VENEZUELAN EQUINE ENCEPHALITIS Venezuelan equine encephalitis viruses are separated into epizootic viruses (subtypes IA/B and IC) and enzootic viruses (subtypes ID, IE, and IF). Closely related enzootic viruses are Everglades virus, Mucambo virus, and Tonate virus. Enzootic viruses are found primarily in humid tropical-forest habitats and are maintained between culicoid mosquitoes and rodents. These viruses cause human disease but are not pathogenic for horses and do not cause epizootics. Enzootic viruses are common causes of acute febrile disease. Everglades virus has caused encephalitis in humans in Florida. Extrapolation from the rate of genetic change suggests that Everglades virus may have been introduced into Florida <200 years ago. Everglades virus is most closely related to the ID subtype viruses that appear to have given evolutionary rise to the epizootic variants active in South America.

Epizootic viruses have an unknown natural cycle but periodically cause extensive epizootics/epidemics in equids and humans in the Americas. These epizootics/epidemics are the result of high-level viremia in horses and mules, which transmit the infection to several types of mosquitoes. Infected mosquitoes in turn infect humans and perpetuate virus transmission. Humans also have high-level viremia, but their role in virus transmission is unclear. Epizootics of Venezuelan equine fever occurred repeatedly in South America at intervals of ≤10 years from the 1930s until 1969, when a massive epizootic spread throughout Central America and Mexico, reaching southern Texas in 1971. Genetic sequencing suggested that the virus from that outbreak originated from residual "un-inactivated" IA/B subtype virus in veterinary vaccines. The outbreak was terminated in Texas with a live attenuated vaccine (TC-83) originally developed for human use by the U.S. Army; the epizootic virus was then used for further production of inactivated veterinary vaccines. No further epizootic disease was identified until 1995, when additional epizootics took place in Colombia, Venezuela, and Mexico. The viruses involved in these epizootics as well as previously epizootic IC viruses are close phylogenetic relatives of known enzootic ID viruses. This finding suggests that active evolution and selection of epizootic viruses are under way in South America.

During epizootics, extensive human infection is the rule, with clinical disease in 10–60% of infected individuals. Most infections result in notable acute febrile disease, while relatively few infections (5–15%) result in neurologic disease. A low rate of CNS invasion is supported by the absence of encephalitis among the many infections resulting from exposure to aerosols in the laboratory setting or from vaccination accidents. The most recent large epizootic of Venezuelan equine fever occurred in Colombia and Venezuela in 1995; of the more than 85,000 clinical cases, 4% (with a higher proportion among children than adults) included neurologic symptoms/signs, and 300 cases ended in death.

The prevention of epizootic Venezuelan equine fever depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that variant. Enzootic viruses are genetically and antigenically different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective. Humans can be protected by immunization with similar vaccines prepared from Everglades virus, Mucambo virus, and Venezuelan equine encephalitis virus, but the use of the vaccines is restricted to laboratory personnel because of reactogenicity, possible fetal pathogenicity, and limited availability.

WESTERN EQUINE ENCEPHALITIS The primary maintenance cycle of western equine encephalitis virus in the United States is between *C. tarsalis* and birds, principally sparrows and finches. Equids and humans become infected, and both suffer encephalitis without amplifying the virus in nature. St. Louis encephalitis virus is transmitted in a similar cycle in the same regions harboring western equine encephalitis virus; disease caused by the former occurs about a month earlier than that caused by the latter (July through October). Large epidemics of western equine encephalitis occurred in the western and central United States and Canada during the 1930s through 1950s, but in recent years the disease has been uncommon. From 1964 through 2010, only 640 cases were reported in the United States. This decline in incidence may reflect in part the integrated approach to mosquito management that has been employed in irrigation projects and the increasing use of agricultural pesticides. The decreased incidence of western equine encephalitis almost certainly reflects the increased tendency for humans to be indoors behind closed windows at dusk—the peak biting period by the major vector.

After an incubation period of ~5–10 days, western equine encephalitis virus causes a typical diffuse viral encephalitis, with an increased attack rate and increased morbidity among the young, particularly children <2 years old. In addition, the lethality rate is high among the young and the very elderly (3–7% overall). One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants <1 year old—particularly those in the first months of life—are at serious risk of motor and intellectual damage. Twice as many males as females develop clinical encephalitis after 5–9 years of age. This difference in incidence may be related to greater outdoor exposure of boys to the vector but may also be due in part to biologic differences. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available.

FEVER AND MYALGIA

The fever and myalgia syndrome is most commonly associated with zoonotic virus infection. Many of the numerous viruses listed in Table 233-1 probably cause at least a few cases of this syndrome, but only some of these viruses have prominent associations with the syndrome and are of biomedical importance. The fever and myalgia syndrome typically begins with the abrupt onset of fever, chills, intense myalgia, and malaise. Patients may also report joint or muscle pains, but true arthritis is not found. Anorexia is characteristic and may be accompanied by nausea or even vomiting. Headache is common and may be severe, with photophobia and retroorbital pain. Physical findings are minimal and are usually confined to conjunctival injection with pain on palpation of muscles or the epigastrium. The duration of symptoms/signs is quite variable (generally 2–5 days), with a biphasic course in some instances. The spectrum of disease varies from subclinical to temporarily incapacitating. Less constant findings include a nonpruritic maculopapular rash. Epistaxis may occur but does not necessarily indicate a bleeding diathesis. A minority of the patients may develop aseptic meningitis. This diagnosis is difficult to make in remote areas, given patients' photophobia and myalgia as well as the lack of opportunity to examine the CSF. Although pharyngitis or radiographic evidence of pulmonary infiltrates is found in some patients, the agents causing this syndrome are not primary respiratory pathogens.

The differential diagnosis includes anicteric leptospirosis, rickettsial diseases, and the early stages of other syndromes discussed in this chapter. The fever and myalgia syndrome is often described as "influenza-like," but the usual absence of cough and coryza makes influenza an unlikely confounder except at the earliest stages. Treatment is supportive, but acetylsalicylic acid is avoided because of the potential for exacerbated bleeding or Reye's syndrome. Complete recovery is the general outcome for people with this syndrome, although prolonged asthenia and nonspecific symptoms have been described in some patients, particularly after infection with lymphocytic choriomeningitis virus or dengue virus types 1–4.

Efforts at prevention of viral infection are best based on vector control, which, however, may be expensive or impossible. For mosquito control, destruction of breeding sites is generally the most economically and environmentally sound approach. Emerging containment technologies include the release of genetically modified mosquitoes and the spread of *Wolbachia* bacteria to limit mosquito multiplication rates. Depending on the vector and its habits, other possible approaches include the use of screens or other barriers (e.g., permethrin-impregnated bed nets) to prevent the vector from entering dwellings, judicious application of arthropod repellents such as *N,N,*-diethyltoluamide (DEET) to the skin, wearing of long-sleeved and ideally permethrin-impregnated clothing, and avoidance of the vectors' habitats and times of peak activity.

Arenaviruses Lymphocytic choriomeningitis/meningoencephalitis is the only human arenavirus infection resulting predominantly in fever