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# Emerging Viral Infections

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Unique disorders appear episodically in human populations and cause life-threatening systemic or neurological disease. Historical examples of such disorders include von Economo encephalitis, a disorder of presumed viral etiology; acquired immune deficiency syndrome, caused by the human immunodeficiency virus; and severe acute respiratory syndrome, caused by a member of the coronavirus family. This article describes the factors that contribute to the emergence of infectious diseases and focuses on selected recent examples of emerging viral infections that can affect the nervous system of infants, children, and adolescents.

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Throughout history infectious diseases have emerged and dramatically altered the course of human civilization. Plague, the result of infection with *Yersinia pestis*, a rodent-borne gram-negative bacterium, decimated Europe in the 14th century and caused the deaths of approximately 50% percent of the England's population.<sup>1</sup> Similarly, the influenza pandemic of the early 20th century affected an estimated one-half billion people and caused more than 20 million deaths.<sup>2</sup> Human immunodeficiency virus infection and the acquired immune deficiency syndrome (HIV/AIDS), a disease that appeared in the early 1980s, remains a distressing human affliction, especially among the peoples of sub-Saharan Africa.<sup>3</sup> More than 30 million persons are living with HIV/AIDS worldwide, and nearly 2 million children and adults die from HIV/AIDS annually.<sup>3</sup> Although the recent pandemic of the H1N1 strain of influenza was far less dramatic from a human health perspective,<sup>4</sup> such outbreaks illustrate how infectious pathogens can cause human suffering, economic loss, and widespread anxiety.

This article describes factors that contribute to the emergence of infectious diseases and summarizes selected disorders that have emerged recently to cause neurological disease. The viruses and disorders discussed herein include West Nile virus, an arboviral infection that swept across the United States in the early years of the 21st century; Nipah encephalitis, a paramyxovirus-induced disorder endemic to

India, Bangladesh, and South Asia; chikungunya, a mosquito-borne viral disorder that affects persons in Africa, India, and Southeast Asia; dengue virus, an arthropod-borne Flavivirus that infects more than 100 million persons annually; and parechovirus, a picornavirus that can cause severe disease in neonates and permanent neurodevelopmental disability in surviving infants. Neurological diseases attributed to the H1N1 strain of influenza and lymphocytic choriomeningitis virus, 2 additional emerging or emerged infections, are discussed elsewhere in this issue.

## How Infections Emerge

Several factors, including human or animal behaviors, travel, climate change, natural disasters, antimicrobial use, and mutation of a pathogen's genomic material, contribute to the phenomenon of emergence of infectious pathogens, whether viral, bacterial, fungal, or parasitic. The emergence of an infectious disease is often multifactorial, reflecting certain human behaviors and changes in the ecology of vectors or the genetics of microorganisms.

The emergence of Nipah virus encephalitis in the late 1990s illustrates the complex interaction of factors that can contribute to the emergence and spread of infectious diseases.<sup>5</sup> Human disease due to Nipah virus, a member of the *Henipavirus* genus of the *Paramyxoviridae* family, first appeared in 1999 in an outbreak of encephalitis among Malaysian pig farmers.<sup>6</sup> Nearly all initial infections in Malaysia, as well as subsequent infections in Singapore, resulted from direct contact with pigs, their respiratory secretions, or tissues. This association enabled public health official to identify the source of human contagion and isolate the causative agent, known now as Nipah virus, a name denoting the location of the case from which the virus was first isolated.<sup>6</sup>

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Infection control measures, including the slaughter and disposal of >1 million pigs, contained the disease; during this outbreak, human-to-human transmission of Nipah virus was not observed.

Because bats transmit the Hendra virus, another novel paramyxovirus closely related to the Nipah virus, researchers suspected that bats were also the environmental reservoir of Nipah virus.<sup>6</sup> This theory was later confirmed when laboratory studies demonstrated that several species of fruit bats native to South Asia<sup>7</sup> possessed antibodies to Nipah virus or shed the virus in their urine or saliva. In 2001, and again in 2004, Nipah virus encephalitis reemerged, this time in Bangladesh.<sup>8</sup> Bats in the region of the Bangladesh outbreaks were found to harbor Nipah virus, suggesting that they again served as the original source of infection; however, in contrast to the Malaysian outbreak, pigs did not participate in the transmission of the virus to humans. Rather, contact with sick humans was strongly associated with contracting Nipah virus encephalitis, and the Nipah virus was isolated from samples of human urine. Now, human-to-human transmission of Nipah virus was occurring.

So how did the virus originally emerge and cause human disease? The Nipah virus had apparently existed endemically for some time among fruit bats in the remote rainforests of Malaysia and other parts of Asia. In the late 1990s, the bats' natural habitat and food supply were disrupted when millions of acres of rainforest were cleared for human use. Some biologists have theorized that the clearing of the land and the haze caused by the fires used to clear the land forced the bats to search for new sources of food.<sup>9</sup> The bats began to colonize the fruit trees planted by humans and fertilized by the pig manure from the farms that had replaced the forests.<sup>9</sup> Pigs raised on these farms became infected with Nipah virus and ultimately passed the virus to humans. By infecting and replicating in humans, the virus adapted to a new host, and because humans lacked previous exposure to the virus, Nipah encephalitis, a severe potentially fatal disease, was the outcome.

Rather than being medical curiosities, such phenomena take place remarkably frequently, leading some authors to suggest that approximately 75% of the emerging human infections are zoonotic, that is, diseases that are transmissible from animals to humans.<sup>10</sup> Subacute adult respiratory syndrome, for example, a disease that caused nearly 1000 deaths during an outbreak in 2004, also traces its origin to a bat virus. Bats worldwide harbor several ancient coronaviruses and appear to serve periodically as the source of human viruses, including the coronavirus causing subacute adult respiratory syndrome.<sup>11</sup> Events that facilitate host switching, such as changes in the ecology of potential vectors or modifications in virus genes or proteins, enable viruses to infect and replicate in additional animal species, including humans. Other notable examples of host switching leading to human disease include Hantavirus pulmonary syndrome, Lyme disease, Ebola hemorrhagic fever, dengue fever, and HIV/AIDS.

## Selected Disorders

### West Nile Virus

#### Epidemiology

First isolated from humans in Uganda in the 1930s, West Nile virus emerged in Egypt and Israel in the 1950s<sup>12</sup> and rarely caused recognized human disease. West Nile virus circulates in bird–mosquito cycle, involving rural or urban wild birds and *Culex* or *Aedes* mosquitoes. Beginning in the mid-1990s, human outbreaks became more frequent, and fatal cases began to appear in Israel, Algeria, and Romania.<sup>13</sup> Mutation of the virus genome leading to enhanced virulence for humans was suspected. In 1999, West Nile virus infections occurred in the United States, marking the initial appearance of the virus in the Western hemisphere. A virus closely related to a West Nile virus strain that had been identified in the Middle East in 1998 caused 7 deaths during an encephalitis outbreak in the New York City metropolitan area.<sup>14</sup>

In 2000, West Nile virus activity was detected in 12 states surrounding New York State, and by the end of the following year, West Nile virus had infected persons in 27 different states and in the District of Columbia.<sup>15</sup> Because mosquitoes and birds in North America had no previous exposure to West Nile virus, the infection spread rapidly, resulting in a massive human outbreak in 2003 that affected nearly 10,000 US inhabitants from New York to California. Only 2 western states (Oregon and Washington) did not report West Nile virus activity in that year.<sup>16</sup> By 2009, nearly 30,000 cases of West Nile virus-induced human disease had been reported to the Centers for Disease Control and Prevention.

#### Clinical Manifestations

To date, the majority of persons with neuroinvasive West Nile virus infections have been adults >25 years of age. Neurological manifestations, including meningitis, encephalitis, myelitis, polio-like illness, and others, occur in approximately 1 of every 150 infected persons.<sup>8</sup> Asymptomatic West Nile virus infections outnumber symptomatic cases by approximately 5:1.<sup>15</sup> After an incubation period of 2–14 days, systemic symptoms of fever, malaise, headache, nausea, and vomiting occur in symptomatic infections. Of symptomatic patients, 50% have a maculopapular rash and lymphadenopathy.

West Nile virus encephalitis, the most common manifestation of neuroinvasive West Nile virus disease, begins with a systemic prodrome, as described previously, or abruptly with high fever and coma.<sup>17,18</sup> Features in West Nile virus encephalitis include altered mental status, diffuse muscle weakness (proximal greater than distal), respiratory paralysis, and less commonly, tremor, myoclonus, and parkinsonian features. Less frequent neurological manifestations of West Nile virus infection include aseptic meningitis, myelitis, optic neuritis, and the Guillain–Barré syndrome (GBS).<sup>17,18</sup> Involvement of the anterior horn cells can produce a poliomyelitis-like disorder with asymmetric paralysis of the upper or lower extremities.<sup>19</sup>

A single case report suggests that West Nile virus can be transmitted to the fetus, causing intrauterine infection of the

central nervous system.<sup>20</sup> In late 2002, an infant was born to a woman who had experienced West Nile virus meningoencephalitis during her pregnancy. At birth, the infant had bilateral chorioretinitis and cystic encephalomalacia. A subsequent epidemiological study that evaluated the outcomes of West Nile virus infections during the pregnancies of 71 women identified no additional cases of congenital West Nile virus infections.<sup>21</sup>

### Diagnosis

West Nile virus infections can be confirmed by detecting West Nile virus-specific immunoglobulin M (IgM) in serum or cerebrospinal fluid (CSF) using IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA).<sup>22</sup> Neuroinvasive disease is supported by detecting pleocytosis, protein elevation, and West Nile virus-specific IgM in CSF. West Nile virus RNA can also be detected in CSF by reverse transcription polymerase chain reaction (RT-PCR), but MAC-ELISA analysis of CSF is more sensitive. Persons with West Nile virus infections can also have hyponatremia and anemia. Magnetic resonance imaging (MRI) findings include leptomeningeal enhancement and subtle abnormalities of the thalamus and brainstem, especially on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences.<sup>23</sup>

### Treatment, Prevention, and Prognosis

Treatment of neuroinvasive West Nile virus infections consists of supportive care; no currently available antiviral drugs have proven efficacy against West Nile virus. Control measures include the personal use of mosquito repellants, avoidance of outdoor activities during nights and evenings when mosquitoes are most active, and mosquito-abatement programs. The American Academy of Pediatrics recommends that N,N-diethyl-m-toluamide (DEET), an effective insect repellant, be avoided in infants <2 months and that DEET concentrations not exceed 30% in lotions or sprays used by infants and children.<sup>24</sup> Persons with West Nile virus-induced meningitis and encephalitis gradually recover, whereas patients with limb paralysis usually have permanent deficits.<sup>17,19</sup>

## Nipah Virus

### Epidemiology

Nipah virus exists endemically in several species of fruit bats, and humans become infected through consumption of raw fruit or date palm juice contaminated with the virus; contact with the tissues or secretions of intermediate hosts, such as pigs, cows, and other mammals; or direct contact with infected humans.<sup>7,8</sup> As of late 2009, there had been at least 1 dozen human outbreaks of Nipah virus disease among persons living in India, Bangladesh, Malaysia, and other parts of South Asia.<sup>25</sup>

### Clinical Manifestations

After an incubation period of 4-45 days, Nipah virus produces an influenza-like pulmonary disorder, consisting of fever, cough, and myalgias, or neurological disease, consisting of aseptic meningitis or encephalitis.<sup>26,27</sup> Encephalitis is associated with headache, seizures, cerebellar signs, motor

abnormalities, and coma.<sup>26,27</sup> As many as 50% of Nipah virus infections are asymptomatic.<sup>28</sup> Thus far, the majority of persons with symptomatic Nipah virus infections have been adults.

### Diagnosis

The diagnosis is made by detecting Nipah virus by RT-PCR or cell culture or by detecting Nipah virus-specific IgM in serum by using enzyme-linked immunosorbent or immunofluorescent assays.<sup>25</sup> The CSF in Nipah virus encephalitis shows lymphocytic pleocytosis, elevated protein content, and normal glucose concentration. MRI features consist of disseminated small (<7 mm) signal hyperintensities, best seen on FLAIR sequences, predominately involving white matter.<sup>27</sup>

### Treatment, Prevention, and Prognosis

Treatment of Nipah virus infections consist of supportive care. The risk of infection can be reduced by boiling date palm juice, a potential source of infection in endemic areas, and by using standard precautions when in contact with infected animals or humans.<sup>25</sup> As many as 75% of symptomatic Nipah virus infections are fatal; approximately 15% of survivors have neurological sequelae.<sup>25</sup>

## Chikungunya Virus

### Epidemiology

Chikungunya virus, a positive-strand RNA alphavirus transmitted to humans by *Aedes* species mosquitoes, exists endemically in equatorial Africa, India, Southeast Asia, and the island nations of the Indian Ocean, including Madagascar and Reunion. The virus, first associated with human disease in Tanzania in the early 1950s, reemerged in 2005-2006 when >200,000 persons living in the Reunion Islands contracted chikungunya disease<sup>29</sup>; nearly 1000 deaths among children and adults were reported. The reemergence of chikungunya in the Reunion Islands was attributed to participation of a new mosquito vector, *Aedes albopictus*, and a genetic mutation in the chikungunya virus, known as E1-A226V, which favored replication and persistence in *Aedes albopictus*.<sup>30</sup> This change in viral-vector relationship has the alarming potential to facilitate spread of chikungunya virus to other regions, including the United States, inhabited by *Aedes albopictus*.

In 2007, >1 million persons were infected with chikungunya virus in India, and cases of chikungunya were also identified in Malaysia, Sri Lanka, and Indonesia.<sup>30</sup> In the same year, chikungunya cases were observed in Italy as a consequence of travel from endemic regions, and subsequently, imported cases were detected in Europe, Australia, and the United States.<sup>30</sup> In the native dialect of the Tanzanian region where the infection first appeared, chikungunya means "that what contorts or bends" and translates into Swahili as "the illness of the bended walker."<sup>30</sup>

### Clinical Manifestations

After a short incubation period of 2-7 days, persons with symptomatic chikungunya virus infections experience fever, chills, headache, nausea, vomiting, maculopapular rash, and intense myalgias and arthralgias, hallmarks of the condi-



tion.<sup>29,30</sup> The latter symptoms cause protracted disability that can last several weeks or months. A proportion of persons with chikungunya fever experience hepatitis, cardiovascular complications, renal failure, and neurological disorders, usually encephalitis.<sup>30</sup> Although adults, especially the elderly, seem more vulnerable to chikungunya, cases in children have been reported.<sup>31</sup> Neurological conditions in children infected with chikungunya virus include febrile seizures, aseptic meningitis, and encephalitis-/encephalopathy-producing headache, seizures, and altered mental status.<sup>31</sup> Neonatal disease, with fever, hepatitis, rash, and meningoencephalitis, can occur when the mother transmits the virus vertically during the week before the delivery.<sup>32</sup> Congenital infections producing birth defects or fetal death appear to be extremely uncommon.

### Diagnosis

The diagnosis of chikungunya can be made by detecting infectious virus by cell culture, viral RNA by RT-PCR, or chikungunya virus-specific IgM using MAC-ELISA or immunofluorescent methods.<sup>30</sup> The duration of viremia is very short, reducing the sensitivity of cell culture, but serologic responses can persist for several months, making serologic studies highly sensitive and specific.<sup>30</sup> CSF examination may reveal lymphocytic pleocytosis and protein elevation; MRI can show features of acute disseminated encephalomyelitis.<sup>31</sup>

### Treatment, Prevention, and Prognosis

Treatment of chikungunya fever consists of supportive care; nonsteroidal anti-inflammatory drugs and corticosteroids can reduce the morbidity associated with myalgias and arthralgias.<sup>30</sup> Although vaccines to prevent chikungunya disease in humans are not yet available, potentially effective control measures include the use of insect repellants, such as DEET, and mosquito abatement programs. Although most persons with chikungunya gradually recover, mortality rates of up to 33% can be observed among the elderly.<sup>30</sup>

## Dengue Virus

### Epidemiology

Dengue fever, also known as “breakbone fever” because of the intense myalgias, arthralgias, and bone pain experienced by persons with the disease, results from infection with 1 of 4 related RNA, arthropod-borne Flaviviruses (dengue virus serotypes 1-4) endemic to Southeast Asia, sub-Saharan Africa, Indonesia, and South and Central America.<sup>33</sup> After the initial transmission from monkeys to humans during the past 800 years, dengue virus infected humans infrequently. The events of World War II facilitated transport of mosquito vectors into historically nonendemic regions, and during the past 60 years, dengue has emerged throughout the tropical and subtropical world.<sup>33</sup> In the US, dengue cases have been observed in Puerto Rico, considered an endemic location, and recently in Key West, Florida, and along the Texas–Mexico border.<sup>33</sup>

The *Aedes aegypti* and *Aedes albopictus* mosquitoes serve as the virus reservoirs and transmit the virus to humans during a blood meal. Persons of any age living in endemic regions and travelers to these regions are at risk of infection. More

than one-third of the world’s population lives in endemic regions, and as many as 100 million people experience dengue fever annually. In endemic areas, outbreaks of dengue occur annually, particularly during warm, humid, and rainy seasons, conditions that favor mosquito proliferation.<sup>33</sup> Because infection with 1 virus serotype does not confer immunity to the other virus serotypes, humans can experience recurrent dengue fever. Although as many as one-half of dengue virus infections produce no symptoms or signs, severe dengue fever causes several thousand deaths annually worldwide.<sup>33</sup>

### Clinical Manifestations

After a brief incubation period of 4-7 days symptomatic dengue virus infections begin with fever and mild nonspecific systemic symptoms, such as malaise and headache. Older children or adults can have more severe illness with high fever, myalgias, retro-orbital pain, bone pain, arthralgias, nausea, vomiting, petechiae, and a diffuse erythematous maculopapular rash.<sup>33</sup> Persons with dengue hemorrhagic fever and shock syndrome, the most severe form of dengue virus infection, have hepatomegaly and hemorrhage, including epistaxis, gingival hemorrhage, and gastrointestinal hemorrhage. Massive gastrointestinal hemorrhage, disseminated intravascular coagulation, plasma leak, and shock may be fatal during this phase. Neurological complications, uncommon manifestations of dengue fever, include altered mental status, seizures, and focal neurological signs or, rarely, GBS.<sup>34-36</sup>

### Diagnosis

The diagnosis of dengue fever can be established by isolating dengue virus using cell culture methods, detecting viral RNA in serum, plasma, or CSF by using RT-PCR, or identifying dengue virus specific IgM and/or immunoglobulin G in serum obtained during the acute and convalescent phases of infection.<sup>33</sup> CSF examination may demonstrate lymphocytic pleocytosis and protein elevation, and MRI may show areas of increased T2 signal, especially in cases of dengue virus-induced acute disseminated encephalomyelitis. Patients with dengue virus-induced GBS may show an albuminocytologic dissociation and abnormal electrophysiologic studies.<sup>36</sup>

### Treatment, Prevention, and Prognosis

Currently available antiviral agents are not effective against dengue virus; treatment consists of supportive care and fluid resuscitation.<sup>33</sup> Because of the potential for hemorrhagic disease, acetaminophen should be used to treat pain and fever, and ibuprofen, aspirin, and naproxen should be avoided.<sup>33</sup> Dengue virus infections can be prevented by mosquito abatement and personal use of insect repellants, especially DEET. Although most cases of dengue fever are mild, as many as 25,000 deaths are attributed annually worldwide to dengue hemorrhagic fever and dengue shock syndrome.

## Parechovirus

### Epidemiology

Parechoviruses, initially considered members of the Echovirus genus of the Picornavirus family, were first identified in

humans approximately 50 years ago in association with an outbreak of gastroenteritis.<sup>37</sup> Based on their biological and molecular properties, human parechoviruses, which have at least 6 distinct serotypes, are now considered members of a new genus of Picornaviridae.<sup>38</sup> Although parechoviruses are members of a distinct genus, they share many biological and epidemiological characteristics with the other nonpolio enterovirus, the echoviruses, and coxsackieviruses. Humans serve as the primary source of infection and transmit the parechoviruses in stool, saliva, and respiratory secretions.<sup>39</sup> Most infections with parechoviruses occur in young children, and by adulthood, virtually all individuals in many regions possess serological evidence of previous infection.<sup>38</sup> Human parechoviruses have been detected in monkey feces, suggesting that monkeys may serve as a zoonotic reservoir.<sup>40</sup>

### Clinical Manifestations

The majority of symptomatic parechovirus infections occur in childhood. Infections with serotypes 1, 2, 4, 5, and 6 have been associated with fever and mild gastrointestinal or respiratory illnesses in young children.<sup>41</sup> In contrast, serotype 3 has been linked to severe, sepsis-like disease and meningoencephalitis in neonates.<sup>42,43</sup> Infants with human parechovirus disease can exhibit fever, seizures, irritability, abdominal distension, and erythematous rash, clinical features that can be indistinguishable from neonatal enteroviral infections.<sup>42,44</sup>

### Diagnosis

The diagnosis of human parechovirus infection can be established by detecting parechovirus RNA in saliva, respiratory secretions, feces, or tissues using RT-PCR.<sup>42-45</sup> Sequence analysis of viral RNA or serologic methods can be used to identify parechovirus serotypes. Infants with parechovirus meningoencephalitis may have CSF pleocytosis or periventricular white matter abnormalities detected best by MRI.<sup>42,43</sup>

### Treatment, Prevention, and Prognosis

Parechovirus infections cannot be treated with any of the currently available antiviral agents. Mild childhood infections require no treatment; infants with severe disease require supportive care. Infants with severe neonatal parechovirus infections and meningoencephalitis can have permanent sequelae consisting of cerebral palsy and developmental delay.<sup>42,43</sup> Death in association with pediatric parechovirus infections has been reported, although the role of parechovirus in the deaths of the infants described in 1 report is uncertain.<sup>45</sup>

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