

# Emerging Vector-Borne Diseases

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Several mosquito-borne viral infections have recently emerged in North America; West Nile virus is the most common in the United States. Although West Nile virus generally causes a self-limited, flulike febrile illness, a serious neuroinvasive form may occur. Dengue is the most common vector-borne viral disease worldwide, and it has been a significant public health threat in the United States since 2009. Known as breakbone fever for its severe myalgias and arthralgias, dengue may cause a hemorrhagic syndrome. Chikungunya also causes flulike febrile illness and disabling arthralgias. Although meningoencephalitis may occur with chikungunya, bleeding is uncommon. Symptoms of Zika virus infection are similar to those of dengue, but milder. Zika virus increases the risk of fetal brain abnormalities, including microcephaly, if a pregnant woman is infected. Zika virus is spread through *Aedes albopictus* mosquito bites, is transmitted sexually, and may rarely spread nonsexually from person to person. Diagnosis of these vector-borne infections is clinical and serologic, and treatment is supportive. Other, well-established vector-borne diseases are also important. Ehrlichiosis is a tick-borne bacterial disease that presents as a nonspecific syndrome of fever, headache, malaise, and myalgias. It is diagnosed via blood smear testing, with confirmatory serology. Ehrlichiosis is treated with doxycycline. Rickettsial infections are transmitted by fleas, mites, and ticks, and severity ranges from mild to life threatening. Rocky Mountain spotted fever, the most significant rickettsial infection, is primarily a clinical diagnosis that presents as fever, headache, myalgias, petechial rash, and tick exposure. Doxycycline is effective for rickettsial infections if administered promptly. Vector avoidance strategies are critical to the prevention of all of these infections. (*Am Fam Physician*. 2016;94(7):551-557. Copyright © 2016 American Academy of Family Physicians.)

**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 542.

Author disclosure: No relevant financial affiliations.

Vector-borne diseases are infections that are primarily or exclusively transmitted through an invertebrate, generally insects.<sup>1</sup> Some pathogens undergo an obligate stage of their life cycle inside the vector; others use the vector only for transport and inoculation. The most common vector-borne diseases are carried through mosquitoes and ticks. Vector-borne diseases account for 17% of all infections worldwide.<sup>1</sup> The main impact of these diseases occurs abroad,<sup>1</sup> but they are becoming more common in North America. *Tables 1 and 2* summarize common vector-borne diseases.

Although the potential for importation of vector-borne diseases by travelers has been the focus of attention in recent months, other factors are likely more important in the emergence and reemergence of vector-borne disease in the United States. As a result of widening breeding sites and increased food supplies, vector populations and their distribution have increased. Simultaneously, the range of human residence and recreation has widened, driven by urbanization. The increasing overlap of human and vector habitats has made exposure more likely.<sup>2</sup>

## Emerging Viral Diseases

Currently, West Nile virus, dengue, chikungunya, and Zika virus are of particular importance because of their potential to become significant public health threats.

### WEST NILE VIRUS

West Nile virus infection is the most common vector-borne viral disease in the United States, with 2,205 U.S. cases reported in 2014 (predominantly between July and September).<sup>3</sup> Symptomatic West Nile virus infection

#### WHAT IS NEW ON THIS TOPIC: VECTOR-BORNE DISEASES

- All pregnant women with a history of travel to a Zika virus outbreak area are advised to undergo viral testing and fetal ultrasonography.
- Men with confirmed Zika virus infection should abstain from sexual intercourse or use condoms for six months after the onset of infection.
- Men who have traveled to areas of Zika virus transmission but have no known infection should abstain from sexual intercourse or use condoms for at least six months after departure from the area.
- Rare nonsexual, person-to-person transmission of Zika virus has been reported.

**Table 1. Selected Vector-Borne Viral Diseases**

Condition	Pathogen	Vector	Clinical presentation
Chikungunya	Chikungunya virus	<i>Aedes</i> mosquito	Fever (abrupt onset, remitting recurring), shaking chills, immobilizing arthralgias (especially in small joints), rash (initial flushing develops into a maculopapular rash on the trunk and limbs), myalgias, pharyngitis Generally self-limited but may have long-term sequelae Laboratory: leukopenia with relative lymphocytosis (often normal); thrombocytopenia
Dengue	Dengue virus	<i>Aedes</i> mosquito	Fever (abrupt onset), severe myalgias and bone pain, rash, mild bleeding (positive tourniquet test result); can progress, after defervescence, to capillary leak syndrome and severe bleeding diathesis (dengue hemorrhagic fever or dengue shock syndrome); potentially fatal, but this is rare if well managed Laboratory: leukopenia, thrombocytopenia, mild transaminitis
West Nile virus infection	West Nile virus	<i>Culex</i> , <i>Ochlerotatus</i> , <i>Culiseta</i> , and <i>Aedes</i> mosquitoes	Fever (acute onset), headache, malaise, myalgias, arthralgias, retro-orbital pain; often nausea, vomiting, diarrhea, brief rash; rarely central nervous system involvement (mostly in older persons) leading to acute flaccid paralysis (like polio), typically with meningoencephalitis; the neuroinvasive form may be fatal Laboratory: pleocytosis in patients with central nervous system disease (initially neutrophilic and subsequently lymphocytic); elevated cerebrospinal fluid protein; may have hyponatremia
Zika virus infection	Zika virus	<i>Aedes albopictus</i> mosquito	Fever, rash, myalgias, arthralgias, headache, conjunctivitis; generally self-limited If a pregnant woman is infected, there is a risk of fetal microcephaly and malformations Laboratory: nonspecific

DEET = diethyltoluamide.

\*—Insect protection measures include use of permethrin spray for clothing, insect repellent (e.g., DEET 20% to 50%, picaridin, IR3535, oil of lemon eucalyptus), and barriers (e.g., long-sleeved shirts, long pants, well-screened windows, insecticide-impregnated bed nets).

†—The Centers for Disease Control and Prevention's National Notifiable Diseases Surveillance System is available at <https://www.cdc.gov/nndss/default.aspx>.

is usually a self-limited, nonspecific, flulike febrile illness, although a maculopapular eruption with defervescence is typical.<sup>3</sup> The neuroinvasive form occurs in one out of 30 to 70 cases. This form has a fatality rate of approximately 5% to 10% and may lead to flaccid paralysis, typically with meningoencephalitis.<sup>3</sup> Extrapyramidal symptoms can occur with West Nile encephalitis. Flaccid paralysis is asymmetric and can involve facial and respiratory muscles. Guillain-Barré syndrome and other neuropathies have also been associated with West Nile virus. Neuroinvasive infection can be diagnosed by detecting West Nile virus-specific immunoglobulin M (IgM) antibodies in the serum of cerebrospinal fluid. However, cross-reactivity with related Flaviviridae, such as dengue, can occur, and antibodies may not be present in the first week of illness. Treatment is supportive.<sup>3,4</sup>

## DENGUE

Although unknown before the mid-20th century, dengue is the most common vector-borne viral disease in the

world.<sup>5</sup> Before 2009, only a few sporadic, imported cases had been reported in the United States. Since then, it has consistently been a U.S. public health concern, with 837 cases reported in 2013.<sup>6</sup> Most of these were travel related, but outbreaks of local transmission have occurred in Texas and Florida. Most recently in 2015, an outbreak occurred on Hawaii Island.<sup>7</sup> Dengue is now endemic in Puerto Rico.

Like West Nile virus infection, dengue presents abruptly as a flulike febrile illness, but with myalgias and arthralgias so severe the disease is also known as breakbone fever. The characteristic rash of dengue is erythematous and confluent with patches of unaffected skin, occurring mainly on the limbs. Petechiae sometimes can be seen at sites of compression, such as with blood pressure cuffs or tourniquets. Thrombocytopenia is also characteristic. In patients who have previously been infected with any of the other four serovariants of the virus, dengue hemorrhagic fever or dengue shock syndrome can arise after resolution of the initial febrile illness. This is characterized by capillary leak syndrome

<i>Diagnosis</i>	<i>Treatment options</i>	<i>Prevention</i>
<p>Clinical: severe arthralgias, largely indistinguishable from dengue</p> <p>Serologic and molecular diagnostics are available</p> <p>Positive findings on viral culture of serum; may not be detectable in first two weeks of illness</p>	<p>Acute supportive care: analgesics, antipyretics</p> <p>Chronic arthralgias: nonsteroidal anti-inflammatory drugs, corticosteroids; chloroquine (Aralen) and hydroxychloroquine (Plaquenil) in refractory cases</p>	<p>No vaccine available</p> <p>Mosquito control and avoidance*</p> <p>Nationally notifiable disease†</p>
<p>Clinical: severe myalgias and arthralgias; characteristic erythematous and confluent rash on limbs with patches of unaffected skin</p> <p>Serologic testing is available but may cross-react with other Flaviviridae</p> <p>Antigenic and molecular diagnostics are not widely available</p>	<p>Supportive care: analgesics, antipyretics (aspirin and nonsteroidal anti-inflammatory drugs should be avoided), aggressive but judicious fluid resuscitation, blood product replacement</p>	<p>No vaccine available in the United States (newly available in Mexico)</p> <p>Mosquito control and avoidance*</p> <p>Nationally notifiable disease†</p>
<p>Clinical: self-limited, nonspecific flulike illness; a maculopapular eruption with defervescence is typical</p> <p>Serologic testing is available but may cross-react with other Flaviviridae; may not be detectable in first week of illness</p> <p>Antigenic, molecular, and culture methods lack sensitivity</p>	<p>Supportive care: analgesics, antipyretics</p>	<p>No vaccine available</p> <p>Mosquito control and avoidance*</p> <p>Blood donor screening</p> <p>Nationally notifiable disease†</p>
<p>Clinical: nonspecific viral syndrome</p> <p>Serology is available, but may cross-react with other Flaviviridae; molecular testing is also available</p> <p>Viral culture has low sensitivity</p> <p>Real-time reverse transcriptase polymerase chain reaction testing of urine is recommended if symptoms began less than 14 days earlier</p>	<p>Supportive care: analgesics, antipyretics (not aspirin)</p>	<p>No vaccine available (in phase I trials)</p> <p>Mosquito control and avoidance*</p> <p>Nationally notifiable disease†</p> <p>Use of condoms may decrease the risk of sexual transmission</p>

and a severe bleeding diathesis, and is uncommon in the United States. Dengue is rarely associated with neurologic complications.

Dengue can be diagnosed through a blood test showing IgM antibodies to dengue virus. However, cross-reactivity with related viruses can produce false-positive results. Treatment is supportive, although aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided because of the potential for worsened bleeding and Reye syndrome.

#### CHIKUNGUNYA

Chikungunya virus was first isolated in East Africa in 1952 and gained notoriety in the 2005 Indian Ocean epidemics.<sup>8</sup> Transmission has subsequently become established in the Caribbean and the Americas, where *Aedes* mosquitoes are ubiquitous and further spread is anticipated.<sup>9</sup>

Although not phylogenetically related to dengue, chikungunya is a similar disease producing flulike febrile illness often associated with a maculopapular rash and

distinctively disabling arthralgias. Compared with dengue, chikungunya is less likely to cause constitutional symptoms (fever is occasionally absent), leukopenia, and thrombocytopenia, and is more likely to involve small joints (e.g., ankles, wrists, interphalangeal joints).<sup>10</sup> Bleeding is rare with chikungunya. Ocular complications may occur, and meningoencephalitis is possible in children. Chikungunya can be diagnosed by detecting IgM antibodies to the virus in blood; however, antibodies may be undetectable in the first two weeks of infection. Treatment is supportive; it is wise to avoid aspirin and NSAIDs until dengue has been excluded. Corticosteroids, NSAIDs, and, in refractory cases, chloroquine (Aralen) and hydroxychloroquine (Plaquenil) have been recommended to treat the chronic arthritis that can be a sequela of the acute illness.<sup>11</sup>

#### ZIKA VIRUS

Zika virus infection, like dengue and chikungunya, spreads rapidly. Zika virus was initially reported in Oce-

**Table 2. Selected Vector-Borne Bacterial Diseases**

Condition	Pathogen	Vector	Clinical presentation
Ehrlichiosis	<i>Ehrlichia</i> , <i>Neorickettsia</i>	<i>Amblyomma americanum</i> (Lone star) tick	Fever, headache, malaise, myalgia
Tick-borne spotted fever rickettsial infections (including Rocky Mountain spotted fever)	<i>Rickettsia</i>	<i>Dermacentor</i> , <i>Rhipicephalus</i> and <i>Amblyomma maculatum</i> (Gulf Coast) ticks	Abdominal pain, fever, myalgias, rash on the extremities, eschar
Tularemia	<i>Francisella tularensis</i>	<i>Dermacentor</i> and <i>Amblyomma</i> ticks, <i>Chrysops discalis</i> (deer fly)	Fever, skin ulcer at site of inoculation, regional lymphadenopathy
Typhus (e.g., flea-borne [murine typhus], louse-borne [epidemic typhus], mite-borne [scrub typhus])	<i>Rickettsia</i> , <i>Orientia</i>	Rat flea ( <i>Xenopsylla</i> ), human body louse ( <i>Pediculus</i> ), squirrel flea ( <i>Orchospea</i> ), larval mite chigger ( <i>Leptotrombidium</i> )	Murine: fever, headache, myalgias, rash Epidemic: intractable headache, unproductive cough, rash (late) Scrub: eschar, deafness, fever, headache, malaise, myalgias, regional lymphadenopathy, tinnitus

DEET = diethyltoluamide; IM = intramuscularly; IV = intravenously.

\*—Insect protection measures include use of permethrin spray for clothing, insect repellent (e.g., DEET 20% to 50%, picaridin, IR3535, oil of lemon eucalyptus), and barriers (e.g., long-sleeved shirts, long pants, well-screened windows, insecticide-impregnated bed nets).

†—The Centers for Disease Control and Prevention's National Notifiable Diseases Surveillance System is available at <https://wwwn.cdc.gov/nndss/default.aspx>.

ania. An outbreak occurred in Brazil in May 2015, and the virus has since been identified throughout the Americas.<sup>12</sup> It is carried by *Aedes albopictus* mosquitoes, which have a wide range in the United States. This suggests a significant potential for spread once it is introduced in this country. In July 2016, local mosquito-borne transmission was confirmed in the United States.<sup>13</sup> Zika virus mosquito-borne transmission is endemic in the U.S. territories of Puerto Rico, the Virgin Islands, and American Samoa. Other current endemic regions include the rest of the Caribbean, Mexico, Central and South America (except Chile and Uruguay), Papua New Guinea and several islands in Oceania, and the Cape Verde Islands off the west African coast.<sup>14,15</sup>

Symptoms of Zika virus infection are similar to those of dengue, but generally less debilitating. Like West Nile virus infection, Zika virus infection is associated with Guillain-Barré syndrome.<sup>16</sup>

Infection in pregnant women increases the risk of structural brain abnormalities in the fetus, including microcephaly<sup>17,18</sup>; this risk may be lower if infection

occurs in the third trimester.<sup>19</sup> Women who are pregnant or potentially pregnant should avoid travel to areas in which Zika is spreading. If they choose to travel to these areas, mosquito avoidance measures should be taken.<sup>20</sup> All pregnant women who have traveled to areas of Zika transmission are advised to undergo testing for Zika virus infection and fetal ultrasonography.<sup>21</sup>

Unusual among arboviruses, Zika virus appears to be sexually transmitted by infected men to male and female sex partners.<sup>22,23</sup> For this reason, men with confirmed infection should abstain from sexual intercourse or use condoms for six months after the onset of infection. Men who have traveled to areas of Zika virus transmission should take similar precautions for at least six months after departure from the area.<sup>24</sup> Suspected female-to-male sexual transmission and a case of nonsexual person-to-person transmission have also been reported.<sup>25,26</sup>

Although diagnosis can be made with the detection of IgM antibodies to Zika virus, this method is hampered by extremely limited testing facilities and cross-reactivity with related viruses (such as dengue). The Centers for

Diagnosis	Treatment options	Prevention
Clinical: nonspecific flulike illness, meningoencephalitis Elevated transaminases, leukopenia, thrombocytopenia Characteristic inclusions (morulae) may be demonstrated on blood smears Serologic confirmatory tests are available	Doxycycline: 100 mg every 12 hours (adults), 2.2 mg per kg every 12 hours (children < 45 kg [100 lb])	Tick avoidance* Nationally notifiable disease†
Clinical: nonspecific flulike illness Rash is initially macular and later petechial, and can involve the hands and soles (Rocky Mountain spotted fever) Culture, microscopic, molecular, and serologic methods are available; only polymerase chain reaction and culture are specific for Rocky Mountain spotted fever ( <a href="http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm">http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm</a> )	Doxycycline: 100 mg every 12 hours (adults), 2.2 mg per kg every 12 hours (children < 45 kg) Treatment should be initiated promptly on clinical suspicion, without waiting for laboratory confirmation	Tick avoidance* Nationally notifiable disease†
Primarily a clinical diagnosis, with appropriate exposure history Serologic confirmatory tests are available	Streptomycin: 15 mg per kg IM twice per day for 10 days Alternatives Doxycycline: 100 mg orally or IV twice per day for 14 to 21 days Ciprofloxacin: 400 mg IV or 750 mg orally twice per day for 10 days	Tick avoidance* Glove use when skinning or handling rabbits or rodents Cook meat well Nationally notifiable disease†
Primarily a clinical diagnosis, with appropriate exposure history Biopsy, molecular, and serologic confirmatory tests are available	Doxycycline: 100 mg every 12 hours (adults), 2.2 mg per kg every 12 hours (children < 45 kg)	Tick avoidance* Avoidance of crowded conditions, good personal hygiene to decrease exposure to body lice

Disease Control and Prevention (CDC) recommends using real-time reverse transcriptase polymerase chain reaction testing of urine if symptoms began less than 14 days earlier. Testing of serum is also recommended in the first week of the illness.<sup>27</sup> However, because real-time reverse transcriptase polymerase chain reaction testing might be falsely negative if the viremia has waned, serum IgM antibody testing for Zika and dengue viruses is recommended in the person with suspected Zika infection.<sup>28</sup>

## Bacterial Diseases

### EHRlichiosis

Ehrlichiosis presents as a nonspecific syndrome of fever, headache, malaise, and myalgias.<sup>29</sup> A rash occurs in 30% of adults and 60% of children. Leukopenia and thrombocytopenia are common.<sup>30</sup> Most cases occur in the south-central and southeastern United States.<sup>29</sup> Ehrlichiosis incidence increased by fourfold from 2000 to 2008, but decreased between 2008 and 2010.<sup>29</sup> The latest national surveillance data show an increased fatality rate in children younger than five years.<sup>31</sup> Physician

hesitancy to prescribe doxycycline to children younger than eight years is a significant barrier to effective treatment. The CDC and the American Academy of Pediatrics recommend doxycycline for treatment of presumed or confirmed ehrlichiosis regardless of age.<sup>29</sup> There is a low risk of tooth staining from limited courses of doxycycline, and treatment with other antibiotics leads to higher fatality rates.<sup>31</sup>

### RICKETTSIAL INFECTION

Spotted fever *Rickettsia* infections are transmitted by fleas, mites, and ticks. These infections range from mild to life threatening. In the United States, 13,599 cases of spotted fever rickettsiosis were reported from 2008 to 2012.<sup>31</sup> Rocky Mountain spotted fever has the highest fatality rate of rickettsial infections (4% with antibiotics and up to 20% to 25% without antibiotics).<sup>32</sup> The most common life-threatening complications include meningitis, encephalitis, renal failure, and acute respiratory distress syndrome; the median time from onset of symptoms to death is seven days.<sup>31</sup> The fatality rate

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Women who are pregnant or potentially pregnant should avoid travel to areas where Zika virus is spreading. If they choose to travel to these areas, mosquito avoidance measures should be taken.	C	20	Although malformation and microcephaly are associated with Zika virus infection, the risk of acquiring an infection when bitten by an infected mosquito and the risk of adverse fetal effects if infected are unknown.
Men with confirmed Zika virus infection should abstain from sexual intercourse or use condoms for six months after the onset of infection. Men who have traveled to areas of Zika virus transmission but have no known infection should abstain from sexual intercourse or use condoms for at least six months after departure from the area.	C	24	—
Doxycycline is the drug of choice for rickettsial infections, even in children younger than eight years.	C	34	Benefit outweighs risk
Insect repellents with DEET 20% to 50% are effective for the prevention of many vector-borne diseases. Other agents such as picaridin, IR3535, and oil of lemon eucalyptus also appear to be effective.	C	38	Use in conjunction with physical barriers and other arthropod avoidance measures.
Insecticide-impregnated bed nets are effective for the prevention of mosquito-borne disease in endemic areas.	A	39	Significant benefit in decreasing incidence of malaria, a mosquito-borne infection

DEET = diethyltoluamide.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

is higher in children than in older populations.<sup>32</sup> Rocky Mountain spotted fever is primarily a clinical diagnosis, with the presence of fever, headache, myalgias, petechial rash, tick exposure, and sometimes eschar.<sup>33</sup> Doxycycline should be initiated promptly in suspected cases of rickettsial infection, even in children younger than eight years.<sup>34</sup>

### Other Vector-Borne Diseases

Other important vector-borne diseases in the United States and worldwide include Lyme disease, Chagas disease, and malaria. These have been reviewed previously in *American Family Physician*.<sup>35-37</sup>

### Prevention

Because curative therapies for vector-borne diseases are limited, prevention is an important focus. Patients should be counseled on minimizing their risk, generally via vector avoidance. The risk of transmission of mosquito-borne diseases is generally highest from dusk to dawn. However, *A. albopictus* mosquitoes feed day and night, and most ticks are daytime feeders.

An effective strategy against most insect bites is consistent use of insecticides (permethrin 0.5%) and repellents (diethyltoluamide [DEET] 20% to 50%, picaridin, IR3535, oil of lemon eucalyptus).<sup>38</sup> Barriers, such as long-sleeved shirts and long pants, well-screened windows, and insecticide-impregnated bed nets,<sup>39</sup> are essential components to insect avoidance.

**Data Sources:** In addition to a literature search of PubMed, we searched Essential Evidence Plus, the American Academy of Family Physicians, the World Health Organization website, and the CDC website using the term vector-borne disease and individual names of the diseases included in this article. Search dates: December 2015 through July 2016.

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