

Eastern, Western and Venezuelan Equine Encephalomyelitis

Sleeping Sickness

Eastern Equine Encephalomyelitis (EEE), Eastern Equine Encephalitis, Eastern Encephalitis

Western Equine Encephalomyelitis (WEE), Western Equine Encephalitis

Venezuelan Equine Encephalomyelitis (VEE), Peste Loca, Venezuelan Equine Encephalitis, Venezuelan Encephalitis, Venezuelan Equine Fever

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Importance

Eastern equine encephalomyelitis (EEE), western equine encephalomyelitis (WEE), and Venezuelan equine encephalomyelitis (VEE) viruses are mosquito-borne pathogens that can cause nonspecific illnesses and encephalitis in equids (horses, mules, burros, donkeys and zebras) and humans in the Americas. Some of these viruses also affect birds and occasionally other mammals. No specific treatment is available, and depending on the virus, host and form of the disease, the case fatality rate may be as high as 90%. Epidemic VEE viruses are also potential bioterrorist weapons.

Etiology

Eastern, western and Venezuelan equine encephalomyelitis result from infection by the respectively named viruses in the genus *Alphavirus*, family *Togaviridae*. In the human literature, the disease is usually called eastern, western or Venezuelan equine encephalitis.

Eastern equine encephalomyelitis virus

Until recently, eastern equine encephalomyelitis virus (EEEV) contained four genetic lineages. Lineage I was considered to be the North American variant of EEEV, while lineages II, III and IV were the South American variants. The latter three lineages have now become a new viral species, Madariaga virus. Unless otherwise specified, “EEEV” in this factsheet refers to all viruses formerly classified under this name, rather than lineage I viruses alone.

The North American EEEV seems to be more virulent than Madariaga virus in people, and under some conditions, it is also more pathogenic in experimentally infected nonhuman primates (e.g., marmosets), sparrows and rodents. Comparative studies in horses have not been published, but severe illness has been reported in this species in both North and South America.

Western equine encephalomyelitis viruses

The western equine encephalomyelitis virus complex contains western equine encephalomyelitis virus (WEEV) and several closely related alphaviruses including Sindbis virus, Whataroa virus, Fort Morgan virus (and variants Stone Lakes virus and Buggy Creek virus), aura virus, and highlands J virus. WEEV is the most important virus in this complex in the Western Hemisphere, although highlands J virus and Fort Morgan virus can affect some birds. Sindbis virus and Whataroa virus cause a febrile illness with polyarthritis in humans, but occur only in the Eastern Hemisphere, and are not discussed in this factsheet. Aura virus, found in South America, has not been linked to any illness in humans or animals.

Venezuelan equine encephalomyelitis viruses

The Venezuelan equine encephalomyelitis complex contains a number of viruses, which have been classified into 6 viral subtypes, I to VI, with subtype I further subdivided into five antigenic variants or serovars, AB to F. The currently recognized viral species in this complex are Venezuelan equine encephalomyelitis virus (VEEV), which contains variants AB, C, D and E in subtype I (i.e., variants I-AB, I-C, I-D and I-E), Mosso das Pedras virus (variant I-F), Everglades virus (subtype II), Mucambo virus (subtype III variants A, C and D), Tonate virus (subtype III variant B), Pixuna virus (subtype IV), Cabassou virus (subtype V) and Rio Negro virus (subtype VI). One isolate of Tonate virus, which was detected in the U.S. Rocky Mountains region in the 1970s, is also called Bijou Bridge virus. VEE complex viruses are sometimes referred to by their subtype and variant designation, rather than their species name.

VEE complex viruses are divided into epidemic (or epizootic) and enzootic (or endemic) groups, based on their epidemiological characteristics. All viruses except VEEV variants I-AB and I-C are considered to be enzootic. Enzootic VEE viruses occur in limited geographic areas, where they are maintained in cycles involving wild animals. They are not amplified in equids, and do not usually cause disease in these animals. In contrast, epidemic VEE viruses are detected only sporadically, are amplified in equids, and can cause extensive epidemics affecting both equids and

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humans. The origins of epidemic VEE viruses are uncertain, as I-AB and I-C viruses do not seem to be maintained in natural cycles between outbreaks. Some evidence suggests that they may arise when mutations in enzootic VEE viruses allow efficient amplification in horses, and die out once the epidemic ends.

One enzootic I-E virus strain, which has been detected in Mexico since the 1990s, differs from other enzootic viruses in that it affects horses. This virus has caused extensive outbreaks in Mexico, although it has not spread further. Like other enzootic VEE viruses, it is not thought to be amplified in equids.

Species Affected

Eastern equine encephalomyelitis

Passerine birds are thought to be the principal reservoir hosts for North American EEEV in natural cycles, but small mammals (e.g., rodents) might also amplify the virus. The primary reservoir hosts for Madariaga virus (South American EEEV) are still uncertain, but small mammals might play a more prominent role. Some experiments have suggested that reptiles (especially snakes) might help maintain EEEV over the winter. Domesticated mammals including equids are not important in virus amplification.

Most infections in passerine birds appear to be asymptomatic, although a few species become ill after experimental inoculation. Clinical cases have been reported in some non-passerine birds including chukar partridges, pheasants, turkeys, ratites (emus, ostriches), pigeons (*Columba livia*), egrets, glossy ibises (*Plegadis falcinellus*), whooping cranes (*Grus americana*) and African penguins (*Spheniscus demersus*), and antibodies to EEEV have been found in psittacines. Among mammals, EEEV mainly causes disease in horses and other equids, but clinical cases have also been reported in sheep, cattle, dogs, South American camelids (llamas and alpacas), pigs, deer and a captive harbor seal (*Phoca vitulina*), as well as in some experimentally infected rodents and nonhuman primates. Some other species susceptible to infection, without reported disease to date, include goats, moose (*Alces alces*), certain rodents, bats, reptiles and amphibians.

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Passerine birds are the usual reservoir hosts for WEEV, but this virus may also cycle in blacktail jackrabbit (*Lepus californicus*) populations. Reptiles have been proposed as possible overwintering hosts. Domesticated mammals including equids are not important in virus amplification.

WEEV causes disease in equids and some species of birds such as emus, turkeys, pheasants and chukar partridges. Other species reported to be susceptible to infection (usually asymptomatic) include cattle; various small mammals including squirrels, other rodents and snowshoe hares (*Lepus americanus*); opossums; and snakes, tortoises and frogs.

Other WEE complex viruses

Highlands J virus mainly seems to infect wild birds. Although this virus is not known to be a significant cause of illness in mammals, it was isolated from the brain of at least one horse with encephalitis. It can also cause disease in experimentally infected young chickens and partridges, and turkeys of various ages.

Fort Morgan virus occurs in cliff swallows (*Petrochelidon pyrrhonota*) and house sparrows, and can affect house sparrow nestlings. It is not known to infect other species.

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Wild rodents are thought to be the usual reservoir hosts for enzootic VEE viruses, but birds may be involved in a few cycles (e.g., the Bayou Bridge variant of Tonate virus). Although rodent reservoir hosts in endemic areas seem to be unaffected, other wild and laboratory (or pet) rodents can become ill. Mice and hamsters are generally more susceptible than guinea pigs. Enzootic VEE viruses can also infect opossums (*Didelphis marsupialis*), bats and various other mammals including dogs. They are not known to cause any illness in equids, other domesticated livestock, dogs or cats, with the exception of one Mexican I-E variant, which is pathogenic for equids. Horses do not seem to be efficient amplifying hosts for any enzootic VEE viruses, including this variant.

Epidemic VEE viruses mainly affect equids and are also amplified in these animals. These viruses can infect wild and laboratory rodents, and cause severe disease in some species (including guinea pigs, mice and hamsters); however, there is no evidence that they are maintained in rodents or other animals between epidemics. Infections have also been reported in other mammals (e.g., pigs, cattle, goats, sheep, dogs, rabbits) and some birds, but most infections appear to be subclinical.

Zoonotic potential

Human illnesses have been reported after infection with EEEV, Madariaga virus, WEEV, epidemic VEE viruses and most enzootic VEE viruses. EEEV in North America is generally thought to be more virulent for humans than Madariaga virus in South America; however, both viruses can cause severe illness. Highlands J virus and Fort Morgan virus do not appear to affect people.

Humans infected with epidemic strains of VEEV can develop viremia sufficient to infect mosquitoes, but are not thought to be important in the epidemiology of this disease. People do not appear to transmit EEEV or WEEV to mosquitoes.

Geographic Distribution

All EEE and VEE complex viruses and most WEE complex viruses occur only in the Western Hemisphere.

WEEV has been isolated from western North America, including Canada, and as far south as Argentina. Highlands

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J virus circulates in the eastern U.S., while Fort Morgan virus (with its variants) is widespread in North America.

EEEV has been detected in eastern Canada, all U.S. states east of the Mississippi, and some additional states such as Arkansas, Minnesota, South Dakota and Texas. This virus is usually associated with swamps and marshes, and its distribution is not homogeneous: it is particularly common along the Gulf coast from Texas to Florida, along the Atlantic coast, and in some midwestern states around the Great Lakes. Madariaga virus occurs in parts of Central and South America, especially along the Gulf coast.

Enzootic VEE viruses have varying distributions in parts of Mexico, South and Central America. They are absent from Canada and most of the U.S.; however, Everglades virus (subtype II) occurs in Florida, and Tonate virus (variant III-B) was detected in Colorado and South Dakota in the 1970s. Enzootic VEEV I-E viruses pathogenic for equids have been detected only in Mexico; I-E viruses currently found in other parts of Latin America do not seem affect these animals.

Epidemics caused by epidemic VEE viruses (VEEV I-AB and I-C) tend to occur in northern South America, but also affect other parts of South and Central America. Some outbreaks have spread into North America.

Transmission

Eastern equine encephalomyelitis

In North America, EEEV is normally maintained in wild bird populations. *Culiseta melanura*, a mosquito that preferentially feeds on birds, is the most important vector in this sylvatic cycle. Other, mosquito species that feed on both birds and mammals (“bridge vectors”) may transmit EEEV to humans and domesticated mammals; however, recent evidence suggests that *C. melanura* may also play a direct, and perhaps significant, role. *Culex* spp. might be the main vectors for Madariaga virus (EEEV lineages II-IV) in South American sylvatic cycles. Other arthropods including chicken lice, chicken mites (Dermanyssidae) and assassin bugs can be infected with EEEV, and chicken mites can transmit the virus experimentally. How EEEV survives the winter in cold climates is still uncertain, but several mechanisms, including persistence in reptiles, prolonged persistence in birds, vertical transmission in mosquitoes, and periodic reintroduction by migrating birds, have been suggested.

When birds are in close contact, EEEV can sometimes spread by methods not involving arthropods. This has been documented in captive game birds (e.g., pheasants), which can be infected by the oral route. The presence of large amounts of virus on the feathers of these birds suggests that transmission might occur by pecking, feather picking or preening. Cannibalism could also play a role. Emus can shed large amounts of virus in rectal and oral secretions, and in regurgitated material.

Horses, humans and other mammals are generally considered to be incidental (dead end) hosts for EEEV, but some horses develop a transient viremia sufficient to infect

mosquitoes, and horse to horse transmission has been demonstrated by this route in the laboratory.

Western equine encephalomyelitis

WEEV is normally maintained in wild bird populations, and *Culex tarsalis* appears to be the most important vector for this virus in North America. WEEV can also be transmitted by other mosquitoes, especially some members of the genus *Aedes*. A sylvatic cycle between the mosquito *Aedes melanimon* and blacktail jackrabbits (*Lepus californicus*) has also been reported, probably after they become infected from the bird/mosquito cycle. Overwintering mechanisms for WEEV are uncertain, but similar mechanisms as for EEEV have been proposed.

Horses and humans infected with WEEV do not develop significant viremia, and are true dead-end hosts. This virus can cross the placenta in humans, and congenitally infected infants have been reported.

Other WEEV complex viruses

Highlands J virus is transmitted by *Culiseta melanura* mosquitoes, but the main vector for Fort Morgan virus is the cimicid swallow bug (*Oeciacus vicarius*), an ectoparasite of swallows.

Venezuelan equine encephalomyelitis

Enzootic VEE viruses are mainly thought to cycle between mosquitoes in the genus *Culex* and wild small mammals, especially rodents. In the North American Rocky Mountains, the cycle for Tonate virus (Bijou Bridge virus) was reported to involve birds and the swallow bug *Oeciacus vicarius*. Equids do not amplify enzootic VEE viruses.

Horses are the main amplifiers for epidemic VEE viruses. Other mammals do not seem to be epidemiologically significant in transmission, although sufficient viremia to infect mosquitoes has been reported in humans, and occasionally in other species (e.g., cattle, pigs, dogs). Many species of mosquitoes can transmit epidemic VEEV, and efficient vectors have been described in the genera *Aedes*, *Anopheles*, *Culex*, *Mansonia*, *Psorophora* and *Deinocerites*. Blackflies could be important mechanical vectors for epidemic strains during some outbreaks. Mites are also capable of transmitting these viruses mechanically. Ticks including *Amblyomma cajennense* and *Hyalomma truncatum* can be infected by both enzootic and epidemic VEEV strains, although their role in nature (if any) is unclear. Horses can shed epidemic VEEV in body fluids, and some authorities suggest that these viruses might be spread occasionally by direct contact or via aerosols. However, there are no reports of direct transmission between horses, or from horses to humans, in nature.

Most people are infected by exposure to VEEV-infected arthropods, but cases have also been documented after laboratory accidents or exposure to aerosolized debris from the cages of infected laboratory rodents. Person-to-person transmission has never been reported, although VEEV has been detected in pharyngeal secretions and horizontal

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transmission is theoretically possible. VEEV can cross the placenta in pregnant women.

VEEV is reported to persist for a time in the environment, in dried blood and exudates. In a recent experiment, inactivation of 90% of an epizootic strain of VEEV on a glass surface took approximately 98 hours at room temperature (20-25°C) in the dark. Whether viruses in the environment would infect animals or humans this long is uncertain, as the researchers used various procedures such as sonication to recover as much bound virus from the glass as possible. The persistence of EEEV and WEEV in the environment is unknown, but EEEV has been isolated from feather quills for up to 6 days.

Disinfection

As enveloped viruses, alphaviruses are likely to be susceptible to many common disinfectants including 1% sodium hypochlorite, 70% ethanol, quaternary ammonium compounds, phenolic disinfectants, 2% glutaraldehyde and formaldehyde. EEEV is known to be inactivated by exposure to 50% ethanol for 1 hour. Alphaviruses are susceptible to moist or dry heat, and to drying or ultraviolet light. Togaviruses have been inactivated by heat of 65°C for 15 minutes.

Infections in Animals

Incubation Period

The incubation period for WEE or EEE in horses is 5-14 days. The initial signs of VEE can occur 1-5 days after infection, although neurological signs usually appear around day 5.

Clinical Signs

Eastern and western equine encephalomyelitis complex viruses in equids

Eastern and western equine encephalomyelitis are very similar in horses, although the course of EEE may be shorter. Some animals may have asymptomatic infections or mild cases without neurological signs; however, in classic cases of encephalitis, an initial prodrome characterized by nonspecific signs (e.g., fever, anorexia and depression) is followed by neurological signs that may include altered mentation, hypersensitivity to stimuli, involuntary muscle movements, impaired vision, behavioral changes (e.g., aimless wandering, head pressing, circling), an inability to swallow, ataxia, paresis, paralysis and/or convulsions. Periods of excitement or intense pruritus have been reported, and laterally recumbent animals sometimes have a characteristic paddling motion. In addition, some animals may develop diarrhea or constipation, or have significant weight loss. Some affected horses die within a few days, particularly when infected with EEEV. Horses that recover from encephalitis have a high incidence of residual deficits.

Other WEEV complex viruses in equids

Highlands J virus has been linked rarely with encephalitis in horses. Fort Morgan virus is not known to affect mammals.

Venezuelan equine encephalomyelitis in equids

Infections with epidemic VEE viruses may be asymptomatic, mild or resemble clinical EEE and WEE. In symptomatic horses, a febrile prodrome with depression, tachycardia, and inappetence is sometimes followed by neurological signs indicative of encephalitis. Some animals also have diarrhea and colic. Death can occur within hours after the onset of neurological signs; after a protracted illness accompanied by dehydration and extreme weight loss; or in animals without signs of encephalitis. Sudden death has also been reported. Animals that recover may have permanent neurological signs.

Enzootic VEE viruses usually infect equids subclinically or cause only mild, nonspecific clinical signs. However, an I-E strain found in Mexico can cause severe illness with encephalitis and high mortality.

Equine encephalomyelitis viruses in other mammals

Neurological signs caused by EEEV have been reported in various animals including llamas, alpacas, deer, sheep, cattle, dogs, pigs and a harbor seal. In one published report, all affected dogs were young (≤ 6 months of age), and the clinical signs included fever and diarrhea as well as signs of encephalitis. The clinical signs in these dogs progressed rapidly to recumbency, seizures and other CNS signs within 24-36 hours, and all affected dogs died or were euthanized. During outbreaks in pigs, the illness was most severe in nursing piglets, with reported signs including fever, lethargy, frank CNS signs and high mortality in some outbreaks. Emaciation, dyspnea and excessive salivation, as well as neurological signs, were documented in white-tailed deer (*Odocoileus virginianus*). A young sheep remained alert and maintained a good appetite until it was euthanized, despite fever and neurological involvement that progressed from front limb incoordination to forelimb and hindlimb paralysis with muscle fasciculation and paddling. Seizures were the main sign in a harbor seal, together with anorexia and lethargy; the latter signs may also have been related to molting.

Deaths have been reported in various mammals including rabbits, goats, dogs and sheep during some VEE epidemics; however, laboratory experiments suggest that illnesses in most of these species are unusual. Fatal infections have been documented in experimentally infected rabbits; however, goats, sheep and dogs inoculated with epidemic VEE viruses had few or no clinical signs (although some dogs infected via mosquitoes developed leukopenia and lymphopenia in addition to fever). Susceptible rodents can develop nonspecific signs (e.g., lethargy, anorexia, weight loss) and/or neurological signs after inoculation, and

nonspecific febrile illness has been reported in nonhuman primates.

Western and eastern equine encephalomyelitis viruses in birds

WEEV and EEEV infections are asymptomatic in many birds; however, EEE outbreaks have been reported in several avian species, with syndromes ranging from neurological signs to hemorrhagic enteritis. Clinical signs reported in pheasants included fever, depression, weakness and profuse diarrhea, in addition to neurological signs such as incoordination, circling, tremors, and partial or complete paralysis of the legs. Chukar partridges infected with EEEV were dull and listless, typically found with ruffled feathers, sitting on their hocks with the beak on the ground, while lethargy, ataxia and paresis of the legs and neck were reported in whooping cranes. In a colony of African penguins, early signs of anorexia, mild lethargy and intermittent vomiting, were followed by persistent regurgitation, ataxia, seizures, and diarrhea that was mild in most birds but voluminous in a few. Most penguins recovered, but subtle, intermittent ataxia persisted in some birds. Hemorrhagic enteritis, with signs of depression, diarrhea (which may contain varying amounts of blood) and regurgitation, has been reported in ratites. The onset of disease is usually rapid in these birds, and the mortality rate high. EEEV can also cause depression, decreased egg production and death in turkeys. Although adult chickens are usually unaffected, experimentally infected, 2-week-old chickens developed severe depression, followed by abdominal distention and growth retardation. Some of these chickens died.

WEE has been linked less often with disease in birds. WEEV-infected emus can be mildly to severely affected, with clinical signs that may include anorexia, lethargy, weight loss, watery diarrhea or hemorrhagic enteritis, neurological signs and sudden death. Turkeys can experience a drop in egg production and poor egg quality.

Highlands J virus has caused death in experimentally infected young chickens, turkeys and partridges, and nonspecific signs of illness and decreased egg production in adult turkeys. Fort Morgan virus can cause encephalitis and hepatitis in house sparrow nestlings, but is not known to affect other species.

Post Mortem Lesions

The gross lesions of equine encephalitis are usually nonspecific. Equids with VEE may have no lesions in the CNS or there may be extensive necrosis with hemorrhages. Necrotic foci are sometimes seen in the pancreas, liver and heart, but in general, the extracranial lesions are too variable to be diagnostically useful. Congestion of the brain and meninges has been found in some cases of EEE and WEE, and antemortem trauma can result in ecchymotic hemorrhages with any of the encephalomyelitis viruses. Piglets experimentally infected with EEEV had multifocal necrosis and inflammation in the myocardium, in addition to

encephalitis. Most birds affected by EEE or WEE have encephalitis, but hemorrhagic enteritis with multiple petechiae on the viscera has been reported in some species, including EEEV-infected emus.

Microscopic analysis of the brain tissue is often diagnostic. The typical lesion is severe inflammation of the gray matter; neuronal degeneration, infiltration by inflammatory cells, gliosis, perivascular cuffing and hemorrhages may be seen. WEE, EEE and VEE sometimes differ in the location and pattern of the lesions in the brain.

Diagnostic Tests

Eastern and western equine encephalomyelitis

In equids, EEE and WEE can be diagnosed by serology, particularly the presence of antibodies in an IgM antibody-capture ELISA, or a 4-fold rise in titer in the plaque reduction neutralization (PRN) test. Unlike in humans, cerebrospinal fluid (CSF) is not considered more reliable for detecting EEEV-specific IgM than serum. Hemagglutination inhibition (HI) and complement fixation tests can also detect antibodies to WEEV and EEEV, but cross-reactions are more of an issue than with the PRN test. In addition, complement fixing antibodies tend to appear late and do not persist, making this assay less useful for diagnosis. A presumptive diagnosis may be obtained with a high titer in a single sample from an unvaccinated horse, particularly when a combination of serological tests is used.

Because viremia usually occurs early in the infection (before the onset of neurological signs), blood is unlikely to contain EEEV in affected horses. This virus may be isolated from the brain after death, as the amount of virus in this tissue is often high, but it can disappear if the illness is prolonged. It can also be found sometimes in extracranial tissues such as the liver or spleen. Virus isolation is rarely successful in WEEV-infected horses. A number of vertebrate and mosquito cell lines can be used to isolate EEEV and WEEV viruses, including primary chicken or duck embryo fibroblasts, African green monkey kidney (Vero) cells, rabbit kidney (RK-13) cells, and baby hamster kidney (BHK-21) cells, as well as embryonating chicken eggs. If necessary, these viruses may also be recovered in newborn mice or newly hatched chicks. North American EEEV can only be distinguished from Madariaga virus with specialized tests not typically available in diagnostic laboratories. Tests that can be used to detect EEEV or WEEV antigens and nucleic acids in tissues, particularly the brain, include immunohistochemistry and reverse transcription PCR (RT-PCR).

Similar tests can be used to diagnose EEEV infections in other mammals. This virus has been isolated from the brain of some animals, including dogs, after death. Clinical EEE or WEE is relatively difficult to diagnose in birds. Avian infections have usually been diagnosed by virus isolation, but serology, immunohistochemistry to detect viral antigens in the brain, or RT-PCR may also be helpful.

Venezuelan equine encephalomyelitis

VEE can be diagnosed by virus isolation or serology. Epidemic strains of VEEV can often be recovered from the blood during the early, febrile stage of disease, but equids are usually no longer viremic once they develop neurological signs. In this situation, it may be helpful to collect blood for virus isolation from other febrile equids found nearby. VEEV is sometimes isolated from the brain at necropsy, but it may no longer be present in many symptomatic cases. This virus has been found occasionally in other tissues, such as the pancreas. Systems that have been used for virus isolation include Vero, RK-13, BHK-21 and other cell lines; duck or chicken embryo fibroblasts; and guinea pigs, mice or 1-4 day-old hamsters. VEE subtypes and variants can be identified at reference laboratories with tests such as immunofluorescence, differential PRN tests and nucleic acid sequencing. RT-PCR assays have been published.

Serological tests that have been used to detect infected horses include virus neutralization (PRN), IgM capture ELISAs, complement fixation and hemagglutination inhibition. Because antibodies develop early, some horses with encephalitis may not have a fourfold increase in paired IgG titers. Paired serum samples taken from febrile herdmates may be helpful in this situation. Antibodies from vaccination, and cross-reactivity with enzootic VEE viruses (which do not usually cause disease in horses), complicate serological diagnosis.

Treatment

There is no specific treatment for WEE, EEE or VEE other than supportive care.

Control

Disease reporting

EEE, WEE and VEE viruses are usually reportable in North America, although the specific requirements can differ with the disease and location. In addition to detecting the incursion of epidemic VEEV, which is exotic to the U.S. and Canada, reporting allows endemic diseases to be recognized when populations of infected mosquitoes threaten domesticated animals. In addition, animal cases are a warning that humans may be at risk from mosquito-borne transmission.

Prevention

Vaccination is the main method of protecting equids from EEE, WEE and VEE. Because equids are the primary amplifiers for epidemic VEEV, vaccination and movement controls on these animals are also important in controlling outbreaks. Some susceptible species of birds may be vaccinated for EEE, and the efficacy of vaccination has been tested in experimentally infected pigs. Preventing transmission from mosquitoes is difficult, but methods that have been suggested include housing animals in screened barns, particularly during the hours of high mosquito activity, and the use of mosquito repellents and fans. Mosquito abatement measures may also be implemented.

Morbidity and Mortality

Eastern and western equine encephalomyelitis

EEE and WEE tend to occur during summer and fall in temperate areas, but can be seen year-round in tropical regions. In temperate areas, these outbreaks usually end when infected mosquitoes are killed by freezes, and do not continue the following spring. Before vaccines were developed, EEE and WEE outbreaks of varying severity occurred regularly in the U.S. and Canada. Some epidemics were extensive: one WEE outbreak in 1937-38 affected more than 350,000 horses and mules in North America, and a 1947 EEE outbreak killed an estimated 12,000 horses in Louisiana. Since vaccines became available, the incidence of both diseases has decreased significantly. Relatively few cases of WEE have been reported recently, although EEE outbreaks may still be seen, particularly in unvaccinated horses or in the southern U.S., where the long mosquito season may outlast the duration of immunity from vaccination. EEE and WEE have been documented less often in South America; however, one EEE (Madariaga virus) outbreak in 2008-2009 affected more than 200 horses in Brazil, with a case fatality rate of 73%.

EEE is a life-threatening disease in equids, with a case fatality rate as high as 90% in horses with encephalitis. Many surviving animals have severe residual neurological signs. Asymptomatic infections have been recognized in serological studies, but their incidence is uncertain. Although such infections are thought to be uncommon, a recent study from Canada (Quebec) found that approximately 7-9% of unvaccinated horses had antibodies to EEEV. WEE is more likely to be asymptomatic or mild in horses than EEE; the case fatality rate is usually 20-30%, although 50% of sick animals died during one severe outbreak in 1930.

EEE can also cause significant morbidity and mortality in some other mammals and birds. All clinical cases in dogs were fatal in one report, and case fatality rates as high as 89% have been reported in alpacas and llamas. In pigs, high mortality was reported only in nursing piglets. Reported case fatality rates range from 5% to 75% in EEEV-infected pheasants, while the morbidity rate in emus was 76% during one outbreak, and the case fatality rate was 87%. High mortality has also been reported in EEEV-infected whooping cranes and glossy ibises. In a penguin colony, the prevalence of infection was 64%, and 93% of clinically affected birds recovered with intensive supportive care. Symptomatic infections have been reported less often in WEEV-infected birds; however, the morbidity rate in eight flocks of WEEV-infected emus ranged from 15% to 50%, and approximately 9% of the birds died.

Venezuelan equine encephalomyelitis

Epidemic VEE viruses arise sporadically, but can cause epidemics that may last for several years. Up to 90% of susceptible equids may be infected, with morbidity rates ranging from 10-40% in some areas to 50-100% in others. Case fatality rates in horses are estimated to be 38-90%.

Most enzootic VEE viruses do not cause serious disease or deaths in horses, but some I-E strains in Mexico have caused limited outbreaks of encephalitis. During some of the initial outbreaks in the 1990s, the case fatality rates were 30-50%.

Infections in Humans

Incubation Period

Although sources vary, the incubation period is estimated to be 1 to 7 days for VEE, 2-10 days for WEE and 4-10 days for EEE.

Clinical Signs

Eastern equine encephalomyelitis

EEE usually begins abruptly, with fever, chills, myalgia, arthralgia and abdominal pain, which may be severe enough to mimic an acute abdominal emergency. This prodrome is often but not always followed within a few days by neurological signs suggestive of encephalitis, which may include headache, irritability, focal neurological deficits, neck stiffness, confusion, somnolence or stupor, disorientation, tremors, seizures and paralysis. Some cases progress to coma. Vomiting and diarrhea may also be seen, and children sometimes develop generalized edema, facial edema or periorbital edema. The illness may be biphasic in some cases, with apparent recovery from the prodromal illness before the onset of encephalitis. Infants can develop encephalitis without other symptoms. The mortality rate for EEE encephalitis is high, and permanent brain damage, often severe, occurs in many survivors. However, people who do not develop neurological signs usually recover completely after an illness of 1 to 2 weeks. Subclinical infections also occur.

Western equine encephalomyelitis

WEE resembles EEE, but tends to be milder in most age groups. As with EEE, the initial signs are nonspecific and resemble other febrile illnesses (e.g., fever, chills, headache, vomiting, myalgia), and occasionally include respiratory signs. This prodrome may be followed by neurological signs such as restlessness, irritability, tremor and signs of focal meningeal irritation - or, infrequently, by more severe neurological signs that resemble EEE. CNS signs are more likely to occur in children, especially infants under a year of age, and are uncommon in healthy adults. Patients who recover from encephalitis can have fatigue, headaches, irritability or tremors for up to two years. Infants may have severe, lasting CNS deficits, but permanent sequelae in older children (≥ 1 year) are usually limited to persistent seizures if there were convulsions during the illness. Most adults recover completely, although permanent neurological damage is possible.

Venezuelan equine encephalomyelitis

In humans, VEE is usually an acute, often mild, systemic illness. The symptoms caused by endemic and

epidemic strains are similar. The initial signs are nonspecific and may include fever, chills, generalized malaise, severe headache, photophobia and myalgia particularly in the legs and lumbosacral region. Coughing, sore throat, nausea, vomiting and diarrhea may also be seen. A macular rash and arthralgia in the wrists and ankles were reported in some epidemics. Mild to severe neurological signs can be seen in a small percentage of affected children, and to a lesser extent in adults over the age of 50 years, but in few healthy adults (e.g., less than 1% of symptomatic young adults). VEE usually resolves within 1 to 2 weeks, with acute symptoms subsiding after 4 to 6 days, and deaths are rare.

In pregnant women, VEE can affect the fetus; fetal encephalitis, placental damage, abortion/ stillbirth or severe congenital neurological anomalies may be seen.

Diagnostic Tests

Eastern, Western and Venezuelan equine encephalitis are often diagnosed by serology in humans. A definitive diagnosis can be made by serology if 1) specific IgM is found in cerebrospinal fluid (CSF), 2) there is greater than a fourfold increase between paired titers in other serological tests, or 3) conversion from IgM to IgG is seen. A single high antibody titer may be used for presumptive identification.

In some circumstances, VEEV, WEEV or EEEV can be detected directly with virus isolation, tests to detect viral antigens or RT-PCR. VEEV may be found in blood or throat swabs, mainly during the early febrile stage of the disease, and in CSF. EEEV and WEEV can be hard to find in living patients, but EEEV can sometimes be found in the blood during the prodromal stage of the illness, and WEEV or EEEV may be detected in the CSF of patients with CNS signs. Throat swabs are occasionally positive. At autopsy, encephalitic viruses may be found in the brain, and possibly in other tissues.

Treatment

Treatment consists of supportive care. Mechanical ventilation, as well as other measures, may be necessary in some cases. The efficacy of antiviral drugs is currently unknown.

Control

Measures to prevent mosquito bites, including the use of repellants and protective clothing (e.g., long pants and long-sleeved shirts) can reduce the risk of infection. Outdoor exposure should be limited at times when mosquitoes are active, especially during outbreaks. Mosquito abatement programs such as habitat modification (e.g. the removal of standing water sources around the home) and/or the application of larvicides or adulticides may reduce the risk of human infection. Improved irrigation management has decreased vector populations in California, where a primary mosquito vector for WEEV is associated with irrigation systems.

During VEE epidemics, controlling these viruses in horses can help prevent human infections. Even when equids

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are not important in the epidemiology of a disease (i.e., EEE or WEE), cases in horses can provide an early warning for human disease. Surveillance programs in birds (including sentinel chickens) are also helpful in predicting EEE outbreaks. .

Precautions should be taken to prevent exposure to body fluids when performing necropsies on horses. Containment level 3 is required for work with EEEV, WEEV or VEEV in the laboratory. Investigational VEEV and EEEV vaccines may be available for people at high risk of infection, but have limited availability, and are not without side effects.

Morbidity and Mortality

Eastern equine encephalomyelitis

In North America, the annual incidence of EEE varies from 0 to 36 cases, with an average of 5-10 cases per year in the U.S. since the 1960s. Approximately 4-5% of people who become infected with this virus are thought to develop EEE, but studies from the 1950s and 60s suggested that few people may be exposed. Clinical cases of encephalitis occur most often in people over 55 years of age and children younger than 15. Estimates of the case fatality rate vary from 30% to 75% (survival has improved in recent years), and permanent neurological deficits can occur in survivors. Only 10% of patients are estimated to recover fully, and many survivors with severe impairment die within a few years. Permanent neurological damage and death are particularly common in children.

Clinical cases caused by Madariaga virus are infrequently reported in Latin America. During a recent outbreak in Panama, there were no deaths among 13 confirmed clinical cases, although one person with suspected EEE died. Some affected people were, however, hospitalized with severe neurological signs, and sequelae were common in these cases. Antibodies to EEEV were detected in 3% of healthy people living nearby.

Western equine encephalomyelitis

WEE was relatively common in North America at one time. Between 1955 and 1984, an average of 34 confirmed cases were reported annually in the U.S., with a range of 0 to 172. Extensive epidemics were also seen at times, with more than 3000 cases in the U.S. and Canada in 1941, and 375 confirmed cases and nine deaths reported in California in 1952. However, clinical cases have rarely been reported in North America in recent decades. The reason for this decline is uncertain; however, it does not appear to be due to reduced virus virulence. Some studies suggest that seroprevalence in healthy people has also diminished (e.g., from 34% in 1960 to < 3% in the 1990s). WEE is uncommonly reported in Central and South America, but some cases might be attributed to other diseases common in tropical regions.

WEE is usually much milder than EEE in symptomatic cases; the overall case fatality rate is estimated to be 3-4%, although it was as high as 8-15% during a severe epidemic in 1941. Adults tend to be mildly affected or remain

asymptomatic, but cases can be more severe in children and the elderly. Approximately 5-30% of young patients, and 56% of infants under a month of age, have permanent neurological damage. Except in infants (≤ 1 year), this damage mainly consists of persistent seizures.

Venezuelan equine encephalomyelitis

VEE can be widespread in human populations during epidemics, and more than 10% of the population in an area may be affected. During these outbreaks, cases usually begin weeks after the first illnesses are noted in horses. Serological studies suggest that enzootic VEE viruses might also cause significant numbers of clinical cases in Latin America; however, they may be misdiagnosed as other diseases such as dengue.

Most infections with epidemic or enzootic VEE viruses are mild or asymptomatic, with an overall case fatality rate estimated to be $\leq 1\%$ in healthy adults. Very young or elderly patients are more likely to develop severe disease. Mild to severe neurological signs may occur in 4-15% of symptomatic VEE cases, mainly in children. In these patients, estimates of the case fatality rate range from 10% to 35%, with the highest rates in children. The prognosis is considered to be excellent in patients who recover.

Internet Resources

[Centers for Disease Control and Prevention \(CDC\) Eastern Equine Encephalitis.](#)

[CDC Diseases A to Z](#)

[Pan American Health Organization \(PAHO\). Venezuelan Equine Encephalitis](#)

[Public Health Agency of Canada, Pathogen Safety Data Sheets](#)

[The Merck Manual \(Professional\)](#)

[The Merck Veterinary Manual.](#)

[United States Animal Health Association. Foreign Animal Diseases](#)

[World Health Organization. Viral encephalitis.](#)

[World Organization for Animal Health \(WOAH\)](#)

[WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals](#)

[WOAH Terrestrial Animal Health Code](#)

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