



# Identifying and Managing Vector-Borne Diseases in Migrants and Recent Travelers in the Emergency Department

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## Abstract

**Purpose of Review** Recognition and treatment of neglected tropical and vector-borne diseases is paramount as travel and immigration resume after a brief lull during the COVID-19 pandemic. These patients often present initially to the emergency department, and increasing physician knowledge of symptoms and treatment can reduce morbidity and mortality. This paper aims to summarize typical presentations of common tropical diseases, both neglected and vector borne, and provide the emergency physician with a diagnostic pathway based on current recommendations.

**Recent Findings** Co-circulation of ZIKV, CHIKV, and DENV is increasingly common in many countries throughout Caribbean and the Americas, requiring that patients be tested for each virus upon presentation. Dengvaxia is now approved as a vaccine against dengue in pediatric and young adult patients. A malaria vaccine, RTS,S/AS01, is currently in phase 3 trials and has been approved as a short-term vaccine by WHO for children in regions with high transmission risk after showing a 30% reduction in severe malaria. Mayaro is currently a neglected arbovirus that presents similarly to Chikungunya and is continuing to spread throughout the Americas at a rapid rate, gaining more attention after the 2016 Zika outbreak.

**Summary** Emergency physicians should consider internationally acquired illnesses to appropriately identify which patients require admission among well-appearing febrile immigrants or recent travelers presenting to the emergency department. Identifying symptomatology and understanding the appropriate workup and treatment for tropically acquired diseases will assist in recognizing severe complications with prompt treatment.

**Keywords** Mosquito-borne illness · Chikungunya · Zika · Dengue · Emergency department · Tropical infectious diseases

## Introduction

As the restrictions on travel and immigration ease after the COVID-19 pandemic, emergency physicians need to be able to recognize common tropical illnesses and appropriately treat based on symptomatology. Most vector-borne illnesses present in days to weeks following initial infection, increasing the likelihood that a returned traveler or new immigrant develop symptoms while in the USA. This article aims to aid emergency physicians in identifying mosquito and vector-borne illnesses based on signs, and symptoms, acute vs chronic presentations, and recent travel history to help guide management based upon current guidelines.

## Prevention

Country-specific guidelines are available through the World Health Organization (WHO) and Centers for Disease Control (CDC), but general considerations include prophylactic antibiotics, protection from insect bites, avoiding infected water sources, and vaccines when appropriate. However, by far the most important goal in mitigating risk of contracting mosquito or other vector-borne illnesses is bite prevention. Wearing brightly colored clothing with long sleeves and pants, sleeping with bed netting, utilizing mosquito repellent, and avoiding areas with standing-water are all recommended. Planning travel to avoid the rainy season can also reduce likelihood of infection. It is also necessary to understand the timing of activity of the *Aedes aegypti* mosquito as it is responsible for transmitting most viruses discussed in this article. This species is most active throughout the day, specifically in early morning hours after sunrise and afternoon hours leading up to sunset. The biting pattern of

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*A. aegypti* is inconspicuous, very commonly approaching from behind, biting ankles and elbows, further emphasizing appropriate skin coverage.

### Who is most at risk?

Most at risk are recent travelers returning from endemic areas, people who have migrated from endemic areas, field workers, Peace Corps Volunteers, and healthcare providers, educators, and medical students returning from medical missions.

### Management of at-risk patients

Obtaining a thorough history and physical in patients presenting to the ED after recent travel is important, with special consideration given to recent region of travel, timing since return, medical comorbidities, weather, and pregnancy. Workup should reflect a broad differential in a febrile patient as pathogens causing travel-acquired illnesses can present similarly and include complete blood count with differential, blood smear, comprehensive metabolic panel, coagulation screen, CK level, blood cultures, urinalysis, pregnancy test, and chest x-ray. These tests are useful in determining severity of illness and assist in establishing appropriate dispositions.

### Chikungunya

Chikungunya is a viral disease that is transmitted to humans by the vector *Aedes aegypti* mosquito, the same mosquito responsible for transmitting dengue, Zika, and Mayaro throughout the Caribbean and Central America. Chikungunya was originally discovered in Tanzania during an outbreak in 1952 and has since been identified in over 40 countries. The term Chikungunya comes from the African Makonde language meaning “bone-breaking pain.” The incubation phase is roughly 2–6 days after a mosquito bite after which symptoms usually begin to develop anywhere from 2 to 12 days. Patients will often develop an abrupt fever that lasts about 1 week accompanied with severe joint pain lasting 7–10 days, followed by headache, muscle ache, fatigue, and rash [1]. Polyarthralgia and polyarthritis is characteristic for Chikungunya and typically last weeks to months in 95% of patients.

Diagnosis is typically clinical as the development of acute arthralgia and fever is highly predictive in areas where disease is endemic. Main laboratory findings demonstrate lymphopenia and are closely associated with viremia. Other lab abnormalities can include thrombocytopenia, increased

transaminases, and hypocalcemia (Table 1). Definitive diagnosis is made by RT-PCR during the first week which is the viremic phase. RT-PCR can be utilized to simultaneously detect other arboviruses. If patients present beyond the viremic phase with concerns for ongoing joint pain, serum IgM is also considered diagnostic and is detectable for several months after infection [2]. For patients with chronic signs and symptoms of chikungunya, elevated levels of C-reactive protein, proinflammatory cytokines, and anti-chikungunya virus IgG and IgM correlate with disease activity and can provide information on viral persistence [3]. Understanding the different phases of CHIKV is important as patients can present to the emergency department with active or chronic presentation, which determines the appropriate workup.

There is no vaccine or antiviral drug for Chikungunya. Treatment is largely supportive, including bed rest, acetaminophen every 6 h for pain and fever, and emphasis on increased fluid intake. Education on viral persistence in the chronic phase of CHIKV is important when polyarthralgia and polyarthritis can persist from several months to years.

### Dengue

Dengue is a viral disease that is transmitted to humans by *A. aegypti*, which most commonly affects infants, young children, and adults. The disease has a seasonal pattern, corresponding to the warmer, rainy months. More than 500 million people are at risk for dengue, and in 2022, greater than 2.8 million cases were reported globally [4]. Dengue continues to be a cycling endemic problem for countries in the Americas and Caribbean with tens of thousands of cases reported annually (Fig. 1).

Symptoms can range from a mild fever to incapacitating fever with severe headache, pain behind the eyes, rash, muscle, and joint pain. Dengue can evolve into more severe forms characterized by shock, respiratory distress, severe bleeding, and organ impairment. Symptoms can progress in as quickly as a few hours and 1 in 20 people who contract dengue will develop severe symptoms, so early identification and management is important [4].

The variety in symptomatology is thought to be due to the various serotypes, known as DEN-1, DEN-2, DEN-3, and DEN 4 [5]. If a person is infected with one serotype, it is postulated that this person now has immunity against the original serotype of infection. However, this does not mean this person is immune to the other serotypes, and in fact, is at increased risk for developing severe dengue in subsequent infections versus those who have not been previously infected.

Dengue can be categorized based on a classification scheme established by WHO [7] including dengue without warning signs, dengue with warning signs, and severe dengue (see Table 1):

**Table 1** Neglected and vector-borne diseases and their clinical presentations

	Chikungunya	Chagas	Dengue	Malaria	Mayaro	West Nile Virus	Zika
Infection	Alphavirus	Trypanosoma	Flavivirus	Plasmodium	Alphavirus	Flavivirus	Flavivirus
Vector	<i>Aedes aegypti</i> <i>Ae albopictus</i>	<i>Tritomine</i> insect	<i>Aedes aegypti</i> <i>Ae albopictus</i>	<i>Anopheles</i> spp.	<i>Aedes aegypti</i> <i>Ae albopictus</i>	<i>Culex</i> spp. <i>Anopheles</i> spp.	<i>Aedes aegypti</i> <i>Ae albopictus</i>
Symptoms	Fever, malaise, arthralgias, rash, headache	Fever, headache, abdominal pain, lymphadenopathy, swelling near bite	Fever, headache, retro-orbital pain, petechial rash, bone pain	Cyclic fever, headache, altered mental status, seizure	Fever, malaise, arthralgias, myalgias	Fever, rash, nausea, vomiting, altered mental status, neck stiffness	Fever, headache, malaise, rash
Physical exam	Symmetrical inflammatory arthritis	Adenitis near site of bite	Petechial rash, + tourniquet test, pallor	Jaundice, hepatomegaly	Maculopapular rash	Encephalopathy, tremors	Diffuse maculopapular rash, flaccid paralysis
Lab abnormalities	Lymphopenia, thrombocytopenia, increased LFTs	Eosinophilia, parasitemia	Leukopenia, thrombocytopenia	Parasitemia, DIC, increased LFTs, elevated BUN/Cr	Leukopenia, thrombocytopenia	Leukocytosis, elevated CRP, lymphopenia	Thrombocytopenia
Diagnostic testing	RT-PCR assay, serology	Blood smear, serology	RT-PCR assay, serology	Blood smear	RT-PCR, serology	CSF sampling, serology	RT-PCR assay, serology

- Dengue without warning signs — evidence of recent travel or migration from endemic are with fever plus two of the following:
  1. Positive tourniquet test
  2. Rash
  3. Leukopenia
  4. Headache/rash/myalgia/arthritis
  5. Nausea/vomiting
- Dengue with warning signs — dengue infection as previously described and any of the following:
  1. Persistent vomiting
  2. Mucosal bleeding
  3. Abdominal pain
  4. Hepatomegaly
  5. Clinical fluid accumulation (pleural effusion, ascites)
  6. Lethargy or restlessness
- Severe dengue — infection plus one of the following
  1. Shock
  2. Respiratory distress
  3. Severe bleeding
  4. End organ failure

There is currently no specific treatment for dengue other than supportive care, which includes increased fluid intake and Tylenol for pain/fever. Avoid ibuprofen or aspirin as there is increased risk of bleeding, especially if there is progression to the severe form of dengue. If a patient presents with symptoms of severe dengue, admission to the intensive care unit and infectious disease consult is recommended.

Prevention is largely by avoiding mosquito bites. This includes insect repellent, wearing long pants and long-sleeved shirts, using mosquito nets when sleeping, and preventing stagnant water from collecting as these are hotspots for mosquito eggs. As of 2022, there is a vaccine available for dengue, dengvaxia, approved for children and adolescents 9–16 years old who have laboratory-confirmed previous dengue virus infection and are living in an area where dengue is endemic [7]. The vaccine is a live attenuated vaccine that is designed to protect against all four dengue serotypes.

## Chagas Disease

Chagas disease is caused by *Trypanosoma cruzi* and is considered a neglected disease given its prevalence and risk factors associated with developing and underdeveloped countries. It is endemic in 21 countries, affecting



**Fig. 1** Cases of dengue reported in Caribbean and Central America during 2022. Data extrapolated from Pan-American Health Organization [6]

more than 6 million people, and with increasing rates of migration, infected people can be identified in non-endemic countries [8]. *T. cruzi* parasites are transmitted to humans through the feces of the triatomine bugs, commonly referred to as the “kissing bug,” given their tendency to bite people’s faces. Most of these insects are found in the Caribbean and Americas. Infection commonly occurs at night, where triatomine insects will often drop from ceilings or emerge from dark crevices, depositing feces on a person’s skin while they are sleeping. The person will then scratch the infected area, introducing the insect feces into the eyes, mouth, or open wounds on the skin and is the most likely pathway of infection. Mortality has significantly declined; however, Chagas can cause irreversible and chronic problems affecting the cardiac, digestive, and nervous system. It is important to consider that most Chagas cases reported in the US present as chronic infections in migrants, rather than acute infections in the recent traveler [9].

Symptoms in the acute phase are often mild and may consist of headache, fever, lymphadenopathy cough, abdominal pain, and swelling. There also may be physical findings including a *chagoma*, which is a regional subcutaneous nodule with adenitis at the site of the bite. Even more rare, but typical of this disease, is the *Romana’s* sign, or periorbital soft tissue swelling. Up to 70% of cases progress without symptoms and remain asymptomatic [8].

If left untreated, 20–30% of cases will progress to the chronic phase, resulting in cardiomyopathy, arrhythmias, apical aneurysm, heart failure, gastrointestinal dysmotility, achalasia, and megacolon [9].

Diagnosis of Chagas is predominantly clinical with epidemiologic considerations (travel, migration, extended service in endemic country, etc.) and parasitology, with direct examination and staining of blood smears. A definitive diagnosis

of Chagas in the chronic phase of the disease requires a positive result of at least two different serologic tests (ELISA, indirect immunofluorescence, and indirect hemagglutination) that detect specific antibodies in patient sera (Table 1). Treatment is successful with either benznidazole or nifurtimox. Benznidazole is better tolerated and is FDA approved for use in the USA; however, both are the only drugs with proven efficacy in treating the disease if given soon after infection at the onset of the acute phase [10]. Considering Chagas in the differential of a patient with recent travel history is important to avoid missed diagnosis and progression to chronic phases where symptoms are no longer reversible.

## Malaria

Malaria is a disease caused by the *Plasmodium* parasite that is transmitted through the *Anopheles* mosquito. Significant efforts have been made to help eliminate malaria; however, major setbacks were reported secondary to the COVID-19 pandemic, with a 12% increase in deaths compared to 2015 [11]. Symptoms of malaria most commonly include cyclical fevers, vomiting, and headache, appearing roughly 10–15 days after infection. The most common malarial parasites are *P. vivax* and *P. falciparum* with the *falciparum* being the deadliest of malaria strains, and *vivax* results in more than 77% of infections in the Caribbean and Americas [12]. Mortality in the USA is <0.5% with most cases being diagnosed in patients who have recently traveled or migrated from endemic countries.

Despite recent trends of resurgence of Malaria, there are promising reports of a new vaccine in development. A malaria vaccine, RTS,S/AS01, is currently in phase 3 trials and has been approved by WHO for children in regions with high transmission risk after showing a 30% reduction in

severe malaria [13••]. This vaccine as of late has only been effective in short-term prevention, and long-term protection has yet to show efficacy. Multiple vaccines against both *P. vivax* and *P. falciparum* are currently underway.

Symptoms of Malaria can vary based on which plasmodium species is the cause of infection; however, per the World Health Organization and the CDC, diagnosis is made with a combination of the following symptoms: fever, liver failure or severe jaundice, acute kidney injury, acidosis, hemoglobin < 7, ARDS, hypoglycemia, hemodynamic instability, and neurological symptoms including seizures or altered mental status (AMS). Up to 5–10% of patients will also present with parasitemia [14••, 15].

Diagnosis of malaria is most done through blood smear or PCR. Other laboratory abnormalities seen include thrombocytopenia, elevated transaminases, coagulopathy, elevated BUN and creatinine, and anemia (Table 1). Treatment is multifactorial, dependent on severity of features, comorbidities, and resistance. In the emergency department, chloroquine and hydroxychloroquine are still the first-line approved medications in treatment of Malaria, especially against *P. vivax* which is still quinine susceptible [16]. For all infections with exception of *P. vivax*, artemether-lumefantrine or atovaquone-proguanil is often sufficient [15]. If these are unavailable, quinine with doxycycline or clindamycin is recommended. If *P. ovale* or *P. vivax* are suspected based on recent geographical travel, primaquine should be added to treat hepatic hypnozoites (the latent form of parasites) once testing has confirmed [17]. Primaquine should be avoided in patients with G6PD deficiency, requiring awareness of patient demographics, especially with communities of African and Mediterranean descent [18]. Treatment should be implemented in conjunction with an infectious disease specialist and transfer for the intensive care unit for further management.

## Mayaro

Mayaro virus is a single-stranded RNA arbovirus, belonging to the Togaviridae family, and is transmitted by the *Aedes aegypti* mosquito. It was first identified in 1954 in the sera of forest workers of Trinidad. Originally a virus endemic to the tropical forests of the Amazon in Brazil, it has since regained attention following the Zika outbreak in 2016 [19]. Mayaro virus is considered a neglected tropical disease even though it has since spread throughout several countries in the Caribbean and Latin America. Mayaro virus is closely related to Chikungunya and causes a debilitating flu-like illness with fever, chills, retro-orbital pain, myalgia, and arthralgias which can last upwards of months to years. Severe complications of Mayaro include myocarditis and hemorrhagic and neurological symptoms.

The virus spreads via the blood vessels into the body of an infected host, followed by replication in white blood cells (e.g., monocytes, macrophages). This leads to further spread to bones, muscles, and joints through the main sites of replication occurring in the liver and spleen [20••].

Diagnosis is clinical and based on symptomatology and epidemiology, with confirmation through similar blood work that is utilized to diagnose other mosquito-borne illnesses. PCR and ELISA serological testing are the most reliable; however, if attempting to diagnose Mayaro virus, Chikungunya and Zika should also be considered in the differential as the symptomatology is nearly identical (Table 1) [21]. If symptoms have erupted within the first 5 and testing is indicated, molecular diagnostics is appropriate via RT PCR. For patients presenting with symptoms beyond 5 days, serologic testing is appropriate via ELISA IgM [21].

Currently, there is no vaccine or specific treatment option for Mayaro virus [22]. Like many arboviruses, treatment is supportive with emphasis on fluid resuscitation, analgesics, and avoiding aspirin or NSAIDs until dengue has been ruled out. In severe cases, hospitalization may be indicated for fluid replacement, fever control, and symptom management.

## West Nile Virus

West Nile Virus is the leading cause of mosquito-borne illness in the USA. Despite its prevalence in the USA, there is an interesting absence of WNV in countries south of the US border [23••]. Current theories suggest that this could be attributed to under-reporting, as most infections are asymptomatic and can be masked by other mosquito-borne illnesses that cause similar symptoms [24]. This leads to possible misdiagnoses of Zika, dengue, Chikungunya, malaria, or Mayaro. An additional theory is that co-circulation of other Flaviviridae or arboviruses leads to cross-protection against WNV [24]. As such, considering WNV in a recent traveler or migrant is important and merits further discussion.

Overall, WNV is an asymptomatic illness, with 8 out of 10 patients not developing any symptoms [25]. Of those who do develop symptoms, 1 out of 5 develop a fever with other symptoms including rash, myalgias, arthralgias, vomiting, or diarrhea [25]. Most recover completely without complications; however, in some cases, fatigue and weakness can persist for months after infection [25]. One in 150 people develop serious symptoms, with patient > 60 at greatest risk, affecting the central nervous system including encephalitis or meningitis with accompanying high fever, headache, neck stiffness, stupor, AMS, coma, convulsions, vision loss, numbness, or weakness [25]. Recovery can take weeks to months, with the possibility of permanent CNS symptoms; mortality in patients who develop severe symptoms in the USA is 9% [26].

Diagnosis of WNV is based on clinical presentation, epidemiology, and laboratory testing of blood and spinal fluid. Routine laboratory studies have not shown to be useful in distinguishing WNV from other viral infections. WNV IgM antibody testing can help establish definitive diagnosis, and lumbar punctures should be performed in patients presenting with neurologic symptoms [27]. Testing cerebrospinal fluid for detection of IgM antibody should be performed as IgM may be detectable in CSF before it is detectable in serum. In addition, CSF will usually show an elevated protein ( $< 150$  mg/dL) and moderate pleocytosis ( $< 500$  cells/ $\mu$ L) with predominance of lymphocytes (Table 1) [27].

Treatment of WNV is supportive including analgesics and anti-emetics for nausea and vomiting. Patients with encephalitis should be monitored for signs and symptoms of elevated intracranial pressure and seizures. In some patients, particularly those with poliomyelitis-like symptoms, airway protection and ventilatory support may be needed.

## Zika

Zika virus is a mosquito-borne infection that was initially discovered in Uganda in 1947 in Rhesus macaque monkeys which then led to spread and infection to humans in the early 1950s. Throughout the 1960 to 1980s, Zika was predominantly detected in Asia and Africa. In 2015, a Zika epidemic erupted in Brazil, spreading throughout South America, Central America, and the Caribbean through the *Aedes aegypti* mosquito. During this outbreak, an association with Zika and microcephaly was first identified, along with evidence of sexual transmission and other neurological symptoms including Guillain–Barre Syndrome [28]. Since 2017, Zika transmission has remained prevalent throughout most countries in the Americas and Caribbean [29].

Most people infected with Zika are asymptomatic. In those who do develop symptoms, they typically present 3–14 days after infection and are mild, including rash, conjunctivitis, muscle and joint pain, headache, and malaise. Symptoms can last between 2 and 7 days. Given symptomatology parallels with other arboviruses, diagnosis must be confirmed with laboratory testing.

There are several complications of Zika that have been reported and continue to be studied. Zika virus during pregnancy has led to several complications in infants including microcephaly, limb contractures, increased muscle tone, eye abnormalities, and hearing loss, which have since been defined as congenital Zika syndrome [29]. The risk of congenital malformations following infection during pregnancy is still being studied, but to date, an estimated 5–15% of infants born to women infected with Zika have demonstrated Zika-related complications [30••]. Congenital malformations can occur following either symptomatic

or asymptomatic infection of a pregnant woman, leading to insidious outcomes including fetal loss, stillbirth, and pre-term birth [31].

Zika-associated Guillain–Barre syndrome is estimated to affect 2–3 people per 10,000 ZIKV infections, which is similar to the risk associated with campylobacter infection [32]. Symptom onset is usually within 5–10 days, and management is the same as for classic GBS, with therapeutic plasma exchange or intravenous immune globulin.

For the general population who present with uncomplicated ZIKV infection, PCR and serology testing is not recommended. Given that Zika and dengue are closely related, for symptomatic patients present with  $< 7$  days of symptoms, dengue and Zika nucleic acid amplification tests will confirm acute viral infections. For patients presenting  $> 7$  days post symptom onset, Zika and dengue IgM serology is recommended (Table 1) [33]. If neurological symptoms are present, serum testing is recommended with consideration of cerebral spinal fluid testing. Lastly, if there is concern for ZIKV exposure or asymptomatic infection of ZIKV in a pregnant patient, serum testing is recommended up to 12 weeks after onset of illness, with serial ultrasonography to monitor for congenital ZIKV [30••]. Management of Zika continues to be supportive through rest, IV fluids, and analgesics. For patients with active infections, education is important. Use of barrier protection and contraceptives is recommended for at least 2 months in women and 3 months in men as the virus has shown to last longer in semen compared to other bodily fluids [34].

In conjunction with many arboviruses endemic to the Caribbean and Americas, there is no confirmed vaccine or specific treatment option for Zika. Treatment is supportive with emphasis on fluid resuscitation, analgesics, and avoiding aspirin or NSAIDs until dengue has been ruled out. In severe cases, hospitalization may be indicated for fluid replacement, fever control, and symptom management.

## Conclusion

Many vector-borne illnesses present similarly, and as such, differential diagnosis for a febrile patient with recent international travel or migration remains broad. Given the structure and resources available in emergency departments in the USA, definitive diagnosis is unlikely. However, early identification and management is crucial in establishing an effective disposition for infected patients. Utilizing the WHO and CDC guidelines to initiate diagnostic testing and treatment is appropriate in the ED setting. Awareness of treatments for patients presenting with severe complications and knowledge of which basic labs can be collected to narrow the differential is crucial in establishing the correct care pathway to avoid complications or death in this patient population.

## Declarations

**Conflict of Interest** The author declares that she has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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