A 5-year-old Indonesian girl died of hemorrhagic shock. The presence of dengue virus serotype 3 in her blood was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR).

1. How was the child infected with dengue virus?
2. What are the diseases caused by dengue virus?
3. What types of immune responses are protective? Potentially harmful?
4. Where is dengue prevalent? Why?

Answers to these questions are available on StudentConsult.com.

**TOGAVIRUSES AND FLAVIVIRUSES**

**Togaviruses**

**Trigger Words**

Arboviruses: mosquito, encephalitis
Rubella: German measles, congenital disease, rash, vaccine

**Biology, Virulence, and Disease**

- Small size, envelope surrounds icosahedral nucleocapsid, (+) RNA genome
- Encodes RNA-dependent RNA polymerase, replicates in cytoplasm
- Early and late mRNA and proteins produced
- Antibody can block disease
- Virus spreads in blood to neurons and brain
- Prodrome of flulike symptoms due to interferon and cytokine response
- Arboviruses: equine encephalitis viruses (WEE, EEE, VEE)

**Epidemiology**

- Arboviruses: Zoonosis
  - Reservoir in birds
  - Vectors are *Aedes* and *Culex* mosquitoes

**Rubella:**

Aerosol spread, only infects humans
Unvaccinated individuals at risk
Fetus at high risk

**Diagnosis**

- RT-PCR, ELISA

**Treatment, Prevention, and Control**

- Arboviruses: mosquito control
- Live attenuated rubella vaccine at 1 year of age in MMR; booster at 4-6 years

**Flaviviruses**

**Trigger Words**

Arboviruses: mosquito, encephalitis
Hepatitis C virus: see Chapter 55, Hepatitis Viruses

**Biology, Virulence, and Disease**

- Small size, envelope surrounds icosahedral nucleocapsid, (+) RNA genome
- Encodes RNA-dependent RNA polymerase, replicates in cytoplasm
- Neutralizing antibody can block disease
- Nonneutralizing antibody promotes dengue virus infection
- Virus spreads in blood to neurons and brain
- Prodrome of flulike symptoms due to interferon and cytokine response
- Arboviruses
- Encephalitis viruses: St. Louis, West Nile, Japanese encephalitis viruses
- Hemorrhagic disease: Yellow fever: jaundice, black vomit
  - Dengue: hemorrhagic fever, breakbone fever, dengue shock syndrome

**Epidemiology**

- Endemic to habitat of mosquito
- Arboviruses:
  - Zoonosis
  - Reservoir in birds
  - Vectors are *Aedes* or *Culex* mosquitoes

**Diagnosis**

- RT-PCR, ELISA

**Treatment, Prevention, and Control**

- Arboviruses: mosquito control
- Yellow fever virus: attenuated live vaccine
Answers
1. Dengue is a mosquito-borne virus.
2. Dengue hemorrhagic fever and dengue shock syndrome.
3. Neutralizing antibody is protective, but a nonneutralizing antibody can facilitate uptake into macrophages, where the virus replicates and travels throughout the body. In addition, immune responses are more intense and exacerbate inflammatory responses.
4. Dengue is prevalent where the *Aedes* mosquito vector is prevalent, in tropical regions of the world, including regions of the United States.
The members of the Togaviridae and Flaviridae families are enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses (Box 52-1). The Alphavirus genus of togaviruses and Flavivirus are discussed together because of similarities in the diseases they cause and in their epidemiology. Most are transmitted by arthropods and are therefore arboviruses (arthropod-borne viruses). They differ in size, morphology, gene sequence, and replication.

The Togaviridae (togaviruses) can be classified into the following major genera (Table 52-1): Alphavirus, Rubivirus, and Arterivirus. No known arteriviruses cause disease in humans, so this genus is not discussed further. Rubella virus is the only member of the Rubivirus group; it is discussed separately because its disease manifestation (German measles) and its means of spread differ from those of the alphaviruses. The Flaviridae include the flaviviruses, pestiviruses, and hepaciviruses (hepatitis C and G viruses). Hepatitis C and G are discussed in Chapter 55.

**Box 52-1 Unique Features of Togaviruses and Flaviruses**

- Viruses have enveloped, single-stranded, positive-sense RNA.
- Togavirus replication includes early (nonstructural) and late (structural) protein synthesis.
- Togaviruses replicate in the cytoplasm and bud at plasma membranes.
- Flaviviruses replicate in the cytoplasm and bud at intracellular membranes.

**Table 52-1 Togaviruses and Flaviruses**

<table>
<thead>
<tr>
<th>Virus Group</th>
<th>Human Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togaviruses</td>
<td></td>
</tr>
<tr>
<td>Alphavirus</td>
<td>Arboviruses</td>
</tr>
<tr>
<td>Rubivirus</td>
<td>Rubella virus</td>
</tr>
<tr>
<td>Arterivirus</td>
<td>None</td>
</tr>
<tr>
<td>Flaviviruses</td>
<td>Arboviruses</td>
</tr>
<tr>
<td>Hepacivirida</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>Pestivirus</td>
<td>None</td>
</tr>
</tbody>
</table>

**Alphaviruses and Flaviviruses**

Alphaviruses and flaviviruses are classified as arboviruses because they are usually spread by arthropod vectors. These viruses have a very broad host range, including vertebrates (e.g., mammals, birds, amphibians, reptiles) and invertebrates (e.g., mosquitoes, ticks). Diseases spread by animals or with an animal reservoir are called zoonoses. Examples of pathogenic alphaviruses and flaviviruses are listed in Table 52-2.

**Structure and Replication of Alphaviruses**

The alphaviruses have an icosahedral capsid and a positive-sense, single-strand RNA genome that resembles messenger RNA (mRNA). They are slightly larger than picornaviruses (45 to 75 nm in diameter) and are surrounded by an

**Table 52-2 Arboviruses**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Vector</th>
<th>Host</th>
<th>Distribution</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alphaviruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sindbis*</td>
<td>Aedes and other mosquitoes</td>
<td>Birds</td>
<td>Africa, Australia, India</td>
<td>Subclinical</td>
</tr>
<tr>
<td>Semliki Forest*</td>
<td>Aedes and other mosquitoes</td>
<td>Birds</td>
<td>East and West Africa</td>
<td>Subclinical</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Aedes, Culex</td>
<td>Rodents, horses</td>
<td>North, South, and Central America</td>
<td>Mild systemic; severe encephalitis</td>
</tr>
<tr>
<td>Eastern equine encephalitis</td>
<td>Aedes, Culex</td>
<td>Birds</td>
<td>North and South America, Caribbean</td>
<td>Mild systemic; encephalitis</td>
</tr>
<tr>
<td>Western equine encephalitis</td>
<td>Culex, Culex</td>
<td>Birds</td>
<td>North and South America</td>
<td>Mild systemic; encephalitis</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>Aedes</td>
<td>Humans, monkeys</td>
<td>Africa, Asia</td>
<td>Fever, arthralgia, arthritis</td>
</tr>
<tr>
<td><strong>Flaviviruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue*</td>
<td>Aedes</td>
<td>Humans, monkeys</td>
<td>Worldwide, especially tropics</td>
<td>Mild systemic; breakdown fever, dengue hemorrhagic fever, and dengue shock syndrome</td>
</tr>
<tr>
<td>Yellow fever*</td>
<td>Aedes</td>
<td>Humans, monkeys</td>
<td>Africa, South America</td>
<td>Hepatitis, hemorrhagic fever</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Culex</td>
<td>Pigs, birds</td>
<td>Asia</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>West Nile encephalitis</td>
<td>Culex</td>
<td>Birds</td>
<td>Africa, Europe, Central Asia, North America</td>
<td>Fever, encephalitis, hepatitis</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Culex</td>
<td>Birds</td>
<td>North America</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Russian spring-summer encephalitis</td>
<td>Ixodes and Dermacentor ticks</td>
<td>Birds</td>
<td>Russia</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Powassan encephalitis</td>
<td>Ixodes ticks</td>
<td>Small mammals</td>
<td>North America</td>
<td>Encephalitis</td>
</tr>
</tbody>
</table>

*Prototypical viruses.
envelope (Latin toga, "cloak"). The togavirus genome encodes early and late proteins.

Alphaviruses have two or three glycoproteins that associate to form a single spike. The carboxy (COOH) terminus of the glycoproteins is anchored in the capsid, forcing the envelope to wrap tightly ("shrink-wrap") and take on the shape of the capsid (Figure 52-1). The capsid proteins of all the alphaviruses are similar in structure and are antigenically cross-reactive. The viruses can be grouped (complexes) and also distinguished by different antigenic determinants on their envelope glycoproteins.

The alphaviruses attach to specific receptors expressed on many different cell types from many different species (Figure 52-2). The host range for these viruses includes vertebrates (e.g., humans, monkeys, horses, birds, reptiles, amphibians) and invertebrates (e.g., mosquitoes, ticks). However, the individual viruses have different tissue tropisms, accounting somewhat for the different disease presentations.

The virus enters the cell by means of receptor-mediated endocytosis (see Figure 52-2). The viral envelope then fuses with the membrane of the endosome on acidification of the vesicle to deliver the capsid and genome into the cytoplasm.

Once released into the cytoplasm, the alphavirus genomes bind to ribosomes as mRNA. The alphavirus genome is translated in early and late phases. The initial two thirds of the alphavirus RNA is translated into a polyprotein that is subsequently cleaved into four nonstructural early proteins (NSPs 1 through 4). The protease is part of the polyprotein and precedes the site of cleavage. Each of these proteins is a portion of the RNA-dependent RNA polymerase. The enzymes for replication of the genome assemble on a membrane scaffold, a full-length 42S negative-sense RNA is synthesized as a template for replication of the genome, and more 42S positive-sense mRNA is produced. In addition, a 26S late mRNA, corresponding to one third of the genome, is transcribed from the template. The 26S RNA encodes the capsid (C) and envelope (E1 through E3) proteins. Late in the replication cycle, viral mRNA can account for as much as 90% of the mRNA in the infected cell. The abundance of late mRNAs allows production of a large amount of the structural proteins required for packaging the virus.

The structural proteins are produced by protease cleavage of the late polyprotein that was produced from the 26S mRNA. The C protein is translated first and is cleaved from the polyprotein. A signal sequence is then made that associates the nascent polypeptide with the endoplasmic reticulum. Thereafter, envelope glycoproteins are translated, glycosylated, and cleaved from the remaining portion of the polyprotein to produce the E1, E2, and E3 glycoprotein.
spikes. The E3 is released from most alphavirus glycoprotein spikes. The glycoproteins are processed by the normal cellular machinery in the endoplasmic reticulum and Golgi apparatus and are also acetylated and acylated with long-chain fatty acids. Alphavirus glycoproteins are then transferred efficiently to the plasma membrane.

The C proteins associate with the genomic RNA soon after their synthesis and form an icosahedral capsid. Once this step is completed, the capsid associates with portions of the membrane expressing the viral glycoproteins. The alphavirus capsid has binding sites for the C-terminus of the glycoprotein spike, which pulls the envelope tightly around itself in a manner like shrink-wrapping (see Figures 52-1 and 52-2). Alphaviruses are released on budding from the plasma membrane.

Of interest, the western equine encephalitis virus (WEEV) was created by recombination of two alphaviruses, the eastern equine encephalitis virus (EEEV) and the Sindbis virus. The beginning of the WEEV genome is almost identical to EEEV, with similar glycoproteins and virulence genes, whereas the end of the genome resembles Sindbis.

**Structure and Replication of Flaviviruses**

The flaviviruses also have a positive-strand RNA genome, an icosahedral capsid, and an envelope but are slightly smaller than an alphavirus (40 to 65 nm in diameter). The E viral glycoprotein folds over, pairs up with another E glycoprotein, and lies flat across the surface of the virion to form an outer protein layer (see Figure 52-1). Most of the flaviviruses are antigenically related, and antibodies to one virus may neutralize another virus.

Attachment and penetration of the flaviviruses occur in the same way as described for the alphaviruses. Antibody can enhance infectivity and promote viral uptake into macrophages, monocytes, and other cells that have Fc receptors when the virus is coated with antibody. The major differences between alphaviruses and flaviviruses are in the organization of their genomes and their mechanisms of protein synthesis. The entire flavivirus genome is translated into a single polyprotein in a manner more similar to the process for picornaviruses than for alphaviruses (Figure 52-3). As a result, there is no temporal distinction in the translation of the different viral proteins. The polyprotein produced from the yellow fever genome contains five nonstructural proteins, including a protease and components of the RNA-dependent RNA polymerase, plus the capsid and envelope structural proteins.

Unlike in the alphavirus genome, the structural genes are at the 5′-end of the flavivirus genome. As a result, the portions of the polyprotein containing the structural (not the catalytic) proteins are synthesized first and with the greatest efficiency. This arrangement may allow production of more structural proteins, but it decreases the efficiency of nonstructural protein synthesis and the initiation of viral
replication. This feature of flaviviruses may contribute to the lag before detection of their replication.

The entire flavivirus polyprotein associates with the endoplasmic reticulum membrane and then is cleaved into its components. Unlike the togaviruses, the flaviviruses acquire their envelope by budding into the endoplasmic reticulum rather than at the cell surface. The virus is then released by exocytosis or cell lysis mechanisms. This route is less efficient, and the virus may remain cell associated.

**Pathogenesis and Immunity**

Because the arboviruses are acquired from the bite of an arthropod such as a mosquito, knowledge of the course of infection in both the vertebrate host and the invertebrate vector is important for an understanding of the diseases. These viruses can cause lytic or persistent infections of both vertebrate and invertebrate hosts (Box 52-2). Infections of invertebrates are usually persistent, with continued virus production.

The death of an infected cell results from a combination of virus-induced insults. The large amount of viral RNA produced on the replication and transcription of the genome blocks cellular mRNA from binding to ribosomes. Increased permeability of the target cell membrane and changes in ion concentrations can alter enzyme activities and favor the translation of viral mRNA over cellular mRNA. The displacement of cellular mRNA from the protein synthesis machinery prevents rebuilding and maintenance of the cell and is a major cause of the death of the virus-infected cell.

Female mosquitoes acquire the alphaviruses and flaviviruses by taking a blood meal from a **viremic vertebrate host**. A **sufficient viremia must be maintained in the vertebrate host to allow acquisition of the virus by the mosquito**. The virus then infects the epithelial cells of the midgut of the mosquito, spreads through the basal lamina of the midgut to the circulation, and infects the salivary glands. The virus sets up a persistent infection and replicates to high titers in these cells. The salivary glands can then release virus into the saliva. Not all arthropod species support this type of infection, however. For example, the normal vector for WEEV is the *Culex tarsalis* mosquito, but certain strains of virus are limited to the midgut of this mosquito, cannot infect its salivary glands, and therefore cannot be transmitted to humans.

On biting a host, the female mosquito regurgitates virus-containing saliva into the victim’s bloodstream. The virus then circulates freely in the host’s plasma and comes into contact with susceptible target cells, such as the endothelial cells of the capillaries, monocytes, dendritic cells, and macrophages.

The ultimate nature of alphavirus and flavivirus disease is determined by (1) the specific tissue tropisms of the individual virus type, (2) the concentration of infecting virus, and (3) individual responses to the infection. These viruses are associated with **mild systemic disease**, **encephalitis**, **arthrogenic disease**, or **hemorrhagic disease**.

The initial viremia produces systemic symptoms such as fever, chills, headaches, backaches, and other flulike symptoms within 3 to 7 days of infection. Most of these symptoms can be attributed to the effects of the interferon and other cytokines produced in response to the viremia and infection of host cells. Most viral infections do not progress beyond the mild systemic disease associated with viremia. A secondary viremia can produce sufficient virus to infect target organs (e.g., brain, liver, skin, vasculature), depending on the tissue tropism of the virus (Figure 52-4). The virus gains access to the brain by infecting the endothelial cells lining the small vessels of the brain or the choroid plexus. Hemorrhagic disease and shock, as for dengue virus, results from viral and immune-induced cytolysis of infected vascular endothelial cells exacerbated by extensive cytokine production (cytokine storm), which induces vascular leakage.

The primary target cells of the flaviviruses are of the monocyte-macrophage lineage. Although these cells are found throughout the body and may have different characteristics, they express Fc receptors for antibody and release cytokines on challenge. Flavivirus infection is enhanced 200- to 1000-fold by nonneutralizing antiviral antibody that promotes binding of the virus to the Fc receptors and its uptake into the cell.

**Immune Response**

Replication of the alphaviruses and flaviviruses produces a double-stranded RNA replicative intermediate that is a good inducer of interferon (IFN)-α and IFN-β. The interferon limits replication of the virus and is also released into the bloodstream to stimulate innate and immune responses.

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**Box 52-2 Disease Mechanisms of Togaviruses and Flaviviruses**

Viruses are cytolytic, except for rubella and hepatitis C.
Viruses establish viremia and systemic infection.
Viruses are good inducers of interferon and cytokines, which can account for the flulike symptoms during prodrome.
Viruses, except rubella and hepatitis C, are arboviruses.
Flaviviruses can infect cells of the monocyte-macrophage lineage. Nonneutralizing antibody can enhance flavivirus infection via Fc receptors on cells.

<table>
<thead>
<tr>
<th>Flulike Syndrome</th>
<th>Encephalitis</th>
<th>Hepatitis</th>
<th>Hemorrhage</th>
<th>Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Nile encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venezuelan encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western equine encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern equine encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interferon and other cytokines are produced following infection of plasmacytoid dendritic and other cells in blood, causing rapid onset of the flulike symptoms characteristic of mild systemic disease.

Circulating immunoglobulin (Ig)M is produced within 6 days of infection, followed by production of IgG. Antibody to the viral attachment protein blocks viremic spread of the virus and subsequent infection of other tissues. Through recognition of the type-common antigens expressed on all viruses in the family, immunity to one flavivirus can provide some protection against infection with other flaviviruses. Cell-mediated immunity is also important in controlling the primary infection.

Immunity to these viruses is a double-edged sword. Inflammation resulting from the cell-mediated immune response can destroy tissues and significantly contribute to the pathogenesis of encephalitis. Hypersensitivity reactions (initiated by formation of immune complexes with virions and viral antigens) and the activation of complement can cause arthritides and contribute to hemorrhagic symptoms. An antibody to another flavivirus that does not neutralize the virus can enhance the uptake of flaviviruses into macrophages and other cells that express Fc receptors. Immune responses to a related strain of dengue virus that do not prevent infection can exacerbate immunopathogenesis, leading to dengue hemorrhagic fever or dengue shock syndrome.

**Epidemiology**

Alphaviruses and most flaviviruses are prototypical arboviruses (Box 52-3). To be an arbovirus, the virus must be able to (1) infect both vertebrates and invertebrates, (2) initiate a sufficient viremia in a vertebrate host for a sufficient time to allow acquisition of the virus by the invertebrate vector, and (3) initiate a persistent productive infection of the salivary gland of the invertebrate to provide virus for the infection of other host animals. **Humans are usually “dead-end” hosts** in that they cannot spread the virus back to the vector because they do not maintain a persistent viremia. If the virus is not in the blood, the mosquito cannot acquire it. A full cycle of infection occurs when the virus is transmitted by the arthropod vector and amplified in a susceptible, immunologically naïve host (reservoir), allowing reinfection of other arthropods (Figure 52-5). The vectors, natural hosts, and geographic distribution of representative alphaviruses and flaviviruses are listed in Table 52-2.

These viruses are usually restricted to a specific arthropod vector, its vertebrate host, and their ecologic niche. The most
common vector is the mosquito, but ticks and sandflies spread some arboviruses. Even in a tropical region overrun with mosquitoes, spread of these viruses is still restricted to a specific genus of mosquitoes. Not all arthropods can act as good vectors for each virus. For example, Culex quinquefasciatus is resistant to infection by WEEV (alphavirus) but is an excellent vector for St. Louis encephalitis virus (flavivirus).

Birds and small mammals are the usual reservoir hosts for the alphaviruses and flaviviruses, but reptiles and amphibians can also act as hosts. A large population of viremic animals can develop in these species to continue the infection cycle of the virus. For example, West Nile encephalitis virus (WNV) was first noted in 1999 as an outbreak in New York by the unusual deaths of captive birds at the Bronx Zoo. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis identified the virus as WNV. The virus is transmitted by Culex pipiens mosquitoes, and crows, blue jays, and other wild birds are the reservoir. The virus spread throughout the United States, and by 2006, the virus and human disease had been noted in almost every state. WNV establishes a sufficient viremia in humans to be a risk factor for transmission through blood transfusions. Documentation of two such cases has led to screening blood donors for WNV and rejecting donors who have fever and headache during the week of blood donation.

Arbovirus diseases occur during the summer months and rainy seasons, when the arthropods breed, and the arboviruses are cycled among a host reservoir (birds), an arthropod (e.g., mosquitoes), and human hosts. This cycle maintains and increases the amount of virus in the environment. In the winter, the vector is not present to maintain the virus. The virus may either (1) persist in arthropod larvae or eggs or in reptiles or amphibians that remain in the locale or (2) migrate with the birds and then return during the summer.

When humans travel into the ecologic niche of the mosquito vector, they risk being infected by the virus. Pools of standing water, drainage ditches, and trash dumps in cities can also provide breeding grounds for mosquitoes such as Aedes aegypti, the vector for yellow fever, dengue, and chikungunya viruses. An increase in the population of these mosquitoes, as has occurred in the United States, puts the human population at risk for infection. Health departments in many areas monitor birds and mosquitoes caught in traps for arboviruses and initiate control measures such as insecticide spraying when necessary.

Urban outbreaks of arbovirus infections occur when the reservoirs for the virus are humans or urban animals. Humans can be reservoir hosts for yellow fever, dengue, and chikungunya viruses (see Figure 52-5). These viruses are maintained by Aedes mosquitoes in a sylvatic or jungle cycle, in which monkeys are the natural host, and also in an urban cycle, in which humans are the host. A. aegypti, a vector for each of these viruses, is a household mosquito. It breeds in pools of water, open sewers, and other accumulations of water in cities. St. Louis encephalitis and WNV are maintained in an urban environment because their vectors, Culex mosquitoes, breed in stagnant water, including puddles and sewage, and the reservoir group includes common city birds (e.g., crows). A large number of inapparent infections accompanies the incidence or an outbreak of arbovirus encephalitis.

**Clinical Syndromes**

More humans are infected with alphaviruses and flaviviruses than show significant characteristic symptoms. The incidence of arbovirus disease is sporadic. Alphavirus infections are usually asymptomatic or cause low-grade disease such as flulike symptoms (chills, fever, rash, aches) that correlate with systemic infection during the initial viremia. EEEV, WEEV, and Venezuelan equine encephalitis virus (VEEV) infections can progress to encephalitis in humans. The equine encephalitis viruses are usually more of a problem to livestock than to humans. An affected human may experience fever, headache, and decreased consciousness 3 to 10 days after infection. Unlike herpes simplex virus encephalitis, the disease generally resolves without significant sequelae, but there is the possibility of paralysis, mental disability, seizures, and death. The name chikungunya (Swahili for “that which bends up”) refers to the crippling arthritis associated with serious disease caused by infection with these viruses. Like dengue virus, chikungunya virus is spread by A. aegypti, but a recently developed mutant virus can be spread by A. albopictus (the Asian tiger mosquito). The
incidence of chikungunya has greatly increased since 2000. This disease is prevalent from western Africa across southern Asia to the Philippines and in South America and has spread to the Caribbean Islands and United States because of the return of the *A. aegypti* mosquito, its vector.

Most flavivirus infections are relatively benign, but serious *aseptic meningitis* and *encephalitic or hemorrhagic disease* can occur. The encephalitis viruses include *St. Louis, West Nile*, Japanese, Murray Valley, and Russian spring-summer viruses. Symptoms and outcomes are similar to those of the togavirus encephalitides. Hundreds to thousands of cases of St. Louis encephalitis virus disease are noted in the United States annually. Approximately 20% of individuals infected with WNV will develop West Nile fever, characterized by fever, headache, tiredness, and body aches, occasionally with a rash on the trunk of the body and swollen lymph glands usually lasting only a few days (*Clinical Case 52-1*).

Encephalitis, meningitis, or meningoencephalitis occurs in approximately 1% of WNV-infected individuals. Individuals older than 50 years and the immunocompromised are at higher risk for serious disease.

The hemorrhagic viruses are dengue and yellow fever viruses. *Dengue virus* is a major worldwide problem, with at least 100 million cases of dengue fever and 300,000 cases of *dengue hemorrhagic fever* (DHF) occurring per year. The virus and its vector are present in central and northern South America, and cases have occurred in Puerto Rico, Texas, and Florida. The incidence of the more serious DHF has quadrupled since 1985. Dengue fever is also known as *breakbone fever*; the symptoms and signs consist of high fever, headache, rash, and back and bone pain that last 6 to 7 days.

On rechallenge with another of the four related strains, dengue can also cause DHF and *dengue shock syndrome* (DSS). Nonneutralizing antibody promotes uptake of the virus into macrophages, which causes memory T cells to become activated, release cytokines, and initiate inflammatory reactions. These reactions and the virus result in weakening and rupture of the vasculature, internal bleeding, and loss of plasma, leading to shock symptoms and internal bleeding. In 1981 in Cuba, dengue-2 virus infected a population previously exposed to dengue-1 virus between 1977 and 1980, leading to an epidemic of more than 100,000 cases of DHF/DSS and 168 deaths.

*Yellow fever* infections are characterized by severe systemic disease, with degeneration of the liver, kidney, and heart, as well as hemorrhage. Liver involvement causes the jaundice from which the disease gets its name, but massive gastrointestinal hemorrhages (“black vomit”) may also occur. The mortality rate associated with yellow fever during epidemics is as high as 50%.

### Laboratory Diagnosis

Detection and characterization of the alphaviruses and flaviviruses is now performed by RT-PCR testing of viral mRNA in blood or other samples. Monoclonal antibodies to the individual viruses have become a useful tool for distinguishing the individual species and strains of viruses. The alphaviruses and flaviviruses can be grown in both vertebrate and mosquito cell lines, but most are difficult to isolate. A variety of serologic methods can be used to diagnose infections, but the serologic cross-reactivity among viruses limits distinction of the actual viral species in many cases.

### Treatment, Prevention, and Control

No treatments exist for arbovirus diseases, other than supportive care. *The easiest means of preventing the spread of any arbovirus is elimination of its vector and breeding grounds.* After 1900, when Walter Reed and his colleagues discovered that yellow fever was spread by *A. aegypti*, the number of cases was reduced from 1400 to none within 2 years, purely through control of the mosquito population. Many public health departments monitor bird and mosquito populations in a region for arboviruses and periodically spray to reduce the mosquito population. Avoidance of the breeding grounds of a mosquito vector is also a good preventive measure.

A live vaccine against yellow fever virus and killed vaccines against EEEV, WEEV, Japanese encephalitis virus, and Russian spring-summer encephalitis virus are available. A live Japanese encephalitis virus vaccine is used in China. These vaccines are meant for people working with the virus or at risk for contact. A live vaccine against WEEV is available but only for use in domestic animals. Vaccines consisting of all four strains of dengue virus are being developed to ensure that immune enhancement of the disease on subsequent challenge does not occur. An interesting approach to the dengue virus vaccine consists of chimeric viruses in which the glycoprotein and other genes for each of the other dengue
rubella virus has the same structural properties and mode of replication as the other togaviruses. However, unlike the other togaviruses, rubella is a respiratory virus and does not cause readily detectable cytopathologic effects.

Rubella is one of the five classic childhood exanthems, along with measles, roseola, fifth disease, and chickenpox. Rubella, meaning "little red" in Latin, was first distinguished from measles and other exanthems by German physicians; thus the common name for the disease, German measles. In 1941, an astute Australian ophthalmologist, Norman McAlister Gregg, recognized that maternal rubella infection was the cause of congenital cataracts. Maternal rubella infection has since been correlated with several other severe congenital defects. This finding prompted the development of a unique program to vaccinate children to prevent infection of pregnant women and neonates.

Pathogenesis and Immunity
Rubella virus is not cytolytic, but the replication of rubella prevents (in a process known as heterologous interference) the replication of superinfecting picornaviruses. This property allowed the first isolations of rubella virus in 1962.

Rubella infects the upper respiratory tract and then spreads to local lymph nodes, which coincides with a period of lymphadenopathy (Figure 52-6). This stage is followed by establishment of viremia, which spreads the virus throughout the body. Infection of other tissues and the characteristic mild rash occur. The prodromal period lasts approximately 2 weeks (Figure 52-7). The infected person can shed virus in respiratory droplets during the prodromal period and for as long as 2 weeks after the onset of the rash.

Immune Response
Antibody is generated after the viremia, and its appearance correlates with the appearance of the rash. The antibody limits viremic spread, but cell-mediated immunity plays an important role in resolving the infection. Only one serotype of rubella exists, and natural infection produces lifelong protective immunity. Most important, serum antibody in a pregnant woman prevents spread of the virus to the fetus. Immune complexes most likely cause the rash and arthralgia associated with rubella infection.

Congenital Infection
Rubella infection in a pregnant woman can result in serious congenital abnormalities in the child. If the mother does not have antibody, the virus can replicate in the placenta and spread to the fetal blood supply and throughout the fetus. Rubella can replicate in most tissues of the fetus. The virus may not be cytolytic, but the normal growth, mitosis, and chromosomal structure of the cells of the fetus can be altered by the infection. The alterations can lead to improper development of the fetus, small size of the infected baby, and the teratogenic effects associated with congenital rubella infection. The nature of the disorder is determined by the (1) tissue affected and (2) stage of development disrupted. Since the vaccine era, cytomegalovirus has replaced rubella as the most common cause of congenital defects.
Before the development and use of the rubella vaccine, cases of rubella in schoolchildren would be reported every spring, and major epidemics of rubella occurred at regular 6- to 9-year intervals. The severity of the 1964-1965 epidemic in the United States is shown in Table 52-3. Congenital rubella occurred in as many as 1% of all the children born in cities such as Philadelphia during this epidemic. The immunization program has succeeded in eliminating endemic rubella virus infection in the United States.

### Clinical Syndromes
Rubella disease is normally benign in children. A few days to 21-day incubation period, the symptoms in children consist of a 3-day maculopapular or macular rash and swollen glands (Figure 52-8). Infection in adults, however, can be more severe and include problems such as bone and joint pain (arthralgia and arthritis) and (rarely) thrombocytopenia or postinfectious encephalopathy. Immunopathologic
Box 52-5 Prominent Clinical Findings in Congenital Rubella Syndrome

Cataracts and other ocular defects
Heart defects
Deafness
Intrauterine growth retardation
Failure to thrive
Mortality within the first year
Microcephaly
Mental retardation

Box 52-6 Clinical Summaries

West Nile encephalitis: During August, a 70-year-old man from a swampy area of Louisiana develops fever, headache, muscle weakness, nausea, and vomiting. He has difficulty answering questions. He progresses into a coma. Magnetic resonance imaging results show no specific localization of lesions (unlike in herpes simplex virus encephalitis). His disease progresses to respiratory failure and death. His 25-year-old niece, living next door, complains of sudden onset of fever (39° C [102.2° F]), headache, and myalgias, with nausea and vomiting lasting 4 days. (See website: www.postgradmed.com/issues/2003/07_03/gelfand.shtml.)

Yellow fever: A 42-year-old man had fever (103° F), headache, vomiting, and backache that started 3 days after returning from a trip to Central America. He appeared normal for a short time, but then his gums started to bleed, he had bloody urine and vomited blood, and he developed petechiae, jaundice, and a slower and weakened pulse. He started to improve 10 days after the onset of disease.

Rubella: A 6-year-old girl from Romania developed a faint rash on her face, accompanied by mild fever and lymphadenopathy. Over the next 3 days, the rash progressed to other parts of the body. She had no history of rubella immunization.

Treatment, Prevention, and Control

No treatment is available for rubella. The best means of preventing rubella is vaccination with the live cold-adapted RA27/3 vaccine strain of virus (Figure 52-9). The live rubella vaccine is usually administered with the measles and mumps vaccines (MMR vaccine) after 12 months of age. The triple vaccine is included routinely in well-baby care. Vaccination promotes both humoral and cellular immunity.

The primary reason for the rubella vaccination program is to prevent congenital infection by decreasing the number of susceptible people in the population, especially children. As a result, there are fewer seronegative mothers and a smaller chance they will be exposed to the virus from contact with infectious children. Because only one serotype for rubella exists and humans are the only reservoir, vaccination of a large proportion of the population can significantly reduce the likelihood of exposure to the virus.

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Case Studies and Questions
A 27-year-old businessman experienced a high fever, serious retroorbital headache, and severe joint and back pain 5 days after he and his family returned from a trip to Malaysia. The symptoms lasted for 4 days, and then a rash appeared on his palms and soles, which lasted for 2 days. At the same time, the man’s 5-year-old son experienced mild flu-like symptoms and then collapsed after 2 to 5 days. The boy’s hands were cold and clammy, his face was flushed, and his body was warm. There were petechiae on his forehead and ecchymoses elsewhere. He bruised very easily. He was breathing rapidly and had a weak, rapid pulse. He then rapidly recovered after 24 hours.

1. **What features of these cases pointed to the diagnosis of dengue virus infection?**
2. **Of what significance was the trip to Malaysia?**
3. **What was the source of infection in the father and son?**
4. **What were the significance of and the pathogenic basis for the petechiae and ecchymoses in the child?**

Two weeks after returning from a trip to Pakistan, a 25-year-old man had arthralgia (joint aches) and a mild rash that started on his face and spread to his body. He recalled that he had felt as if he had the flu a few days before the onset of the rash. The rash disappeared in 4 days.

5. **What features of this case pointed to the diagnosis of rubella infection?**
6. **Why is it significant that the symptoms started after a trip outside the United States?**
7. **What precaution could the man have taken to prevent this infection?**
8. **How was this infection transmitted?**
9. **Who was at risk for a serious outcome of this infection?**
10. **If this disease is normally mild in children, why is their immunization so important?**

Answers

1. The diagnosis of dengue virus infection is indicated by the disease signs of high fever, severe headache, and joint and back pain. His trip to Malaysia would have increased his risk of exposure to *Aedes* mosquitoes carrying the virus.
2. The *Aedes* mosquito is endemic in Malaysia and is a carrier of dengue virus, which is prevalent in Malaysia.
3. The virus was transmitted independently by different mosquitoes to the father and son.
4. Petechiae and ecchymoses are indicators of hemorrhagic disease.
5. The diagnosis of rubella infection is suggested by the arthralgia and especially the mild rash. These immune-mediated responses occur after viral replication and viremic spread, which induces interferon, causing the flulike syndrome.
6. Exposure to rubella in the United States is unlikely because of the effective vaccine program there.
7. If the man had been immunized with the measles-mumps-rubella vaccine and received his booster immunization at 15 years of age, he should have been protected against rubella disease.
8. Rubella is the only togavirus that is transmitted by aerosols as a respiratory virus.
9. All unimmunized individuals are at risk for this infection. However, the most serious outcomes occur to the fetus of women who are infected before the 20th week of pregnancy. Rubella causes severe congenital defects.
10. Immunization of the populace (especially children) for rubella prevents congenital defects in babies.