e) St. Louis encephalitis
- f) Russian spring-summer encephalitis
- g) Powassan encephalitis

2. *Hepatitis C*

- a) Hepatitis C virus (will be covered in the *RNA virus III: Hepatitis* Lecture)

## II. Biologic properties/virion structure/genome

A. Virion structure

- 1. *Togaviridae*: enveloped spherical virion; icosahedral capsid, 45-75 nm in diameter
- 2. *Flaviviridae*: enveloped spherical virion; icosahedral capsid, 40 – 50 nm.

B. Biologic properties

1. Virion stability
  - a. Heat labile
  - b. Easily inactivated by detergents and lipid solvents
- C. Genome structure
  1. *Togaviridae*:
    - a) Linear, plus sense ssRNA, 11 - 12 kb (Alphavirus); 10 kb (Rubivirus)
    - b) 5' end of genome is capped; polyadenylated at 3' end
    - c) Genome RNA is infectious
  2. *Flaviviridae*:
    - a) Linear, plus sense ssRNA, 10.5 - 11 kb (Flavivirus); 9.5 kb (Hepatitis C)
    - b) 5' end of genome is capped; 3' end not polyadenylated – a looped structure
    - c) Genome RNA is infectious
- D. Replication
  1. Adsorption and uncoating
  2. Virion RNA acts as mRNA and is translated into a polyprotein which is co-translationally cleaved (post-translational cleavage for *Togaviridae*) to yield non-structural (RNA dependent RNA polymerase) and structural proteins
  3. Cytoplasmic site of replication
  4. Genes for the structural and non-structural proteins are located differently in the two classes and transcription and protein processing different for toga- and flaviviruses.
  5. Bud through plasma membrane (togaviruses) or ER or Golgi (flaviviruses) to assemble

### III. Transmission cycles

- A. Vectors and hosts, sylvan and urban cycles

### IV. Diseases and Clinical Syndromes

- A. Influenza-like syndrome- fever, headache, malaise due to interferon induction common to all the viruses.
- B. Hepatitis, Hemorrhage, Shock
  1. Yellow fever and dengue cause hepatitis
  2. Dengue causes hemorrhagic fever (DHF) and shock (DSS)
  3. Non-neutralizing antibody to one serotype of dengue can cause enhanced infection and disease with another serotype via the Fc receptor on macrophages
- C. Encephalitis
  1. Small proportion of individuals infected (a few days after the onset of fever) may develop drowsiness, neck rigidity, progressing to confusion, paralysis, convulsions and coma
  2. Case-fatality rates average 10 – 20 % (higher in elderly)
  3. Survivors may be left with permanent neurologic sequelae such as mental retardation, epilepsy, paralysis, deafness, and blindness. West Nile 1999

#### D. Fever/Rash/Arthritis

1. Triad of fever/rash/arthritis is characteristic of Chikungunya, o'nyong-nyong, Ross River, Mayaro, and Sindbis viruses
2. Symptoms generally appear after 2-3 days incubation
  - a) fever, chills, myalgia
  - b) polyarthralgia mainly affecting small joints
  - c) maculopapular rash
3. Arthritis generally resolves in a few weeks, but may persist for months, or years in some cases.

#### V. Rubella

1. Caused by Rubella virus
2. Virus enters body via respiratory route
  - a) replicates asymptotically in URT
  - b) gains access to lymphatic system and subsequently enters bloodstream
3. 18 day incubation period; patients are infectious for 7 days before and after rash appears.
4. Mild disease with rash (in children and adults)
  - a) fine, pink, discrete macules of erythematous rash
  - b) appear first on face, then spread to the trunk and limbs
  - c) fade after 48 hours or less
5. Congenital rubella syndrome (CRS)
  - a) infection of fetus during first trimester of pregnancy
  - b) at least 20% of infants have severe birth defects
    - i. neurosensory deafness
    - ii. blindness (total or partial; cataracts are especially common)
    - iii. congenital heart disease
    - iv. microcephaly with mental retardation
  - c) other symptoms associated with CRS
    - i. bone translucency and retarded growth
    - ii. hepatosplenomegaly
  - d) 10 -20% of babies with CRS die within 1 year
  - e) 20 % will develop insulin dependent diabetes mellitus as young adults
  - f) CRS babies continue to shed Rubella virus from their throats for several months after birth and pose a serious risk to pregnant woman.

#### VI. Treatment/Vaccines/control measures

##### A. Encephalitis

1. Vaccines exist for a number of these viruses, but are used mainly for horses, at risk lab workers, and some fowl known to be intermediate hosts. Yellow fever live attenuated virus vaccine used for humans in endemic areas.
2. Control of mosquitoes is major countermeasure

##### B. Rubella

1. An effective live, attenuated vaccine is a component of the MMR vaccine
2. No evidence that vaccine is teratogenic, however
  - a) pregnant women are generally not immunized during first trimester
  - b) non-pregnant vaccinees should avoid pregnancy for 2 – 3 months