

## **EASTERN EQUINE ENCEPHALITIS VIRUS DISEASE**

(Eastern equine encephalitis, EEE)

### **REPORTING INFORMATION**

- **Class B:** Report by the end of the next business day after the case or suspected case presents and/or a positive laboratory result to the local public health department where the patient resides. If patient residence is unknown, report to the local public health department in which the reporting health care provider or laboratory is located.
- Reporting Form(s) and/or Mechanism:
  - The Ohio Disease Reporting System (ODRS) should be used to report lab findings to the Ohio Department of Health (ODH). For healthcare providers without access to ODRS, you may use the [Ohio Confidential Reportable Disease form](#) (HEA 3334).
  - The ODH [Mosquito-borne Illness Case Investigation worksheet](#) is available for use to assist in local disease investigation. Information collected from the form should be entered into ODRS and not sent to ODH, unless otherwise requested. If requested, the form can be faxed to ODH, Bureau of Infectious Diseases (BID) at (614) 564-2456 or uploaded to the ODRS record.
- Key fields for ODRS reporting include: import status (whether the infection was travel-related or Ohio-acquired), date of illness onset, symptoms, all the fields in the Epidemiology module and travel details in the Travel History module (with accurate departure and return dates along with city, province/county, state and country).

### **AGENT**

Eastern equine encephalitis (EEE) virus is an RNA virus belonging to the genus *Alphavirus* (formerly group A of the arboviruses) of the family *Togaviridae*. EEE virus does not confer significant cross-immunity with other alphaviruses (e.g., western equine encephalitis virus).

**Infectious dose:** A single bite from an infectious mosquito.

### **CASE DEFINITION**

#### **Clinical Description**

Most arboviral infections are asymptomatic. Clinical disease ranges from mild febrile illness to severe encephalitis. For the purpose of surveillance and reporting, based on their clinical presentation, arboviral disease cases are often categorized into two primary groups: neuroinvasive disease and non-neuroinvasive disease.

#### *Neuroinvasive disease*

Many arboviruses cause neuroinvasive disease such as aseptic meningitis, encephalitis or acute flaccid paralysis (AFP). These illnesses are usually characterized by the acute onset of fever with headache, myalgia, stiff neck, altered mental status, seizures, limb weakness or cerebrospinal fluid (CSF) pleocytosis. AFP may result from anterior ("polio") myelitis, peripheral neuritis or post-infectious peripheral demyelinating neuropathy (i.e., Guillain-Barre syndrome). Less common neurological manifestations, such as cranial nerve palsies, also occur.

#### *Non-neuroinvasive disease*

Most arboviruses are capable of causing acute systemic febrile illness (e.g., West Nile fever) that may include headache, myalgia, arthralgia, rash or gastrointestinal symptoms. Some viruses can also cause more characteristic clinical manifestations, such as severe polyarthralgia or arthritis due to chikungunya virus or other alphaviruses (e.g., Mayaro, Ross River, O'nyong-nyong).

## **Clinical Criteria**

A clinically compatible case of arboviral disease is defined as follows:

### Neuroinvasive disease:

- Meningitis, encephalitis, acute flaccid paralysis or other acute signs of central or peripheral neurologic dysfunction, as documented by a physician and
- Absence of a more likely clinical explanation. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, paresis and/or nuchal rigidity.

### Non-neuroinvasive disease:

- Fever (chills) as reported by the patient or a healthcare provider and
- Absence of neuroinvasive disease and
- Absence of a more likely clinical explanation. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, paresis and/or nuchal rigidity.

## **Laboratory Criteria for Diagnosis**

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, cerebrospinal fluid (CSF) or other body fluid or
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera or
- Virus-specific immunoglobulin M (IgM) antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen or
- Virus-specific IgM antibodies in CSF or serum.

## **Case Classification**

### Probable:

- Neuroinvasive disease: A case that meets the above clinical criteria for neuroinvasive disease and with virus-specific IgM antibodies in CSF or serum but with no other testing.
- Non-neuroinvasive disease: A case that meets the above clinical criteria for non-neuroinvasive disease and with virus-specific IgM antibodies in serum but with no other testing.

### Confirmed:

- Neuroinvasive disease: A case that meets the above clinical criteria for neuroinvasive disease and one or more the following laboratory criteria:
  - Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF or other body fluid or
  - Four-fold or greater change in virus-specific quantitative antibody titers in paired sera or
  - Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen or
  - Virus-specific IgM antibodies in CSF, with or without a reported pleocytosis, and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.
- Non-neuroinvasive disease: A case that meets the above clinical criteria for non-neuroinvasive disease and one or more of the following laboratory criteria:
  - Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, or other body fluid excluding CSF or
  - Four-fold or greater change in virus-specific quantitative antibody titers in paired sera or

- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen.

## **Comments**

### Imported Arboviral Diseases

Many other exotic arboviruses (e.g., Japanese encephalitis, tick-borne encephalitis, Venezuelan equine encephalitis and Rift Valley fever viruses) are important public health risks for the United States as competent vectors exist that could allow for sustained transmission upon establishment of imported viral pathogens. Healthcare providers and public health officials should maintain a high index of suspicion for cases of potentially exotic or unusual arboviral etiology, particularly in international travelers. If a suspected case occurs, it should be reported to the appropriate local health department and ODH.

### Interpreting Arboviral Laboratory Results

- Serologic cross-reactivity: In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely-related arboviruses occur, serologic testing for more than one virus may be needed and results compared to determine the specific causative virus. For example, such testing might be needed to distinguish antibodies resulting from infections within genera (e.g., flaviviruses such as West Nile, St. Louis encephalitis, Powassan, dengue or Japanese encephalitis viruses).
- Rise and fall of IgM antibodies: For most arboviral infections, IgM antibodies are generally first detectable at 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented (e.g., up to 500 days for West Nile virus). Serum collected within 8 days of illness onset may not have detectable IgM and testing should be repeated on a convalescent-phase sample to rule out arboviral infection in those with a compatible clinical syndrome.
- Persistence of IgM antibodies: Arboviral IgM antibodies may be detected in some patients months or years after their acute infection. Therefore, the presence of these virus-specific IgM antibodies may signify a past infection and be unrelated to the current acute illness. Finding virus-specific IgM antibodies in CSF or a fourfold or greater change in virus-specific antibody titers between acute- and convalescent-phase serum specimens provides additional laboratory evidence that the arbovirus was the likely cause of the patient's recent illness. Clinical and epidemiologic history also should be carefully considered.
- Persistence of IgG and neutralizing antibodies: Arboviral IgG and neutralizing antibodies can persist for many years following a symptomatic or asymptomatic infection. Therefore, the presence of these antibodies alone is only evidence of previous infection and clinically compatible cases with the presence of IgG, but not IgM, should be evaluated for other etiologic agents.
- Arboviral serologic assays: Assays for the detection of IgM and IgG antibodies commonly include enzyme-linked immunosorbent assay (ELISA), microsphere immunoassay (MIA) or immunofluorescence assay (IFA). These assays provide a presumptive diagnosis and should have confirmatory testing performed. Confirmatory testing involves the detection of arboviral-specific neutralizing antibodies utilizing assays such as plaque reduction neutralization test (PRNT).
- Other information to consider: Vaccination history, detailed travel history, date of onset of symptoms and knowledge of potentially cross-reactive arboviruses known to circulate in the geographic area should be considered when interpreting results.

## **SIGNS AND SYMPTOMS**

EEE virus infection can result in one of two types of illness: systemic or encephalitis (involving swelling of the brain). The type of illness will depend on the age of the person and other host factors. Some people who become infected with EEE virus may be asymptomatic.

Systemic infection has an abrupt onset characterized by chills, fever, malaise, arthralgia and myalgia. The illness lasts one to two weeks, and recovery is complete when there is no involvement of the central nervous system. In infants, the encephalitis form is characterized by abrupt onset; in older children and adults, encephalitis is manifested after a few days of systemic illness. Signs and symptoms in encephalitic patients include fever, headache, irritability, restlessness, drowsiness, anorexia, vomiting, diarrhea, cyanosis, convulsions and coma. [See also the [Aseptic Meningitis chapter](#).]

Approximately one-third of people with the encephalitic form of EEE die from the disease. Death usually occurs two to 10 days after onset of symptoms but can occur later. Of those who recover, many are left with disabling and progressive mental and physical sequelae, which can range from minimal brain dysfunction to severe intellectual impairment, personality disorders, seizures, paralysis and cranial nerve dysfunction. Many patients with severe sequelae die within a few years.

## **DIAGNOSIS**

Preliminary diagnosis is often based on a patient's clinical features, places and dates of travel (if patient is from a non-endemic country or area), activities and epidemiologic history of the location where infection likely occurred. In addition to the other more common causes of encephalitis and aseptic meningitis (e.g., herpes simplex virus and enteroviruses) and febrile illnesses, arboviruses such as chikungunya, dengue, LaCrosse, Jamestown Canyon, Powassan, St. Louis encephalitis, West Nile, Western equine encephalitis and Zika viruses should also be considered in the differential etiology.

Laboratory diagnosis of arboviral infections is generally accomplished by testing of serum or cerebrospinal fluid (CSF) to detect virus-specific IgM and neutralizing antibodies. During an acute infection, certain viruses can be isolated through culture or detected by nucleic acid amplification.

In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry and virus culture of autopsy tissues can also be useful. Only a few state laboratories or other specialized laboratories, including those at CDC, are capable of doing this specialized testing.

For clinical samples being sent to CDC's Arbovirus Diagnostic Laboratory for testing, the [CDC Specimen Submission Form](#) must accompany the samples. Be sure the date of illness onset and travel history fields are completed. Use test order code CDC-10282 for arbovirus serology. Please contact ODH's Bureau of Infectious Diseases (BID) at (614) 995-5599 to arrange for testing at CDC.

## **EPIDEMIOLOGY**

### **Source**

EEE is a virus circulated between birds and certain mosquito species, especially in marshy areas and swamps. Horses, humans, pheasants, emus and other animals are accidental, dead-end hosts and are not usually a source of infection to humans. The risk of exposure to EEE virus is primarily in areas where a combination of acid bogs and

cattail marshes exist. These are the breeding sites for the enzootic and epizootic vectors. Outbreaks are more likely in rural and suburban areas.

### **Susceptibility**

All individuals not previously infected with EEE virus (naïve individuals) are at risk for infection and developing disease. EEE virus infection is thought to confer life-long immunity. People who engage in outdoor work and recreational activities in endemic areas (swampy areas) are at increased risk of infection. Persons over 50 years of age and under 15 years seem to be at greatest risk for developing severe disease when infected with EEE virus.

### **Occurrence**

EEE is the rarest of the mosquito-borne arboviral infections. An average of eight sporadically occurring infections in humans are reported annually in the United States; however, the illness is fatal in at least 30% of cases and even higher case fatality rates are observed at the extremes of age. The majority of cases of EEE have been reported from the Atlantic and Gulf Coast states. EEE virus transmission occurs in freshwater hardwood swamps mostly in the Atlantic and Gulf Coast states and the Great Lakes region. There are no records of human cases acquired in Ohio. Ohio's first recorded zoonotic outbreak of EEE occurred in 1991 in Wayne and Holmes counties where 19 confirmed cases in horses were documented. Sporadic equine cases have been reported since then and a recent outbreak of EEE occurred during 2014, which involved 5 horses in Ashtabula and Trumbull counties.

### **Mode of Transmission**

The reservoir of EEE is wild birds, and the virus is transmitted by certain mosquito species. In the upper Midwest, EEE is transmitted by two swamp and marsh-breeding mosquitoes: *Culiseta (Cs.) melanura* and *Coquillettidia (Cq.) perturbans*. *Cs. melanura* is the primary enzootic vector and is a rare mosquito in Ohio. *Cq. perturbans* is a "bridge" vector and can be abundant in marshy areas. *Cq. perturbans* is believed to be the epidemic vector in Ohio, responsible for transmitting the virus to humans and equines.

### **Period of Communicability**

Humans are dead-end hosts for the virus (i.e., they do not circulate sufficient EEE virus in the blood stream to infect a mosquito). The disease cannot be spread from person to person.

### **Incubation Period**

The incubation period is 4 to 10 days.

## **PUBLIC HEALTH MANAGEMENT**

### **Case**

#### Investigation

With serologic identification of EEE infection, a complete travel history for the two weeks prior to onset should be obtained. The patient should also be questioned about donating or receiving blood, blood products and organs in the 4 weeks prior to onset of symptoms. Female patients should be asked whether they were pregnant at the time of infection, and infants should be checked whether they were breastfed before illness onset. Exposure sites can be evaluated for mosquito vectors by standard mosquito collection techniques (BG sentinel traps, light traps, larval samples).

### Treatment

There is no specific therapy for EEE. Supportive care is indicated.

### Isolation and Follow-up Specimens

Since the diagnosis of EEE is often not known until after patient discharge, enteroviral precautions (i.e., fecal, respiratory) are usually indicated for encephalitis. A convalescent sample 2-4 weeks after the acute may be required to confirm a case.

### Public Health Significance

High. Because of the virulence of EEE virus, the prognosis is poor with the high chance for fatality or severe neurologic sequelae. The report of a single case may signify an outbreak is developing. An outbreak in horses occurred in Wayne and Holmes counties for the first time in 1991. A second outbreak in horses occurred in Ashtabula and Trumbull Counties in 2014.

### Special Information

Specific diagnosis is critical to prevention.

### **Contacts**

No treatment or prophylaxis of contacts is indicated.

### **Prevention and Control**

#### Vaccination

There is no vaccine for humans. There is a vaccine for horses only, but vaccination of horses will not prevent the spread of EEE to people.

#### Vector Investigation

With the report of a human or equine case of EEE, a vector assessment should be done in the vicinity of home and travel sites to determine if an outbreak is developing. For advice on vector assessment and control measures, contact the ODH BID Zoonotic Disease Program (ZDP) at (614) 752-1029.

#### Mosquito Bite Avoidance

The best way to prevent EEE virus infection is to avoid mosquito bites. Prevention tips are similar to those for other viral diseases transmitted by mosquitoes, such as dengue or West Nile virus:

- Use insect repellent [registered with the U.S. Environmental Protection Agency \(EPA\)](#) on exposed skin. Always follow the directions on the package. When using both sunscreen and insect repellent, apply the sunscreen first then the repellent.
- Wear long sleeves, pants and socks if feasible.
- Wear permethrin-treated clothing to repel and kill mosquitoes.
- Use screens on windows and doors to exclude mosquitoes. And, when available, A/C can make households less hospitable to mosquitoes.
- Participation in community and homeowner based vector-control strategies:
  - Ensure that water does not collect in containers around the home and community by emptying water from containers such as flowerpots, buckets, barrels and tires. Change the water in pet dishes, and replace the water in bird baths weekly. Drill holes in tire swings so water drains out. Empty children's wading pools and store on their sides after use.
  - Use chemical or biological control of larvae and adult mosquitoes when necessary.

**What is Eastern equine encephalitis (EEE)?**

EEE is a rare but serious disease that is caused by a virus spread by infected mosquitoes. EEE virus is one of a group of mosquito-transmitted viruses that can cause inflammation of the brain (encephalitis). In the United States, approximately 5-10 EEE cases are reported annually.

No human cases have been reported in Ohio, but equine cases occur sporadically and during outbreaks. Two equine outbreaks occurred in Ohio in 1991 in Wayne and Holmes counties and in 2014 in Ashtabula and Trumbull counties.

**How do people get infected with EEE?**

EEE virus is transmitted through the bite of an infected mosquito. Disease transmission does not directly occur from person to person.

**Where and when have most cases of EEE occurred?**

Most cases of EEE have been reported from Atlantic and Gulf Coast states. Cases have also been reported from the Great Lakes region. EEE cases occur primarily from late spring through early fall, but in subtropical endemic areas (e.g., the Gulf states), rare cases can occur in winter.

**Who is at risk for infection with EEE?**

Anyone in an area where the virus is circulating can get infected with EEE. The risk is highest for people who live in or visit woodland habitats and people who work outside or participate in outdoor recreational activities because of greater exposure to potentially infected mosquitoes.

**How soon do people get sick after getting bitten by an infected mosquito?**

It takes 4 to 10 days after the bite of an infected mosquito to develop symptoms of EEE.

**What are the symptoms of EEE disease?**

Severe cases of EEE virus infection (EEE involving encephalitis, an inflammation of the brain) begin with the sudden onset of headache, high fever, chills and vomiting. The illness may then progress into disorientation, seizures and coma. Approximately a third of patients who develop EEE die, and many of those who survive have mild to severe brain damage.

**How is EEE diagnosed?**

Diagnosis is based on tests of blood or spinal fluid. These tests typically look for antibodies that the body makes against the viral infection.

**What is the treatment for EEE?**

There is no specific treatment for EEE. Antibiotics are not effective against viruses, and no effective antiviral drugs have been discovered. Severe illnesses are treated by supportive therapy which may include hospitalization, respiratory support, IV fluid and prevention of other infections.

**Are people previously infected with EEE immune?**

Yes, infection will provide life-long immunity to the EEE virus. It does not however provide any protection for other mosquito-borne viruses.

**Is there a vaccine for EEE?**

There are no human vaccines available, and none are currently in development. A vaccine for horses is available through veterinarians.

**How can people reduce the chance of getting infected with EEE?**

Prevent mosquito bites. It only takes one bite from an infected mosquito to transmit disease.

- Use insect repellent registered with the U.S. Environmental Protection Agency (EPA) on exposed skin and/or clothing. The repellent/insecticide permethrin can be used on clothing to protect through several washes. Always follow the directions on the package.
- Wear long sleeves and pants when weather permits.
- Have secure, intact screens on windows and doors to keep mosquitoes out.
- Eliminate mosquito breeding sites by emptying standing water from flower pots, buckets, barrels and other containers. Drill holes in tire swings so water drains out. Keep children's wading pools empty and on their sides when they aren't being used.

**What should I do if I think a family member might have EEE?**

Consult your healthcare provider for proper diagnosis.

**For more information, please visit these websites:**

- ODH EEE Information: <http://www.odh.ohio.gov/eee>
- CDC EEE Information: <http://www.cdc.gov/EasternEquineEncephalitis/>
- U.S. Environmental Protection Agency (EPA) Registered Insect Repellents: <https://www.epa.gov/insect-repellents>
- CDC Insect Repellent Use and Safety: <http://www.cdc.gov/westnile/faq/repellent.html>
- CDC Eastern Equine Encephalitis Human Case Maps: [https://wwwn.cdc.gov/arbovet/maps/ADB\\_Diseases\\_Map/index.html](https://wwwn.cdc.gov/arbovet/maps/ADB_Diseases_Map/index.html)