Valley fever to the Arabian Peninsula, with epidemic disease in 2000. The virus has also been found in Madagascar and has been introduced into Egypt, where it caused major epidemics in 1977–1979, 1993, and thereafter. Rift Valley fever virus is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably also has a vertebrate amplifier. Increased transmission during particularly heavy rains leads to epizootics characterized by high-level viremia in cattle, goats, or sheep. Numerous types of mosquitoes then feed on these animals and become infected, thereby increasing the possibility of human infections. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of Rift Valley fever virus transmission. High-resolution satellites can also detect the special depressions in floodwaters from which the mosquitoes emerge. In addition, the virus can be transmitted by contact with blood or aerosols from domestic animals. Transmission risk is therefore high during birthing, and both abortuses and placentas need to be handled with caution. Slaughtered animals are not infectious because anaerobic glycolysis in postmortem tissues results in an acidic environment that rapidly inactivates bunyaviruses. Neither person-to-person nor nosocomial transmission of Rift Valley fever has been documented.

Rift Valley fever virus is unusual in that it causes several clinical syndromes. Most infections are manifested as the fever–myalgia syndrome. A small proportion of infections result in VHF with especially prominent liver involvement. Renal failure and DIC are also common features. Perhaps 10% of otherwise mild infections lead to retinal vasculitis, and some patients have permanently impaired vision. Funduscopic examination reveals edema, hemorrhages, and infarction of the retina as well as optic nerve degeneration. In a small proportion of patients (<1 in 200), retinal vasculitis is followed by viral encephalitis.

No proven therapy exists for Rift Valley fever. Both retinal disease and encephalitis occur after the acute febrile syndrome has resolved and serum neutralizing antibody has developed—events suggesting that only supportive care need be given. Epidemic disease is best prevented by vaccination of livestock. The ability of this virus to propagate after introduction into Egypt suggests that other potentially receptive areas, including the United States, should develop response plans. Rift Valley fever, like Venezuelan equine encephalitis, is likely to be controlled only with adequate stocks of an effective live attenuated vaccine, but such global stocks are unavailable. A formalin-inactivated vaccine confers immunity in humans, but quantities are limited and three injections are required; this vaccine is recommended for potentially exposed laboratory workers and for veterinarians working in sub-Saharan Africa. A new live attenuated vaccine, MP-12, is being tested in humans and may soon become available for general use. The vaccine is safe and licensed for use in sheep and cattle.

SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME This is a recently described tick-borne disease caused by a previously unknown and still-unclassified phlebovirus. Numerous human infections have been reported during the past few years from China, and several cases have also been detected in Japan and South Korea. The clinical presentation ranges from mild nonspecific fever to severe VHF with a high (>12%) lethality rate.

Flaviviruses The most important flaviviruses that cause VHF are the mosquito-borne dengue viruses 1–4 and yellow fever viruses. These viruses are widely distributed and cause tens to hundreds of thousands of infections each year. Kyasanur Forest disease virus and Omsk hemorrhagic fever virus are geographically very restricted but important tick-borne flaviviruses that cause VHF, sometimes with subsequent viral encephalitis. Tick-borne encephalitis virus has caused VHF in a few patients. There is currently no therapy for these VHFs, but an inactivated vaccine has been used in India to prevent Kyasanur Forest disease.

SEVERE DENGUE Several weeks after convalescence from infection with dengue virus 1, 2, 3, or 4, the transient protection conferred by that infection against reinfection with a heterotypic dengue virus usually wanes. Heterotypic reinfection may result in classic dengue or, less commonly, in severe dengue. In the past 20 years, *A. aegypti* has progressively reinvaded Latin America and other areas, and frequent travel by infected individuals has introduced multiple variants of dengue viruses 1–4 from many geographic areas. Thus the pattern of hyperendemic transmission of multiple dengue virus serotypes established in the Americas and the Caribbean has led to the emergence of severe dengue as a major problem. Among the millions of dengue virus 1–4 infections, ~500,000 cases of severe dengue occur annually, with a lethality rate of ~2.5%. The induction of vascular permeability and shock depends on multiple factors, such as the presence or absence of enhancing and nonneutralizing antibodies, age (susceptibility to severe dengue drops considerably after 12 years of age), sex (females are more often affected than males), race (whites are more often affected than blacks), nutritional status (malnutrition is protective), or sequence of infections (e.g., dengue virus 1 infection followed by dengue virus 2 infection seems to be more dangerous than dengue virus 4 infection followed by dengue virus 2 infection). In addition, considerable heterogeneity exists among each dengue virus population. For instance, Southeast Asian dengue virus 2 variants have more potential to cause severe dengue than do other variants.

Severe dengue is identified by the detection of bleeding tendencies (tourniquet test, petechiae) or overt bleeding in the absence of underlying causes, such as preexisting gastrointestinal lesions. Shock may result from increased vascular permeability. In milder cases of severe dengue, restlessness, lethargy, thrombocytopenia (<100,000/μL), and hemoconcentration are detected 2–5 days after the onset of typical dengue, usually at the time of defervescence. The maculopapular rash that often develops in dengue may also appear in severe dengue. In more severe cases, frank shock is apparent, with low pulse pressure, cyanosis, hepatomegaly, pleural effusions, and ascites; in some patients, severe ecchymoses and gastrointestinal bleeding develop. The period of shock lasts only 1 or 2 days.

A virologic diagnosis of severe dengue can be made by the usual means. However, multiple flavivirus infections result in broad immune responses to several members of the genus, and this situation may result in a lack of virus specificity of the IgM and IgG immune responses. A secondary antibody response can be sought with tests against several flavivirus antigens to demonstrate the characteristic wide spectrum of reactivity.

Most patients with shock respond promptly to close monitoring, oxygen administration, and infusion of crystalloid or—in severe cases—colloid. The case–fatality rates reported vary greatly with case ascertainment and quality of treatment; however, most patients with severe dengue respond well to supportive therapy, and the overall lethality rate at an experienced center in the tropics is probably as low as 1%.

The key to control of both dengue and severe dengue is the control of *A. aegypti*, which also reduces the risk of urban yellow fever and chikungunya virus circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories (perfect mosquito breeding grounds when filled with water during rainfall) and by insecticide resistance. Urban poverty and an inability of the public health community to mobilize the populace to respond to the need to eliminate mosquito breeding sites are also factors in lack of mosquito control. A tetravalent live attenuated dengue vaccine based on the attenuated yellow fever virus 17D platform is currently being evaluated in phase 3 clinical trials in Latin America, Asia, and Australia. At least two other live attenuated candidate vaccines based on modified recombinant dengue viruses have been evaluated in phase 1 clinical studies, but the results have not been promising.

YELLOW FEVER Yellow fever virus had caused major epidemics in Africa and Europe before its transmission by *A. aegypti* mosquitoes was discovered in 1900. Urban yellow fever became established in the New World as a result of colonization with *A. aegypti*, originally an African mosquito. Subsequently, different types of mosquitoes and nonhuman primates were found to maintain yellow fever virus in Africa and also in Central and South American jungles. Transmission to humans