

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

Additional 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

(+) Stranded RNA Viruses II

Hemorrhagic Fever and Encephalitis and Rubella
(Togaviridae and Flaviviridae)

Togaviridae

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)

Flaviviridae

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

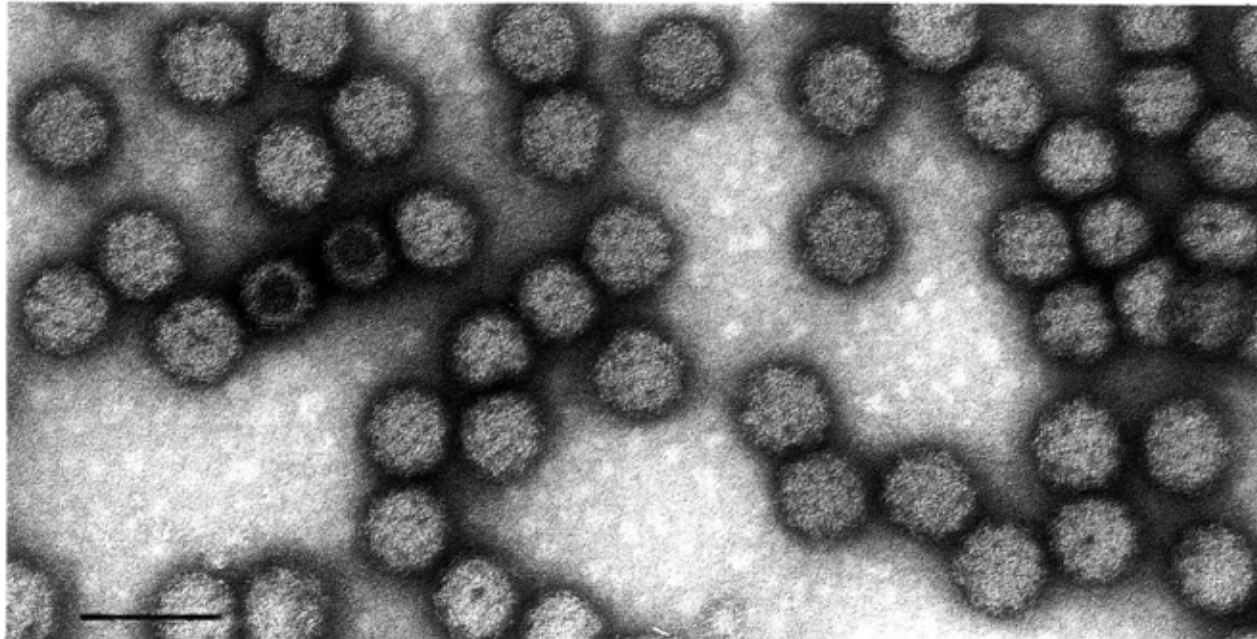
2. *Hepatitis C*
 - a) Hepatitis C virus

Virion structure

1. *Togaviridae*: enveloped spherical virion; icosahedral capsid, 45-75 nm in diameter
2. *Flaviviridae*: enveloped spherical virion; icosahedral capsid, 40 – 50 nm.
3. Heat labile and easily inactivated by detergents

Negatively Stained Virions of Semliki Forest Virus

Togaviridae, genus Alphavirus



Genome structure

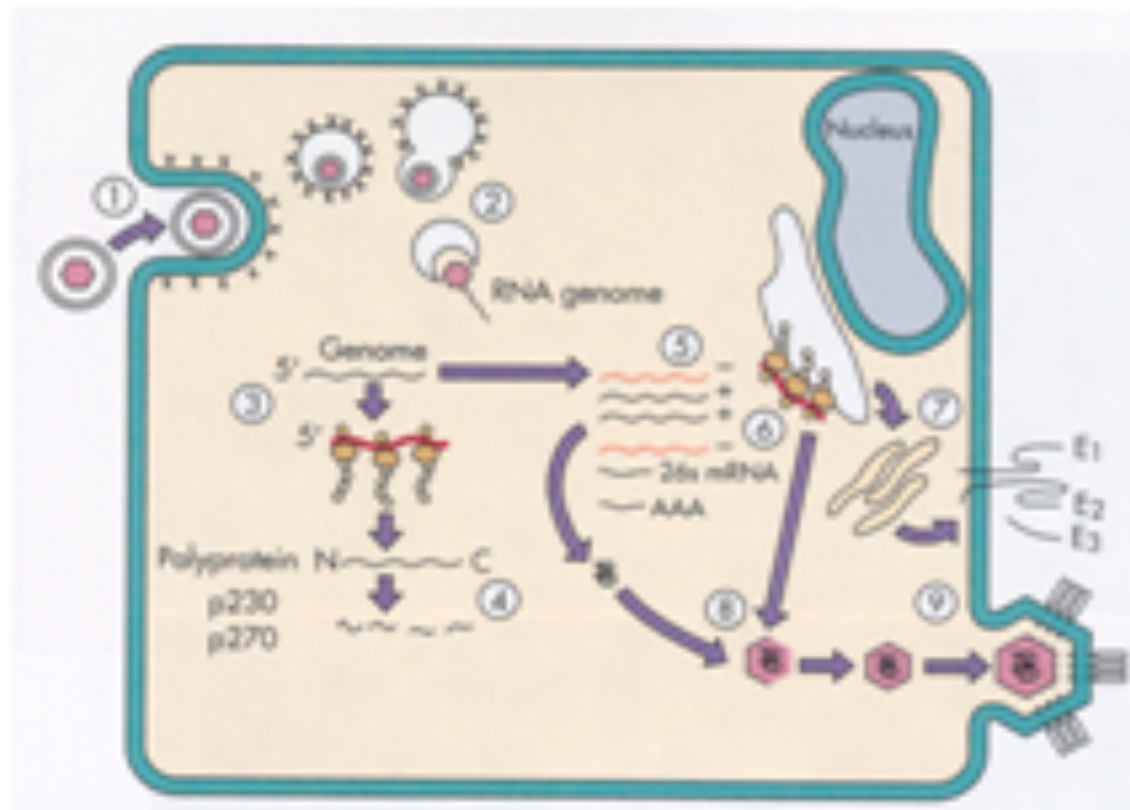
1. *Togaviridae*:

- 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

Fig. 63-2 Togavirus replication

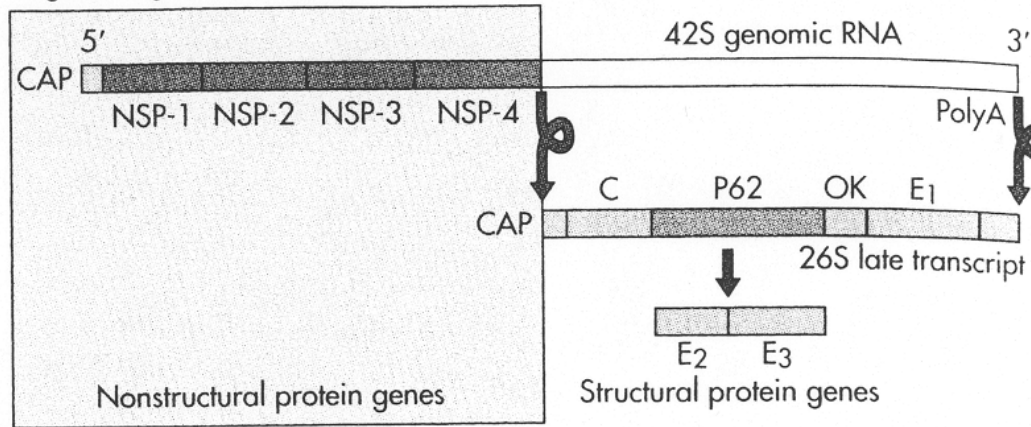


From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 63, published by Mosby Philadelphia,

Replication

1. 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.
2. Cytoplasmic site of replication.
3. Genes for the structural and non-structural proteins are located differently in the two virus classes.
4. Buds through plasma membrane (togavirus) or ER or Golgi (flavivirus).

Togavirus genome (Sindbis virus)



Flavivirus genome (Yellow fever virus)

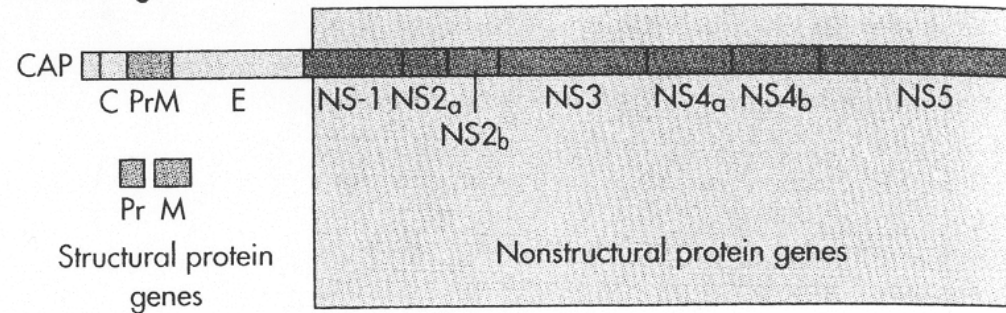


FIGURE 63–3. Comparison of the togavirus (alphavirus) and flavivirus genomes. *Alphavirus*: The enzymatic activities are translated from the 5′-end of the input genome, promoting their early rapid translation. The structural proteins are translated later from a smaller mRNA transcribed from the genomic template. *Flavivirus*: The genes for the structural proteins of the flaviviruses are at the 5′-end of the genome/mRNA, and only one species of polyprotein is made, which represents the entire genome. Poly A, polyadenylate. (Redrawn from Hahn CS et al: *Annu Rev Microbiol* 44:649-688, Copyright 1990 by Annual Reviews, www.AnnualReviews.org.)

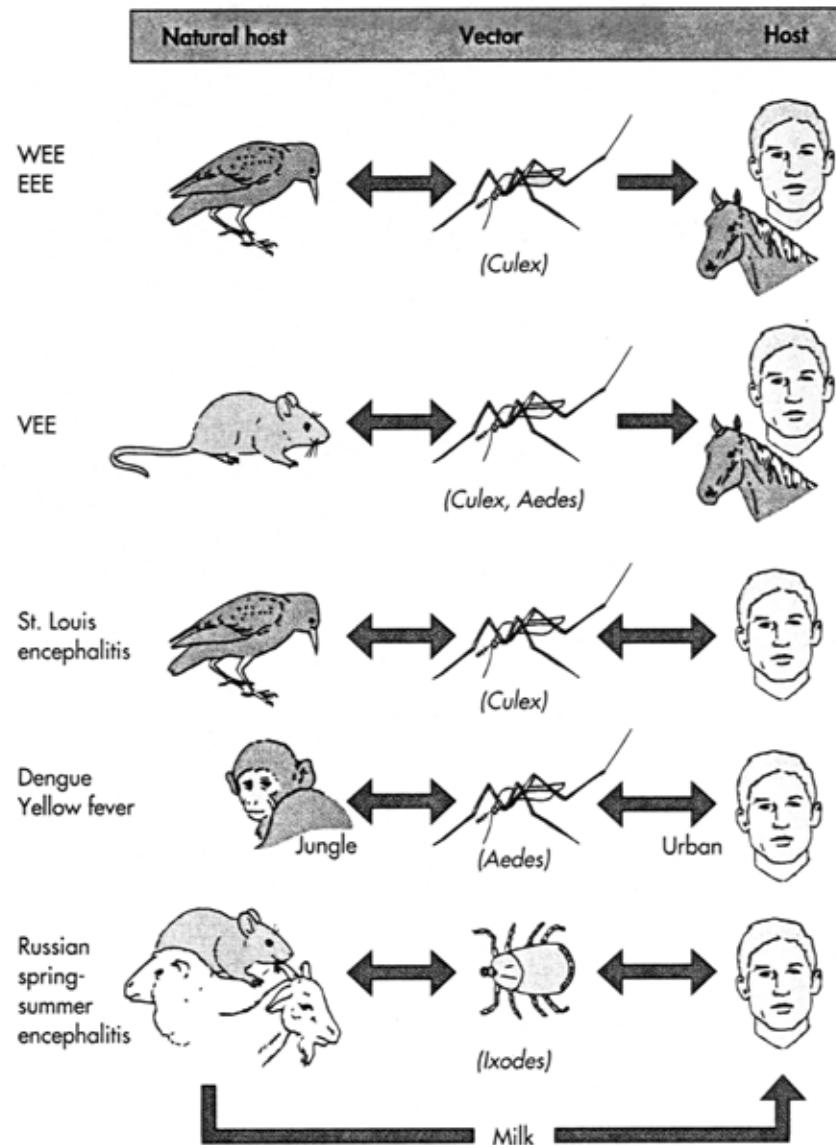
Arboviruses: Vectors, Hosts, and Diseases

TABLE 63-2 Arboviruses

DISEASE	VECTOR	HOST	DISTRIBUTION	DISEASE
ALPHAVIRUSES				
Sindbis*	<i>Aedes</i> and other mosquitoes	Birds	Africa, Australia, India	Subclinical
Semliki Forest*	<i>Aedes</i> and other mosquitoes	Birds	East and West Africa	Subclinical
Venezuelan equine encephalitis	<i>Aedes</i> , <i>Culex</i>	Rodents, horses	North, South, and Central America	Mild systemic; severe encephalitis
Eastern equine encephalitis	<i>Aedes</i> , <i>Culiseta</i>	Birds	North and South America, Caribbean	Mild systemic; encephalitis
Western equine encephalitis	<i>Culex</i> , <i>Culiseta</i>	Birds	North and South America	Mild systemic; encephalitis
Chikungunya	<i>Aedes</i>	Humans, monkeys	Africa, Asia	Fever, arthralgia, arthritis
FLAVIVIRUSES				
Dengue*	<i>Aedes</i>	Humans, monkeys	Worldwide, especially tropics	Mild systemic; break-bone fever, dengue hemorrhagic fever, and shock syndrome
Yellow fever*	<i>Aedes</i>	Humans, monkeys	Africa, South America	Hepatitis, hemorrhagic fever
Japanese encephalitis	<i>Culex</i>	Pigs, birds	Asia	Encephalitis
West Nile encephalitis	<i>Culex</i>	Birds	Africa, Europe, Central Asia	Fever, encephalitis, hepatitis
St. Louis encephalitis	<i>Culex</i>	Birds	North America	Encephalitis
Russian spring-summer encephalitis	<i>Ixodes</i> and <i>Derma-centor</i> ticks	Birds	Russia	Encephalitis
Powassan encephalitis	<i>Ixodes</i> ticks	Small mammals	North America	Encephalitis

*Prototypical viruses.

Fig. 63-5 Patterns of Alphavirus and Flavivirus Transmission



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Diseases of Togaviruses and Flaviviruses

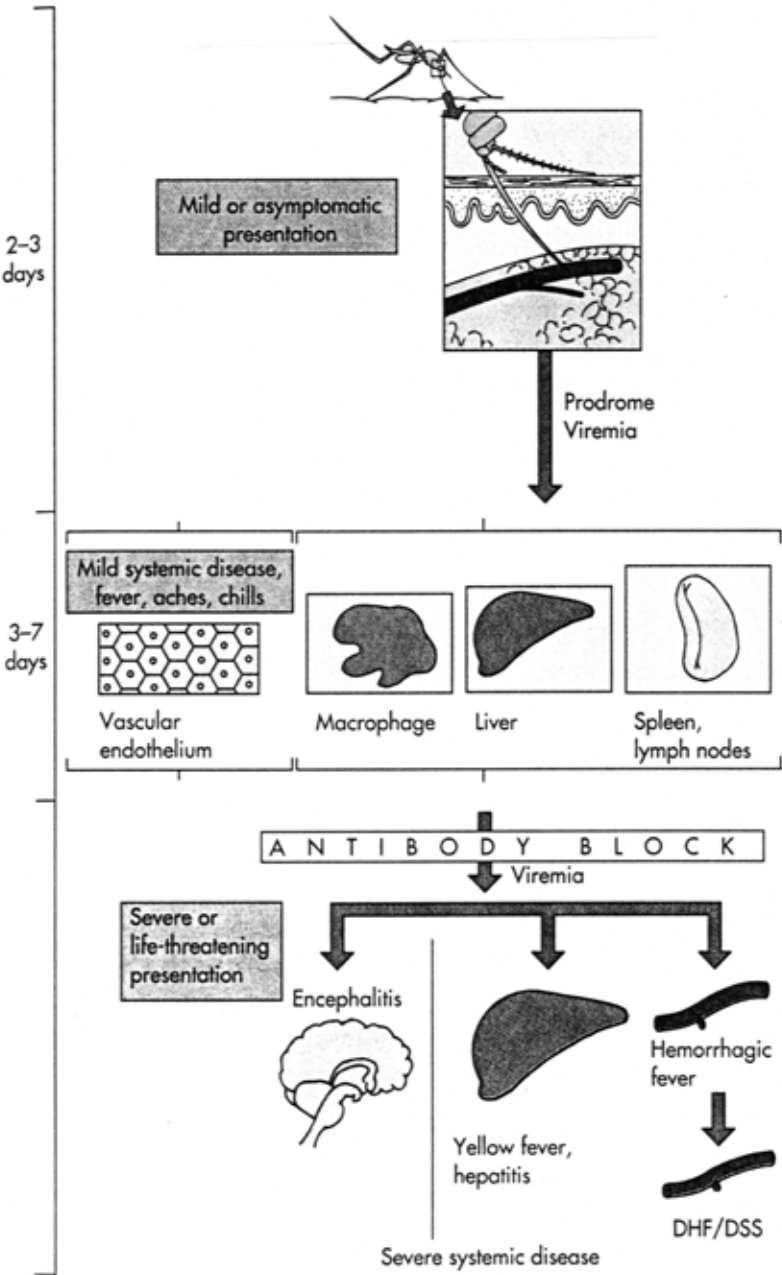
BOX 63-2 Disease Mechanisms of Togaviruses and Flaviviruses

Viruses are cytolytic, except for rubella.
 Viruses establish systemic infection and viremia.
 Viruses are good inducers of interferon, which can account for the influenza-like symptoms of infection.

Viruses, except rubella and hepatitis C, are arboviruses.
 Flaviviruses infect cells of the monocyte-macrophage lineage.
 Nonneutralizing antibody can enhance flavivirus infection via Fc receptors on the macrophage.

	INFLUENZA-LIKE SYNDROME	ENCEPHALITIS	HEPATITIS	HEMORRHAGE	SHOCK
Dengue	+		+	+	+
Yellow fever	+		+	+	+
St. Louis encephalitis	+	+			
Venezuelan encephalitis	+	+			
Western equine encephalitis	+	+			
Eastern equine encephalitis	+	+			
Japanese encephalitis	+	+			

Fig. 63-4 Disease Syndromes of the Alphaviruses and Flaviviruses



From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 63, published by Mosby Philadelphia,.,

Hepatitis, Hemorrhage, Shock

- 1. Dengue (4 serotypes) and yellow fever viruses- hepatitis**
- 2. Yellow fever characterized by severe systemic disease with degeneration of liver, kidney and heart- mortality rate 50% during epidemics**
- 3. Dengue major problem dengue fever- breakbone fever with high fever headache, rash, back and bone pain 6-7 days**
- 4. DHF/DSS in 0.25% of these DF cases**
- 5. Non-neutralizing Ab to one Dengue serotype causes more severe disease with infection of another serotype via Fc receptors on macrophages**

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.**

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.

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

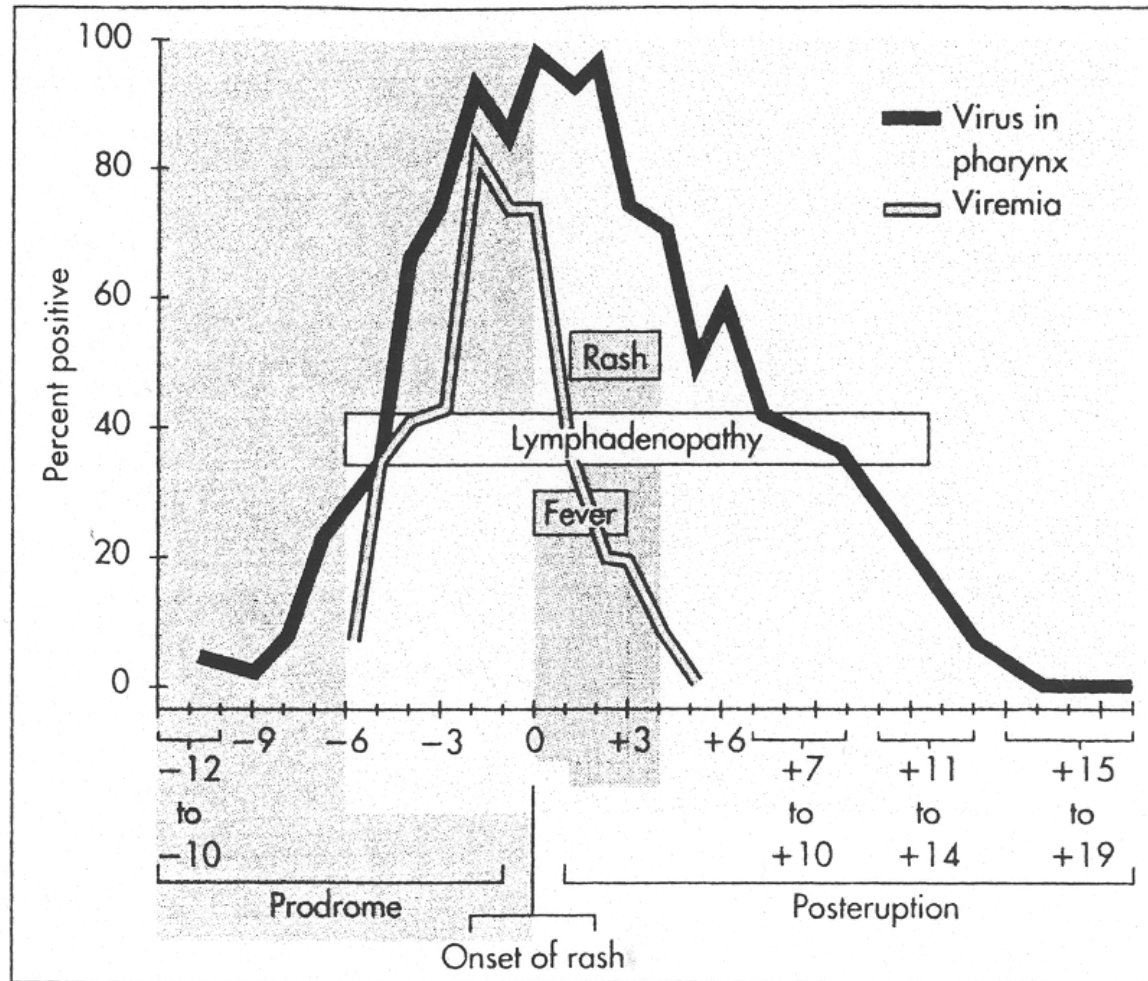


FIGURE 63-7. Time course of rubella disease. Rubella production in the pharynx precedes the appearance of symptoms and continues throughout the course of the disease. The onset of lymphadenopathy coincides with the viremia. Fever and rash occur later. The person is infectious as long as the virus is produced in the pharynx. (Redrawn from Plotkin SA: Rubella vaccine. In Plotkin SA, Mortimer EA, editors: *Vaccines*, Philadelphia, 1988, WB Saunders.)

Congenital Rubella Syndrome



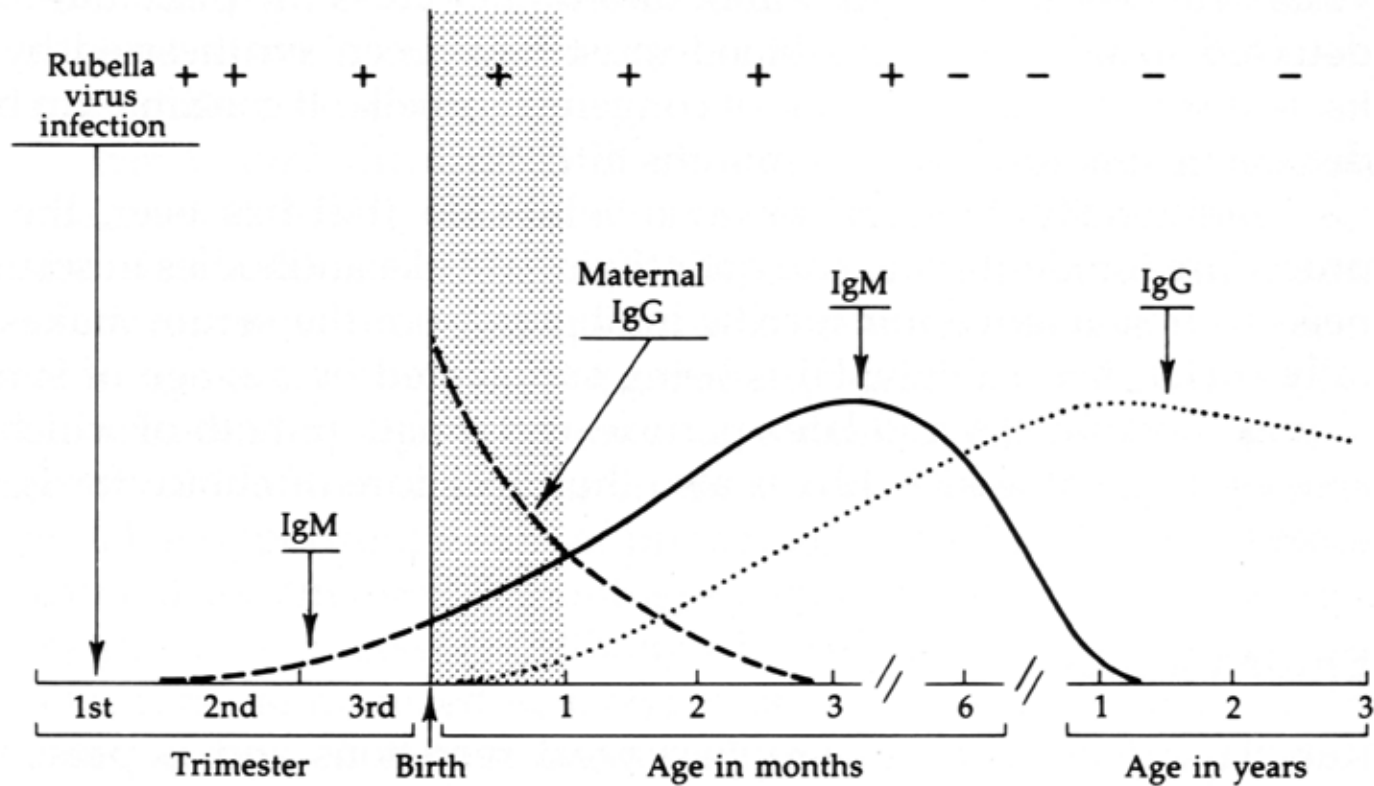
- **severe bilateral deafness**
- **severe bilateral visual defects**
 - **cataract**
 - **corneal opacity**

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
 - iii. Intrauterine growth retardation
- 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 up to a year after birth and pose a serious risk to pregnant women.**

Pattern of Viral Excretion and Infant's Antibody Response in Congenital Rubella

viral excretion (+)



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
2. Control of mosquitoes is major countermeasure.

B. Rubella

1. An effective live, attenuated vaccine (one serotype) is a component of the MMR vaccine. Serum antibody in mother prevents spread of virus to fetus.
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

C. Yellow Fever

1. Live attenuated virus vaccine. Used when going to endemic areas

Arboviruses

Structure

- Positive sense ssRNA genome, icosahedral nucleocapsid, enveloped

Pathogenesis

- Transmitted by bite of insect from host species; sylvan and urban cycles
- replication in cytoplasm; budding
- Viremia to target tissue
- Influenza-like initial symptoms; different viruses cause encephalitis, hemorrhagic fever, hepatitis, rash, arthritis

Diagnosis

- Serology and nucleic acid

Treatment/prevention

- No human vaccines except for Yellow Fever live attenuated vaccine, control of insect population

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West Nile encephalitis	<i>Culex</i>	Birds	Africa, Europe, Central Asia	Fever, encephalitis, hepatitis
St. Louis encephalitis	<i>Culex</i>	Birds	North America	Encephalitis
Russian spring-summer encephalitis	<i>Ixodes</i> and <i>Derma-centor</i> ticks	Birds	Russia	Encephalitis
Powassan encephalitis	<i>Ixodes</i> ticks	Small mammals	North America	Encephalitis

*Prototypical viruses.

Rubella virus

Structure

- Positive sense ssRNA genome, helical nucleocapsid, enveloped

Pathogenesis

- respiratory transmission
- replication in cytoplasm; budding
- Viremia
- Mild rash in adults; congenital rubella syndrome (CRS) after infection in first trimester when virus passes the placenta and infects fetus
- CRS- deafness, blindness, mental retardation

Diagnosis

- Nucleic acid, viral antigen detection

Treatment/prevention

- MMR live attenuated virus vaccine