BRIEF REPORT

Clinical Update on Dengue, Chikungunya, and Zika: What We Know at the Time of Article Submission

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ABSTRACT

Objective: Mosquito-borne diseases pose a threat to individual health and population health on both a local and a global level. The threat is even more exaggerated during disasters, whether manmade or environmental. With the recent Zika virus outbreak, it is important to highlight other infections that can mimic the Zika virus and to better understand what can be done as public health officials and health care providers.

Methods: This article reviews the recent literature on the Zika virus as well as chikungunya virus and dengue virus.

Results: The present findings give a better understanding of the similarities and differences between the 3 infections in terms of their characteristics, clinical presentation, diagnosis methodology, and treatment and what can be done for prevention. Additionally, the article highlights a special population that has received much focus in the latest outbreak, the pregnant individual.

Conclusion: Education and training are instrumental in controlling the outbreak, and early detection can be lifesaving. (*Disaster Med Public Health Preparedness*. 2017;11:290-299)

Key Words: dengue, Zika, chikungunya, clinical update, mosquito

Mosquito-borne diseases have had significant effects on multiple aspects of human life throughout history. The advent of modern transportation, surging human populations, and urbanization have fostered the spread of mosquitoes and consequently disease, including malaria, yellow fever, dengue, and more recently Zika and chikungunya.[1] Mosquito-transmitted diseases caused more deaths between the 17th and 20th centuries than all other etiologies of death combined.[2] As a result of the worldwide movement of troops and supplies during World War II, there was a large spike in vector and disease spread, resulting in the expansion of endemic regions.[3] By the 1980s, the incidence of dengue was expanding at alarming rates; by 1998, 2.5 billion people lived in areas at risk for dengue.[4] In 2015, the World Health Organization noted that there were 214 million cases of malaria alone and an additional 390 million infections per year of dengue.[5,6] Today, more than one-third of the world's population lives in geographic areas at risk for mosquito-transmitted infections.[7] This impact is further amplified in the event of a disaster, as mosquitoes typically breed in standing water, which is fostered by the breakdown or lack of infrastructure.

Beyond the repercussions these diseases have on an individual's health, mosquito-borne diseases have significant effects on a country or region's economy. Few studies have attempted to assess the true financial consequences of disease management, and the studies that are available often look at one specific disease, one single country or region, or one single outbreak, thus making extrapolating global expenditures difficult. Puerto Rico in 1977 had a single dengue outbreak estimated to cost the United States between US $6 and US $16 million.[1,8,9] Included in the cost analysis were both direct costs of medical and epidemic control measures (eg, draining swampland) and indirect costs (eg, lost work days). In Colombia, in 2010, the total cost for management of dengue (including medical and nonmedical expenses) was US $167.8 million; 46% of the cost was attributed to efforts to prevent mosquitoes from entering households.[10] A 2011 study looked at the cost of dengue in North and South America and found a combined expenditure of US $2.1 billion per year, of which approximately 60% of the cost was attributed to work force losses.[11] However, even given this daunting figure, that analysis did not include the economic cost for mosquito prevention. Another group of researchers attempted to estimate disability-adjusted life years, a measure of years lost in the workforce as the result of poor health, morbidity, or mortality due to dengue alone in 8 countries across the Americas and Asia.[12] They estimated an average cost of between US $587

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million and US $1.8 billion per year due to disability-adjusted life years alone, but this figure is thought to be an underestimate owing to underreporting of these diseases in certain areas.[12] Prevention measures and surveillance were also not included in their analysis and would be an additional cost to these countries.

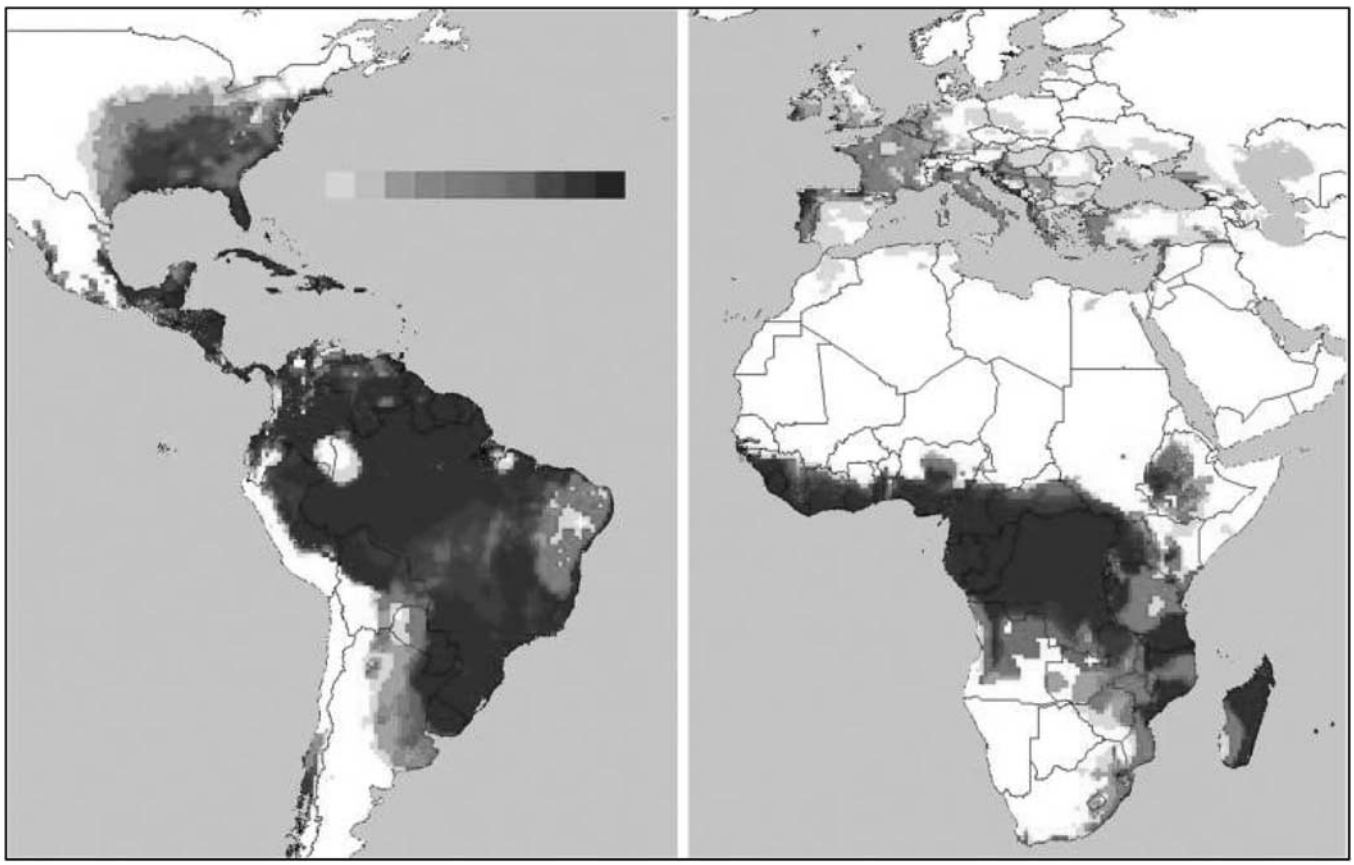
Despite the multifaceted impact mosquito-borne diseases have on society as a whole, the top priority of health care providers and public health officials is preventing morbidity and mortality. This is especially a concern for the tropical and subtropical regions of the world where mosquito vector diseases affecting humans are primarily found. There are over 3500 species of mosquitoes with only a small number capable of carrying diseases that affect humans.[7] However, those that cause disease are growing in population and geography. Malaria is transmitted by the *Anopheles* species of mosquito and is said to be the cause of over 1 million deaths every year.[7] The West Nile virus, carried by the *Culex* species of mosquito, has so significantly impacted the United States since 1999 that it is now the number one cause of arboviral meningoencephalitis in the United States.[7] In the past year, the *Aedes* species of mosquito has received significant press owing to its transmission of dengue virus (DENV), chikungunya virus (CHKV), and Zika virus (ZIKV) infections. These infections have had a significant impact, particularly in Latin America and in tropical and subtropical regions worldwide (Figure 1).[13]

VIRUS OVERVIEW

DENV, CHKV, and ZIKV share many commonalities in presentation, treatment, and prevention. All 3 viruses are transmitted through the same vector, the *Aedes* species of mosquito. Infections are spread not only from the mosquito to the human, but through transmitting the virus back to the mosquito and to other human hosts through blood-borne exposure, which is especially risky during the first week of illness when the patient is the most viremic. Additionally, disease can be spread from the human hosts through

FIGURE 1

Areas in Red Indicate the Distribution of *Aedes* Species of Mosquitoes Associated With the Spread of Dengue Virus, Chikungunya Virus, and Zika Virus Infections.



Source: Benedict MQ, et al. Spread of the tiger: global risk of invasion by the mosquito *Aedes albopictus*. *Vector Borne Zoonotic Dis.* 2007;7(1):76-85.[13]

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blood-borne exposure during the health care process and from mother to child.[14-16] All 3 can present with mild infections with symptoms of fever, rash, myalgia, and arthralgia and go unreported. The mainstay of treatment for all 3 is symptomatic control and prevention of infection by avoiding mosquito bites. However, despite these similarities, each infection has unique characteristics as well.

DENV is the most studied of the 3 viruses. Dengue fever was first described clinically by Benjamin Rush during an outbreak in Philadelphia in the 1770s. Since then, large outbreaks of DENV were identified in Southeast Asia during the 1950s followed shortly by outbreaks in the tropical and subtropical areas of the Americas.[14] Over 500,000 new cases of severe infection are identified each year worldwide, with many more cases of benign self-limited infections that go largely unreported.[7] Dengue is a virus belonging to the Flaviviridae family, which is responsible for many medically important debilitating viruses, including West Nile, yellow fever, and St. Louis encephalitis.[6] While transmission of DENV is primarily through the bite of an infected mosquito, transmission has also been documented through blood transfusions, organ or tissue transplants, occupational exposures in health care settings (ie, needle stick), and vertical transmission.[17,18] In the contiguous United States, Florida has reported the only case of locally transmitted DENV.[19] However, the infection is prevalent to Hawaii, and more than 500 cases of travel-associated dengue were reported in 2015 (Table 1).[7,19-21]

CHKV, belonging to the Togaviridae family, is thought to have originated in Tanzania in the 1950s, but the first observed large outbreak in the Americas did not occur until 2013 in the Caribbean islands.[22] Since then, local transmission has been documented in 45 countries and territories in North, South, and Central America with over 1.7 million suspected cases, and according to the Centers for Disease Control and Prevention (CDC), no locally acquired infections in the United States.[15] Over 600 cases of confirmed CHKV infection have been reported to the CDC, all of which are associated with travel (Table 1).[23] Transmission of CHKV is primarily via the mosquito. However, transmission has been reported in health care workers via blood-borne transmission and in newborns of affected mother via in utero transmission (mostly during the second trimester) or intrapartum transmission (especially when the mother was viremic at time of delivery).[24-26] One study looked at 39 women with intrapartum infection just prior to delivery and found 19 of the neonates to also be infected with CHKV.[25] During the CHKV epidemic in Reunion Island, an insular region of France located in the Indian Ocean close to Madagascar, more than 300,000 people, one-third of the population, contracted CHKV, and the vertical transmission rate for infected mothers to infants at the time of delivery was 48.7%.[26] Infected neonates were commonly asymptomatic at birth but around day 4 of life presented with sepsis, thrombocytopenia, and rarely disseminated intravascular coagulation.[26] One-third of the infants had neurologic manifestations as well, including cerebral edema, encephalitis, and cerebral hemorrhages.[26] Fortunately, no reports of transmission through breastfeeding have been documented.[15]

ZIKV, belonging to the Flaviviridae family, derives its name from the Zika forest in Uganda where the index case occurred in the 1940s.[16,27] It was not until 1964 that the first documented human case of ZIKV was reported.[28,29] Until the later 2000s, only 14 cases were officially documented with possible outbreaks reported in Africa, Southeast Asia, and the Pacific Islands.[16] The virus became more widely reported in 2007 with cases seen throughout these areas.[16] In May 2015, the first documented case was identified in northeastern Brazil; it is unclear when exactly the disease arrived to Brazil, but some public health leaders believe it may have been introduced during the 2014 Soccer World Cup given the huge influx of travelers during this time.[27]

The majority of ZIKV cases manifest in urban slums where large populations inhabit small geographic areas proximate to standing water and poor sanitation.[27] Locally acquired infection with ZIKV has been reported in Puerto Rico and the US Virgin Islands, but as of yet, no local transmission has occurred in the contiguous United States.[16,20] However, this does not mean that the United States is without risk of having a massive outbreak of ZIKV. As of April 6, 2016, 346 travel-associated cases of ZIKV infection have been reported in the United States with additional cases being identified during the writing of this paper (Table 1).[20] Although disease transmission is most common through bites from the mosquito, 7 cases of sexual transmission have been documented as well as the identification of the virus in asymptomatic blood donors.[16,30] Recent studies have also linked the virus to vertical transmission with devastating congenital defects in infants born of infected mothers.[16] However, no viral transmission has been confirmed to infants from breast milk of infected mothers.

PRESENTATION AND DIAGNOSIS

Individuals living and traveling in Latin America, Southeast Asia, and the Pacific Islands are at highest risk for DENV, CHKV, and ZIKV.[13] Clinically, the 3 viruses are often difficult to differentiate owing to similarities in the patient's presenting signs and symptoms. Additionally, current testing shows cross-reactivity among Flaviviruses, making diagnosis more difficult. For patients with acute fever, rash, myalgia, or arthralgia and recent travel within the previous 2 weeks to an endemic area, DENV, CHKV, and ZIKV infections should all be considered and appropriate travel history questions must be asked and documented (Table 2).[31]

Dengue Virus

Infections with DENV can range from an asymptomatic clinical course to severe illness. Up to half of DENV-infected

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TABLE 1

Laboratory-Confirmed DENV, CHKV, and ZIKV disease cases reported to ArboNET by state or territory from 2015-2016[a]

	DENV		CHKV		ZIKV	
State	TAC (N = 540)	LAC (N = 165)	TAC (N = 679)	LAC (N = 0)	TAC (N = 820)	LAC (N = 0)
Alabama	0	0	1	0	2	0
Alaska	0	0	1	0	0	0
Arizona	16	0	19	0	3	0
Arkansas	1	0	4	0	5	0
California	95	0	176	0	52	0
Colorado	9	0	6	0	5	0
Connecticut	3	0	13	0	1	0
Delaware	1	0	0	0	5	0
District of Columbia	9	0	0	0	6	0
Florida	75	1	70	0	162	0
Georgia	6	0	9	0	25	0
Hawaii	19	164	7	0	10	0
Idaho	1	0	3	0	0	0
Illinois	23	0	19	0	16	0
Indiana	0	0	7	0	10	0
Iowa	3	0	2	0	7	0
Kansas	4	0	11	0	2	0
Kentucky	1	0	8	0	6	0
Louisiana	0	0	0	0	7	0
Maine	4	0	2	0	6	0
Maryland	10	0	19	0	26	0
Massachusetts	6	0	30	0	28	0
Michigan	13	0	7	0	9	0
Minnesota	3	0	4	0	19	0
Mississippi	2	0	1	0	3	0
Missouri	2	0	3	0	5	0
Montana	1	0	1	0	1	0
Nebraska	0	0	4	0	2	0
Nevada	1	0	1	0	7	0
New Hampshire	1	0	1	0	4	0
New Jersey	51	0	27	0	17	0
New Mexico	1	0	0	0	3	0
New York	51	0	69	0	198	0
North Carolina	5	0	14	0	15	0
North Dakota	0	0	1	0	0	0
Ohio	10	0	9	0	14	0
Oklahoma	2	0	2	0	6	0
Oregon	4	0	3	0	7	0
Pennsylvania	23	0	8	0	24	0
Rhode Island	3	0	5	0	11	0
South Carolina	4	0	3	0	1	0
South Dakota	2	0	0	0	0	0
Tennessee	8	0	7	0	5	0
Texas	24	0	43	0	42	0
Utah	0	0	3	0	2	0
Vermont	3	0	1	0	1	0
Virginia	19	0	22	0	27	0
Washington	16	0	26	0	5	0
West Virginia	1	0	0	0	6	0
Wisconsin	4	0	7	0	2	0
Wyoming	0	0	0	0	0	0

	DENV		CHKV		ZIKV	
Territories	TAC (N = 0)	LAC (N = 46)	TAC (N = 0)	LAC (N = 202)	TAC (N = 6)	LAC (N = 1854)
American Samoa	NA	NA	NA	NA	0	29
Puerto Rico	0	43	0	198	5	1,804
US Virgin Islands	0	3	0	4	1	21

[a]Abbreviations: CHKV, chikungunya virus; DENV, dengue virus; LAC, locally acquired cases; NA, not available, TAC, travel-associated cases; ZIKV, Zika virus. DENV and CHKV data were current as of January 12, 2016; ZIKV data were current as of June 22, 2016. Cases were reported as either due to local mosquito-borne transmission (ie, locally acquired cases, or LAC) or due to travelers returning from affected areas, their sexual contacts, or infants infected in utero (travel-associated cases, or TAC).

Sources: Centers for Disease Control and Prevention. Zika virus disease in the United States, 2015-2016. http://www.cdc.gov/zika/geo/united-states.html. Accessed June 25, 2016.[20]

Centers for Disease Control and Prevention, United States Geological Survey. CDC-USGS Disease Maps 2016. http://diseasemaps.usgs.gov/index.html. Accessed June 25, 2016.[21]

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TABLE 2

Comparison Between DENV, CHKV, and ZIKV Signs, Symptoms, Laboratory Findings, Diagnosis, Treatment, and Special Considerations[a]

	ZIKV	CHKV	DENV
Vector		*Aedes* species	
Fever	Low-grade	High-grade	High-grade
Rash	Maculopapular erythematous rash	Pruritic, maculopapular rash, petechial rash (rarer)	Pruritic petechiae
Other Signs & Symptoms	Exudative conjunctivitis, myalgia, arthralgia, HA Rare: Guillain-Barré disease	Severe arthralgia (especially small joints), GI sx Rare: myelitis, retinitis, meningoencephalitis conjunctivitis, epistaxis, subconjunctival hemorrhage	DF: HA, myalgia DHF/DSS: DF sx plus extensive hemorrhage, hepatomegaly, third spacing of fluids, shock
Laboratory Findings	Lymphopenia	Neutropenia	DHF/DSS: Thrombocytopenia, lymphopenia, hypoglycemia, hypocalcemia, hyponatremia, lactic acidosis, coagulopathy
Diagnosis	IgM/IgG RT-PCR	IgM/IgG analysis Viral particle analysis of serum/plasma for virus	IgM ELISA/IgG RT-PCR
Treatment		Supportive (avoid NSAIDs in DENV)	
Effect on Infants via Vertical Transmission	Possible increased rates of microcephaly, hearing and vision deficits	Nonspecific viral infection seen in age three to seven days	Increased rate of LBW infants
Complications	Mortality rare, possible association with increased rates of Guillain-Barré and meningoencephalitis	Mortality rare, chronic joint pain	Mortality rare, more common in those with DHF/DSS

[a]Abbreviations: CHKV, chikungunya virus; DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; ELISA, enzyme-linked immunosorbent assay; GI, gastrointestinal; HA, headache; LBW, low birth weight; NSAIDs, nonsteroidal anti-inflammatory drugs; RT-PCR, reverse transcription polymerase chain reaction; sx, symptoms.

individuals will be asymptomatic and another large percentage will have a nonspecific, relatively benign and self-limited course. For these patients, DENV is seldom identified without diagnostic testing. The more benign presentation is especially prevalent in patients under the age of 15 years or those experiencing DENV for the first time.[32] These patients recover fully without the need for hospital care.[14]

Classic dengue fever is commonly seen in children over 15 years of age and in adults following 2 to 7 days of high fever up to 40° C (104° F) with 2 or more associated symptoms.[32] Symptomology often includes, but is not limited to, severe headache, diffuse maculopapular erythematous rash, retro-orbital eye pain, myalgia, arthralgia, and mild hemorrhagic manifestations.[14] High fever associated with dengue fever can be especially precarious as patients are at risk for seizures and other neurological deficits. Hemorrhagic manifestations are often subtle and present in the form of easy bruising or petechiae found on the lower extremities, buccal mucosa, soft and hard palate, and subconjunctival mucosa.[31] Epistaxis, gingival bleeding, gastrointestinal bleeding, or urogenital bleeding may also be associated with dengue fever. Patients will commonly have laboratory studies showing leukopenia with a lymphocyte predominance and varying degrees of thrombocytopenia.[31] Additionally, these patients can have significant nausea and vomiting leading to dehydration. During this phase of the disease process, the infection is virtually indistinguishable from more severe dengue infections; however, if signs of severe sepsis, including hypothermia, leukocytosis, and bandemia, are present, these can be an indicator of a more severe disease with high risk for complications.[14,33]

As the clinical course can drastically range from a self-limited, relatively benign disease to a potentially life-threatening one, careful monitoring of confirmed or suspected patients is essential.[31] In severe dengue fever, there is substantial plasma leak. Patients will display characteristics of 3 pathophysiological phases: a febrile phase, a critical phase, and a convalescence (reabsorption) phase.[31] During the febrile phase, the patient will have a viremia-driven high fever lasting typically 2 to 7 days.[28] These patients can have severe leukopenia (less than 5000 cells/mm^3) with lymphocyte predominance and an increase in atypical lymphocytes.[31] These laboratory findings can also suggest that the fever will resolve within the next 24 hours, suggesting the patient will be entering the next phase of illness.[31] Later in the febrile phase, patients may exhibit hepatomegaly without jaundice before progressing to the critical or plasma leak phase.[31] As defervescence occurs, patients are at high risk of hemorrhage and plasma leak, especially into the pleural and abdominal cavities causing significant pain and shortness of breath. Severe dengue fever is characterized by significant intravascular

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losses, increasing the risk for hypovolemic shock and cardiac compromise.[14] Clinically, evidence of plasma leak can be seen as shock with tachycardia, hypotension, narrow pulse pressures, cool extremities, sudden hematocrit increase (more than 20% with a normal hemoglobin suggestive of hemoconcentration), thrombocytopenia (less than 100,000 cells/mm^3), ascites, pleural effusion, oliguria, and hypoalbuminemia.[14,31] Patients can also experience intracranial hemorrhage, hypoglycemia, hypocalcemia, hyponatremia, lactic acidosis, coagulopathy, fulminant hepatic failure, and prolonged refractory shock resulting in death.[14,31] If recovery is to occur, the critical period of shock should last no longer than 24 to 48 hours.[14,31] The final phase of a severe dengue infection is the convalescence or reabsorption phase, which usually lasts 2 to 4 days.[14,31] During this time, intravascular volume stabilizes, accumulated fluids are reabsorbed, vital signs stabilize, appetite returns, and patients have a general sense of well-being.[14,31] However, patients can still experience rash characterized by confluent, sometimes pruritic, petechiae with multiple small round islands of unaffected skin.[34] Caution at this phase should be exercised with fluid administration, because patients in this phase are at risk for intravascular fluid overload.[14,24,31]

Chikungunya Virus

CHKV infections have an average incubation period of 2 to 4 days with a range of 1 to 12 days.[15] The name chikungunya, which literally means "that which bends up," was derived from the acute onset of bilateral migratory arthralgia that typically affects the small joints of the fingers, wrists, toes, and knees and varies in severity from mildly irritating to completely incapacitating.[15] The arthralgia and arthritis are usually symmetric and affect more than one joint.[22] The clinical course is most often mild and self-limiting, lasting 7 to 10 days; the resulting arthralgia, however, may persist for several years.[15] In addition to arthralgia and arthritis, the infection can also present with fever, myalgia, headache, and occasionally a maculopapular, pruritic rash.[34] The rash, which typically lasts 2 to 3 days, is typically distributed on the torso, limbs, and face and can involve the mucus membranes (especially in children).[34] Rarely, clinicians may see neurologic (meningoencephalitis), ophthalmologic, or hemorrhagic manifestations.[15,35] A distinguishing feature of CHKV infection from DENV is that CHKV infection is typically associated with lymphopenia rather than the neutropenia seen with DENV.[15] Additionally, CHKV generally has a more rapid onset and worse arthralgia compared with DENV and can result in arthritis, which especially when present in the hands and feet helps to distinguish the disease from DENV and ZIKV.[24,36] These more severe manifestations are typically seen in older patients as children generally have a more self-limited infection. Mortality is rare, but possible, in CHKV-infected patients and occurs most commonly in older adults as the result of neuroinvasive disease or cardiopulmonary failure.[37] Women with active infection at the time of delivery have a high risk of vertical transmission.[38] Neonatal infection usually presents between days 3 and 7 of life and manifests with fever, poor feeding, and fussiness.[38,39]

Zika Virus

ZIKV typically causes a self-limited illness with an estimated incubation period of only a few days after a bite from an infected mosquito.[16,40] Of the first reported cases, the majority were seen in individuals between 20 and 40 years of age, but outliers ranged from as young as 4 months to as old as 98 years.[27] It is unclear at this time what population is most at risk of acquiring ZIKV infection. The illness is characterized by a maculopapular erythematous exanthem that starts on the face or trunk and then spreads to the extremities, palms, and soles.[34] This rash is very similar to that seen in CHKV infections. Other symptoms similar to DENV and CHKV infections include low-grade fever, exudative conjunctivitis, myalgia, arthralgia, and headaches.[16,29] Additionally, several neurological conditions, including Guillain-Barré syndrome and meningoencephalitis, have been linked to patients infected with ZIKV.[41,42] Additionally, to be discussed below in its own section, there is a possible causal link noted from the Brazilian outbreak associated with ZIKV-infected mothers and noted increased rates of microcephaly in infants.[16,40,43]

DIAGNOSIS

Clinical presentation and a physical exam by an astute clinician will be vital for diagnosis as confirmatory testing takes time and usually is not timely enough to alter management. Patients presenting with symptoms suggestive of DENV, CHIKV, or ZIKV with the appropriate travel history or sexual contact should be treated appropriately for the infection while confirmatory testing is pending. As patients will present in a wide spectrum of severity, confirmatory testing is especially important in the patient who is ill appearing with hemodynamic instability or other concerning symptoms requiring admission. Testing is also important in women of childbearing age who are pregnant or planning to become pregnant. Additionally, depending on the current CDC guidelines, it can be helpful to send confirmatory testing to monitor the disease outbreak and its potential spread.

Molecular assays and serologic testing for specific immunoglobulins are the most common laboratory protocols used to confirm diagnosis of DENV, CHKV, and ZIKV.[14-16] Reverse transcription polymerase chain reaction (RT-PCR), a manner of amplification to identify specific DNA material from a sample for the purpose of disease identification, is the most common test performed on samples from patients less than 5 days from symptom onset. This is the period of time that viremia is the highest and the actual virus is the most likely to be found in the blood. However, diagnosis, even with serology, can be difficult given the cross-reactivity of many Flaviviridae strains.[14-16] After 5 days from symptom onset, molecular assays are the most appropriate due to decreasing viremia but increasing levels of immunoglobulins

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(IgM and IgG) in the blood.[14-16] For DENV infections, at day 5, there is an 80% chance that IgM will be detected and by day 10 the detection is 99%.[24] For CHKV, testing can also be accomplished by looking for specific viral nucleic acids or neutralizing antibodies in the blood serum.[15] The virus has even been isolated from viral cultures of serum samples.

In the United States, confirmatory testing is the responsibility of the CDC and the individual state's health department.[31] For the CDC, specimens should be frozen and sent on dry ice with official CDC or state health department submission forms that include a brief clinical description of the patient.[44] However, each health department has its own policies and procedures and some institutions will have an infection control team that coordinates submission of samples. Health care providers should check with their own institution for information on diagnostic testing. Results are usually available within 4 to 14 days.[14-16,44] Additional information on confirmatory testing can be found on the CDC's and individual health department's websites.

TREATMENT AND PREVENTION

The *Aedes* species of mosquito, the mosquitoes responsible for the transmission of DENV, CHKV, and ZIKV, poses a unique threat relative to other species of mosquitoes that transmit malaria and West Nile virus. The vectors responsible for malaria and West Nile typically feed from dusk until dawn and are found in wet areas.[14-16] Contrastingly, the *Aedes* species of mosquitoes live predominantly in urban areas and feed continuously throughout the day.[13] The species have adapted as the result of urban development and the scarcity of large bodies of standing water and are often found in window air conditioning units and even in water droplets inside bottle caps.[7] They possess a voracious appetite and preferentially feed on humans. These characteristics make the eradication of these mosquitoes particularly challenging.

Preventing mosquito bites is the most efficacious way of avoiding the negative health impacts of each disease.[14-16] Currently, no vaccine or specific treatment exists for DENV, CHKV, or ZIKV infections. Fortunately, other than rare cases of sexual contact and blood-borne transmission, there does not seem to be a transmission risk for people who are simply in close contact with infected persons. Although no local ZIKV mosquito transmission has occurred yet in the United States, the CDC is now recommending that pregnant women avoid sexual activity with travelers returning from an endemic country with any exposure or symptoms within 2 weeks of returning.[16] When planning travel to countries where DENV, CHKV, and/or ZIKV are endemic, travelers are advised to visit the CDC website to understand the most recent outbreaks, and if outbreaks are present should be advised to wear insect repellent, wear protective clothing (eg, pants and long sleeves), and use mosquito netting at night.[14-16] Insect repellants that contain approved chemicals such as diethyltoluamide (DEET), picardin, and IR3535 should be worn on any exposed skin during travel.[14-16] General precautions should be taken by citizens to avoid mosquito bites.[14-16] The simple precautions outlined above can easily and effectively limit the risk of transmission of DENV, CHKV, and ZIKV in addition to other vector-borne viruses (eg, West Nile and malaria).[14-16]

Treatment for all 3 infections is largely supportive and involves symptomatic control. Most treatment will be started prior to confirmatory testing. Patients should be closely monitored in terms of hemodynamics, hematologic parameters, and volume status. For DENV in particular, early identification of the disease process and mitigation of resulting complications can be life-saving. Mortality rates have been shown to decrease from 20% to only 1% with good supportive medical care.[6] These patients will need close monitoring for hypovolemia, fluid shifts, and hemorrhage; if any of these do occur, these patients will need intensive care and monitoring. The treatment of choice for CHKV infection is high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) to help control symptoms of severe arthralgia.[22] However, since these diseases can present similarly, great care needs to be taken with the history and physical to distinguish presentations because the use of NSAIDs in DENV-infected patients can increase the risk of hemorrhage.[7]

In addition to prevention and treatment, hospitals should also have plans in place to address specific needs to protect the work force. Fortunately, no special precautions need to be taken to prevent transmission other than standard universal precautions.[14-16,24] This includes the typical precautions health care workers use daily with all patients they encounter such as hand hygiene, wearing gloves as needed, and avoiding unnecessary contact with a patient's bodily fluids. A process should be in place for obtaining laboratory specimens and sending these specimens to the appropriate testing facility. Additionally, health care providers should receive additional education and training on how to rapidly and accurately identify those individuals with suspicion of infections. Education should extend beyond clinical presentations because appropriate questions regarding travel history and any sexual contacts could be a major clue in accurate diagnosis and treatment given the similarities in clinical presentation. Furthermore, it is now recommended that individuals with recent travel to endemic countries abstain from blood donation for 4 weeks after return to the United States. Many health care systems are advocating for screening of all pregnant women for travel history and symptoms at each clinic or hospital visit. If a travel screen is positive, additional medical history can be obtained and these patients are encouraged to follow up with a specialist during their pregnancy.[14-16]

SPECIAL POPULATIONS: PREGNANT WOMEN

Although ZIKV has been prevalent since the 1950s, no previous association between the virus and congenital

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abnormalities existed. With increasing numbers of affected pregnant women in Brazil the previous year, there has been a corresponding increase in the number of newborns with microcephaly.[45] Microcephaly is defined as a head circumference of more than 3 standard deviations below the mean for age and sex. Between October 2015 and March 2016, there were a total of 6158 cases of microcephaly or other central nervous system malformations reported in Brazil in newborns.[45] For comparison, the same country reported only an average annual case number of 163 between 2001 and 2014. Additionally, in Brazilian states where ZIKV is endemic with confirmation via laboratory testing, the prevalence of microcephaly is 2.8 infants per 10,000 live births compared to 0.6 infants per 10,000 live births in Brazilian states not involved in the ZIKV outbreak as confirmed by negative ZIKV testing.[43,45] So far, this increase in congenital malformations has only been reported in Brazil and French Polynesia, with 2 additional cases associated with stays in Brazil reported in the United States and Slovenia. There is much debate among experts as to whether these findings truly suggest causation rather than simply a correlation. However, the causation is growing ever stronger due to 2 specific findings. First, the incidence of microcephaly is both temporally and geographically associated with the rise in ZIKV infections, and secondly, multiple virologic studies have confirmed that the virus does cross the placenta and has been detected in infants with microcephaly with infected mothers.[44,45]

Given this associated risk, the CDC has outlined guidelines for the management of pregnant women with potential exposure to ZIKV.[46] Pregnant women with a positive travel history to an endemic area with 2 or more symptoms suggestive of ZIKV and/or who have had an ultrasound concerning for microcephaly or intracranial calcifications should undergo further testing and follow-up.[43] Although increased cases of microcephaly are seen in ZIKV-infected mothers, the rate and risk of this occurring is still unknown. Should an infant be born to a ZIKV-infected mother and not have microcephaly or intracranial calcifications, the infant should still be tested for ZIKV. If the infant tests positive or the test results are inconclusive, the infant should undergo a series of additional tests including cranial ultrasound, hearing and vision screening, and thorough evaluation for neurologic abnormalities or dysmorphic features.[30] If the infant is found to have microcephaly or intracranial calcifications, the infant will warrant close specialist follow-up with repeat hearing screens at 6 months and monitoring for appropriate accomplishments of development milestones. Children with microcephaly have varied clinical outcomes from no effects to seizures, developmental delay, and even death.[41] If fetal loss occurs in suspected ZIKV cases, the current recommendation is for RT-PCR and immunohistochemical testing of fetal tissue, umbilical cord, and placenta.[44,46] This testing is important from a public health standpoint in determining the extent of the outbreak as well as in determining if there is a true link between intracranial birth defects and intrapartum ZIKV infection.

While there is a paucity of data on obstetrical and perinatal effects of CHKV, the available literature suggests that pregnant women have no increase in illness severity compared to the general population.[38] There have been case reports that women with viremia at delivery had increased rates of nonreassuring fetal heart tones; however, as of yet, CHKV has not been associated with any adverse pregnancy outcomes.[15] The virus may cross the placenta and lead to fetal infection as mentioned previously, and women with active infection at the time of delivery have a high risk of vertical transmission.[38]

DENV is the best studied of the 3 discussed viruses; however, the data remain limited on the effects of DENV in pregnant women. There does appear to be a higher rate of low birth weight in infants and it is well established that vertical transmission can occur, although the rate is unknown.[14] Case reports also show an increased rate of preeclampsia in women infected with DENV during pregnancy.[14] One important note is that certain medical conditions, including HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count syndrome) seen peripartum may be difficult to differentiate from DENV given the overlapping clinical findings including thrombocytopenia and systemic shock.[14]

Until further data are available linking these viruses to fetal abnormalities, pregnant women should be encouraged to avoid mosquito bites and avoid travel to endemic areas. All persons, but especially pregnant women, in endemic areas should employ preventative measures as outlined above, including wearing protective clothing and using repellants on any exposed skin. DEET, picardin, and IR3535 are all generally considered safe in pregnancy when used as instructed.[46]

CONCLUSION

The identification of DENV, CHKV, and ZIKV as etiologic agents of acute illness and their recent widespread prevalence is an important public health issue. Their vectors, the *Aedes* species of mosquitoes, co-circulate in many regions, which highlights the challenge in clinically differentiating these infections during outbreaks. Given today's interconnected global populations, there is risk for even larger and more widespread outbreaks, including those in the contiguous United States and Europe. All health care providers should be educated and trained on these 3 infections so that they can appropriately consider, recognize, and treat anyone presenting with concerning symptoms and recent travel to endemic areas. In some cases, early awareness and detection and appropriate treatment can be lifesaving.

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