Malaria, dengue, and chikungunya: what physician assistants need to know

Alicia Christine Weitzel

The University of Toledo

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Malaria, Dengue, and Chikungunya: What Physician Assistants Need to Know

Alicia Christine Weitzel

University of Toledo

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Dedication

I would like to dedicate this scholarly project to my family who has supported me throughout my graduate education and encouraged me to pursue this rewarding career.
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Introduction

International travel among United States residents has increased over the years from 56.3 million trips in 2003 to 61.4 million trips in 2009. While the most common reasons for travel includes tourism and visiting friends or relatives (VFR), trips are also made for business, academics, missionary work, and health treatment (U.S. Department of Commerce, 2010b). In 2009, 12 million visits were made to destinations near the equator such as Asia, Central America, South America, Oceania, the Middle East, and Africa (U.S. Department of Commerce, 2010a). Many of these countries harbor emerging infectious diseases that often affect travelers. Therefore, the Centers for Disease Control and Prevention urges travelers to both gather information about their destination and seek pre-travel advice from a healthcare provider in order to prevent illness (Whatley, Marano, & Kozarsky, 2009). Three mosquito-transmitted infectious diseases of interest are malaria, dengue fever, and chikungunya fever. The three have similar presentations of fever, headache, fatigue, and myalgias and should be considered in a traveler with both a febrile illness and a recent history of travel to an endemic area.

Physician assistants need to be knowledgeable about malaria, dengue fever, and chikungunya fever for four main reasons: 1. they are emerging infectious diseases; 2. there is the potential for observing cases in the US among travelers; 3. because the vectors of these diseases reside in the US, there is the additional threat that the diseases may propagate from person-to-person even without a travel history; and, 4. physician assistants traveling to endemic areas need to be able to diagnose these cases and understand the potential of being exposed to these diseases.

Emerging infectious diseases
Of the various exotic diseases that manifest themselves in various parts of the world, malaria, dengue, and chikungunya are three emerging infectious diseases that require a more in-depth review. Each year there are nearly 500 million cases of malaria worldwide (Arguin & Steele, 2009) and 1,500 cases of malaria in the US (Centers for Disease Control and Prevention {CDC}, 2010, February 8b). Dengue virus causes as many as 50 million infections worldwide every year (World Health Organization {WHO}, 2009, March). While consideration of the above two diseases is virtually self-explanatory, chikungunya fever (CHIK) is included by reason of its morbidity, its ease of transmission, and the fact that it is not known in the developed countries. However, since 2005 CHIK outbreaks have spread from Africa to India and to Italy, and the virus has been reported in 40 countries (WHO, 2008a). Physician assistants should be knowledgeable on these illnesses in order to offer pre-travel advice and to diagnose cases of these infectious diseases.

A recent study set out to determine the frequency of travelers seeking medical attention due to a chief complaint of fever (Wilson et al., 2007). They also sought to determine the most common causes of febrile illnesses among these travelers. Data were gathered from GeoSentinel sites consisting of specialized travel or tropical medicine clinics throughout the world from 1997-2006. Of the 24,920 travelers included in the study, 6957 (28%) reported fever as being their chief complaint. Malaria was the most common diagnosis for those with fever (59% of cases). Other causes of systemic febrile illnesses were dengue (17%), enteric fever (5.6%), and rickettsioses (4.6%). Malaria was most frequently seen among those who traveled to Oceania and sub-Saharan Africa. In contrast, dengue was most often observed among travelers returning from Southeast Asia. However, dengue infections may have been underdiagnosed due to the short incubation period and often mild, non-specific symptoms. Of those who were diagnosed
with malaria, 90% sought care due to fever. Those diagnosed with dengue reported fever as their chief complaint in 82% of cases. This study demonstrates the frequency of malaria and dengue among travelers seeking medical care for a febrile illness (Wilson, et al.) and the importance of clinicians to consider these infectious diseases during medical diagnosis.

**Potential for observing these diseases in the US due to travel**

Physician assistants’ role is to educate traveling patients on preventive care and to inquire about recent travel in their febrile patients. The timely diagnosis and appropriate treatment is necessary to prevent complications of the diseases.

An example that highlights the importance of patient education and pre-travel advice is one that involves a family of seven who returned to the US in 2006 from visiting family and friends in Nigeria. The family did not take malaria chemoprophylaxis before or during their travel because they thought the medications were only to be used for treatment of malaria rather than for prophylaxis. While in Africa, three of the five children developed a febrile illness and were treated with antibiotics, ibuprofen, and sulfadoxine-pyrimethamine by a local physician. Upon returning to the US, four of the children began experiencing influenza-like symptoms of fever and headaches and were treated with amoxicillin and antipyretics. After three days of worsening symptoms, the parents took three of their children to the hospital where they were admitted. The children were febrile and jaundiced and had anemia, thrombocytopenia, hyperbilirubinemia, and elevated aminotransferase levels. Each had at least one manifestation of severe malaria including acidosis, hypoglycemia, or severe anemia. They were diagnosed with malaria and treated with IV quinidine and either doxycycline or clindamycin. One child was so severely ill that he required intubation, dextrose infusion, transfusion of RBCs and fresh frozen plasma, erythrophoresis, and plasmapheresis. The day after hospitalization, the two other
children were tested for *P. falciparum* and were admitted to the hospital as well (CDC, 2006b). This example highlights the importance of travel medical education as well as proper and timely diagnosis of malaria in order to prevent severe malaria from developing. If left untreated, these cases could have resulted in death.

Another, more recent, example in which chemoprophylaxis would have proven beneficial was in the occurrence of malaria in a flight crew that traveled to Ghana. Two female flight attendants and two male pilots had manifestations of malaria including fever, headache, nausea, vomiting, and diarrhea two weeks after a trip to Africa. Malaria was correctly diagnosed and all four were hospitalized. Three developed severe malaria and one required intubation due to respiratory distress. The antimalarial chemoprophylaxis, atovaquone-proguanil, was available to all four of the flight crew. However, none of the four had taken the prophylaxis (CDC, 2010c).

Cases of dengue have been reported in South Texas during times of outbreaks in Northern Mexico. Dengue should be promptly diagnosed and treated aggressively as dengue hemorrhagic fever (DHF) can be life threatening. In 2005 there was one case of DHF in a woman from Brownsville, Texas where fever, chills, headache, nausea, vomiting, abdominal pain, arthralgias, and myalgias were reported. The woman was admitted the hospital where lab results showed proteinuria, hematuria, thrombocytopenia, hypoalbuminemia, and a positive fecal occult blood test. The woman was given IV fluids to treat dehydration as well as antibiotics for a possible urinary tract infection. She improved and was later discharged. However, she was not diagnosed with dengue until after hospital discharge. Despite being misdiagnosed in the hospital, the patient’s health improved (CDC, 2007a). The correct diagnosis affords the clinician an opportunity to monitor the patient for signs of developing DHF.
Between 2006 and 2009, there were 106 reported cases of chikungunya fever in the US in travelers returning from areas where chikungunya was either known to be endemic or was experiencing an outbreak during that time period. There may have been more cases in travelers during this time that were not reported due to the nonspecificity of the complaints, misdiagnosis of chikungunya fever, and erroneous testing. (Gibney et al., 2011). Due to the sequelae of arthralgias, cerebral disorders, and sensorineural impairments (Gerardin et al., 2011), a correct diagnosis of chikungunya infection should be made in order to prepare and treat a patient for potential sequelae.

**Potential introduction to the indigenous mosquito population and propagation among US residents with no travel history**

Another important aspect of US travelers returning home from areas of the world where these diseases are endemic is the potential for these three parasites and viruses to be introduced to the indigenous mosquito population in the US. Because the US harbors the *Aedes* and *Anopheles* species of mosquitoes, there is the potential for the three infectious diseases to become endemic in the US. For example, in 2006, 35 US travelers returning from India and Reunion Island were infected with chikungunya virus. The viremia level in most of the travelers was determined to be sufficient to infect *Aedes* vectors in the US. This illustrates the possibility of chikungunya virus becoming endemic in the US (Lanciotti et al., 2007).

**Physician assistants traveling to endemic areas need to be able to diagnose these cases and understand the potential of being exposed to these diseases.**

Physician assistants may travel to endemic areas because of military obligations, disaster deployments, medical missions, business, or recreation. Therefore, they need to be able to diagnose these cases and understand the potential of being exposed to these diseases.
While malaria and dengue fever are commonly included in the medical curriculum, chikungunya virus has yet to receive sufficient coverage (WHO, 2008a). Therefore, chikungunya virus is a key topic in emerging infectious disease.
Malaria

Malaria is an infectious disease caused by one of four species of Plasmodium: P. falciparum, P. vivax, P. ovale, and P. malariae (Arguin & Steele, 2009). Recently, P. knowlesi, a malaria parasite that infects long-tailed macaque monkeys, was found to cause malaria in humans (Singh et al., 2004). The parasites are transmitted by the bite of a female Anopheles species of mosquito (Figure 1) (Arguin & Steele). The symptoms of malaria may vary greatly. A person infected may be asymptomatic or exhibit the classic symptoms of fever, headache, fatigue, abdominal discomfort, and myalgias. If malaria is not recognized and treated promptly, severe complications may develop and lead to death (WHO, 2010).

Epidemiology

Each year there are 350-500 million cases of malaria worldwide, leading to almost a million deaths (Arguin & Steele, 2009). Of the nearly one million deaths caused by malaria infections in 2006, most were in children under the age of 5. Malaria poses a great threat to many people as it was endemic in 109 countries in 2008 (WHO, 2008b). Malaria is endemic in countries in tropical and sub-tropical climates where the Anopheles mosquito thrives (Figure 2).

The threat that malaria poses to the United States exists mainly due to international travel. Each year there are 1,500 cases of malaria reported in the US (CDC, 2010, February 8b). From 1997-2006, the CDC received notification of 10,745 cases of malaria among US residents with a recent travel history. The majority of the people with malaria (59.3%) reported recent travel to sub-Saharan Africa. Malaria was fatal in 54 of the cases, and most of those cases were due to infection with P. falciparum that occurred in sub-Saharan Africa (Arguin & Steele, 2009). Because the US harbors the vector of malaria, the Anopheles mosquito, it is essential that cases
of malaria be properly diagnosed and treated to prevent reintroduction of malaria into the US (CDC, 2010, February 8b). The reintroduction of malaria has occurred in the past. There have been 63 autochthonous outbreaks of malaria in the US between 1957-2009 (CDC, 2010, February 8b).

**Lifecycle**

Malaria parasites are maintained in a lifecycle involving two hosts, humans and female *Anopheles* mosquitoes. Human infection begins when an infected female *Anopheles* mosquito takes a blood meal and introduces plasmodial sporozites. The lifecycle of malaria is outlined in figure 3. Malaria can also be transmitted via blood transfusions, sharing of needles by infected persons, accidental needle sticks, and organ transfusions (White & Breman, 2008).

**Manifestations**

Malaria may have a variety of different manifestations from asymptomatic to mild to severe with the potential of being fatal (CDC, 2010, February 8c). Incubation period is typically 7-30 days, but months may pass between transmission of the parasite and onset of symptoms (CDC, 2010, February 8c). Classically, malaria is considered an illness with stages of fever, chills, and rigors that occur every 2-3 days. However, this course of symptoms suggests infection with *P. vivax* or *P. ovale* and is rarely seen (White & Breman, 2008). Most often, those with malaria experience the symptoms of uncomplicated malaria without a pattern that was just described. The symptoms commonly include fever, lack of sense of well being, shaking chills, diaphoresis, headache, fatigue, nausea, vomiting, myalgias, orthostatic hypotension and general malaise (Table 1). Physical exam may reveal diaphoresis, splenomegaly, hepatomegaly, mild jaundice, and tachypnea (CDC, 2010, February 8c; White & Breman).
If malaria is treated promptly and adequately, the mortality rate is 0.1% (White & Breman, 2008). Without timely and proper therapy, severe malaria may develop. Severe malaria is defined as the presence of one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or acute pulmonary edema. The case fatality rate in patients with severe malaria receiving treatment is 10-20% (WHO, 2010). These are medical emergencies and the patient requires aggressive therapy. (CDC, 2010, February 8c). Since a patient may present already in a severe malarial state, it is important to present a brief summary of these specific entities.

Cerebral malaria is associated with fatality rates of 20% among adults and 15% among children (White & Breman, 2008). Manifestations include alteration of consciousness, seizures, and coma usually as a result of a diffuse cerebral encephalopathy. The following findings may be evident: divergent eyes, pout reflex, altered muscle tone, retinal hemorrhages (in up to 40%), retinal opacification (30-60%), papilledema (8% of children), and cotton wool spots (<5%). Generalized convulsions affect 50% of children. After recovering from malaria, 15% of children (and only <3% of adults) manifest neurologic defects including hemiplegia, palsies, deafness, cortical blindness, and impaired cognition and learning. Nearly 10% of children who survive will have a persistent language deficit. Children who survive cerebral malaria will have a shorter life expectancy and a greater incidence of epilepsy (White & Breman).

Metabolic acidosis results from the blockage of blood vessels by parasites which leads to anaerobic glycolysis and lactic acidosis. Other contributors of acidosis include hypovolemia and reduced lactate clearance by the liver and kidneys. Respiratory distress and circulatory failure may ensue and result in death (White & Breman, 2008).
Anemia is the result of increased clearance of infected and uninfected RBCs by the spleen. Destruction of RBCs during the lifecycle of the parasite as well as ineffective erythropoiesis contributes to anemia. Anemia may be severe enough to necessitate a transfusion. Rarely, some patients (less than 5% with severe malaria) may experience bleeding and disseminated intravascular coagulation (DIC) (White & Breman, 2008).

In severe malaria, the liver may fail to produce glucose. Along with an increased utilization of glucose by the host and parasites, hypoglycemia may develop. The clinical diagnosis of hypoglycemia is a challenge due to the absence of the normal signs of hypoglycemia as well as the overlap of the neurological signs between hypoglycemia and severe malaria (White & Breman, 2008).

While the mechanism of acute renal failure is not entirely understood, it manifests similar to acute tubular necrosis. With early treatment of dialysis or hemofiltration, the serum creatinine will likely return to normal and the likelihood of survival will increase. Renal failure rarely occurs in children (White & Breman, 2008).

The reason for the development of pulmonary edema is poorly understood and is associated with a mortality rate greater than 80%. Vigorous IV fluid resuscitation may aggravate pulmonary edema and should be monitored closely (White & Breman, 2008).

Other complications of malaria exist, which are not classified as severe malaria. This includes preterm labor and delivery of a baby of low-birth weight in pregnant women with malaria. In addition to these complications, *P. vivax* malaria may cause splenic rupture. *P. malariae* may lead to nephrotic syndrome. Rarely, an individual who has had several previous infections of malaria may develop hyperreactive malarial splenomegaly caused by an abnormal immune response. It is characterized by hepatosplenomegaly, anemia, abnormal immunological
findings, and increased susceptibility to infection (CDC, 2010, February 8c). Finally, malarial infections due to *P. vivax* and *P. ovale* are known to occasionally reactivate after a dormant period in the liver, causing a malaria relapse months or years after the initial illness (CDC, 2010, February 8c).

**Diagnostic Modalities**

A clinical diagnosis of malaria may be made in a patient presenting with a history of travel to a malaria-endemic area and the symptoms of fever, chills, diaphoresis, headaches, myalgias, nausea, and vomiting. The clinical diagnosis, however, should be confirmed by laboratory diagnostic tests (CDC, 2010, February 8a). The gold standard diagnostic test for malaria is microscopy (Arguin & Steele, 2009). A blood smear is stained with Giemsa to visualize RBCs infected with *Plasmodium* (Figure 4). The parasite density may be estimated from the blood smear as well (White & Breman, 2008). A disadvantage to this test is that it must be carried out in a laboratory with proper equipment and performed by an experienced technician (CDC, 2010, February 8a). Rapid diagnostic tests (RDTs) have been manufactured and one is currently FDA-approved for use by hospital and commercial laboratories. These tests detect malaria antigens and provide results in 2-15 minutes. The CDC recommends following this test with microscopy for confirmation of the diagnosis and to estimate the number of infected RBCs (CDC, 2010, February 8a). Polymerase Chain Reaction (PCR) is more sensitive than microscopy. However, results take longer than with microscopy and RDTs, which may not be acceptable for diagnosing cases of acute or severe malaria. Instead, PCR may be used to determine the species of malaria parasite after the diagnosis has been made by microscopy or RDT (CDC, 2010, February 8a).
Other labs, which are not diagnostic, should also be ordered to determine the severity of a case of malaria. A complete blood count (CBC) usually shows normochromic, normocytic anemia. Also, early on there may be monocytosis, lymphopenia, and eosinopenia followed by reactive lymphocytosis and eosinophilia weeks later (White & Breman, 2008). A routine chemistry panel may show severe anemia, hypoglycemia, renal failure, hyperbilirubinemia, and acid-base disturbances. The results will help guide the course of treatment (CDC, 2010, February 8a).

Therapy

The treatment for malaria is chosen based upon three aspects of infection. First, knowing the species of \textit{Plasmodium} causing the infection is essential. The course of malaria varies depending on the infecting species. For example, \textit{P. falciparum} and \textit{P. knowlesi} are known to cause more severe infections and must be treated aggressively. Some species (\textit{P. vivax} and \textit{P. ovale}) may lie dormant in the liver and therefore, require additional treatment to prevent a relapsing infection. Also, \textit{P. falciparum} and \textit{P. vivax} are resistant to certain drugs depending on which area of the world the infection was acquired. A second aspect to consider is the clinical status of the patient. Those with uncomplicated malaria can receive oral medications while those with severe malaria need to be treated parenterally. The third factor is the drug susceptibility of the infecting parasite. It is important to know what area of the world a person was visiting when he or she became infected with malaria because there are different patterns of drug resistance in different parts of the world. This information will guide the proper selection of drug therapies. If there is a confirmed case of malaria without successful determination of the infecting species, treatment that targets \textit{P. falciparum} should be chosen (CDC, 2009).
The treatment of malaria is based upon artemisinin-based combination therapies (ACTs). Chloroquine and primaquine may also be used in certain malarial infections. Table 2 outlines the appropriate treatment for various cases of malaria. It is important to note that therapy for pregnant women may be different than that described in table 2 because safety and efficacy studies have not been performed on all antimalarial drugs. Also, careful attention to proper dosing must be taken when treating children and infants (WHO, 2010).

In addition to anti-malaria drugs, antipyretics such as acetaminophen and ibuprofen should be used to control a temperature greater than 38.5°C. The use of aspirin in children is contraindicated due to the risk of Reye’s syndrome. Antiemetics and anticonvulsants may be used as needed (WHO, 2010).

Patients with severe *P. falciparum* malaria need continuing supportive care. This includes monitoring of the airway, administration of an antipyretic, blood transfusions in the event of severe anemia, and monitoring for pulmonary edema, acute renal failure, metabolic acidosis, and shock. Vital signs, urine output, and blood glucose should be measured regularly (WHO, 2010).

Travelers who become infected with malaria are often at a greater risk of developing severe malaria because they usually do not possess any immunity to malaria. When US residents return home and develop symptoms of malaria, they have a higher case fatality rate. One reason for this is that healthcare providers may not be familiar with malaria and may misdiagnose the patient. If treatment is delayed, uncomplicated malaria may develop into severe malaria. Therefore, travelers with uncomplicated malaria need prompt and effective treatment (WHO, 2010). The recommended drugs for travelers are outlined in table 2.
Another point to recognize is that resistance to antimalarial medications is an ever-growing problem due to the widespread use of the drugs. Adherence to drug regimens and the use of combination antimalarial drugs that target different aspects of the parasite’s lifecycle should help prevent resistance (WHO, 2010). The Global Plan for Artemisinin Resistance Containment (GPARC) developed by the WHO in 2011 is a plan for combating the growing threat of artemisinin-resistant malaria parasites (WHO, 2011). The main goal of GPARC is to maintain the efficacy of artemisinin-based combination therapies (ACTs). This is of utmost importance as ACTs are the first-line treatment for malaria and there are no other drug therapies that are as effective. The GPARC plans to contain, eliminate, and prevent the spread of artemisinin-resistance by focusing on five main areas including prevention of the spread of ACT-resistant malaria parasites, increasing the surveillance of resistance, improving access to diagnostic tests and therapies, investing in ACT research, and mobilizing a disease response effort (WHO, 2011).

Prevention

Travelers can reduce their risk of malaria infection by consulting a healthcare provider before traveling regarding appropriate chemoprophylaxis to prevent malaria. Options for chemoprophylaxis include atovaquone/proguanil, chloroquine, doxycycline, mefloquine, and primaquine. The appropriate drug should be chosen based on the pattern of resistance in the country of travel, the desired frequency of drug administration, and the length of travel (CDC, 2010, February 8d).

A malaria vaccine is considered to be a key component of the long-term control of malaria. The RTS,S/AS02 vaccine developed by GlaxoSmithKline Biologicals and partners shows some promise in malaria prevention. RTS,S is a fusion protein of the *P. falciparum*
circumsporozoite (CS) protein and the hepatitis B surface antigen (HBsAg). The AS02 component of the vaccine contains immunostimulants. The efficacy of the vaccine was first tested in adult men in The Gambia. Participants were randomly assigned to receive either the RTS,S/AS02 vaccine or the rabies vaccine. The vaccine was given in 3 doses (at 0, 1, and 5 months) and later, a booster at month 19 was given due to waning immunity. While adverse effects of pain at the injection site, fever, and malaise were more common in the RTS,S/AS02 group than in the control group, there were no severe adverse effects due to the experimental vaccine. The efficacy of the vaccine was 71% during the first 9 weeks of follow up and later fell to 0%. Vaccine efficacy after 3 doses was 34%. Efficacy during the 9 weeks following administration of the fourth dose was 47% (K. A. Bojang et al., 2001). A follow-up study was performed to assess the safety and immunogenicity of this vaccine after 5 years. The frequency of severe adverse affects were similar among the RTS,S/AS02 and the control group. Of the seven reported deaths, all were determined to be unrelated to the RTS,S/AS02 vaccine. This study found the RTS,S/AS02 vaccine to be safe over the long-term. While the anti-CS antibody concentration dropped over the 5 years, it remained higher than that of the control group (K. Bojang et al., 2009). The efficacy, safety, and immunogenicity of the RTS,S/AS02 vaccine has also been tested in children ages 1-4 living in Mozambique. Adverse effects including injection-site pain, fever, irritability, drowsiness, and anorexia were mainly of mild or moderate intensity, of short duration, and of similar frequency for both the experimental and control vaccine groups. The anti-CS antibody concentration rose after 3 doses and later decreased by 75% over 6 months. The efficacy of the vaccine was determined to be 27.4% and 40% among 2 different study groups. Thus the RTS,S/AS02 vaccine is well tolerated and offers protection in children against *P. falciparum* malaria infection (Alonso et al., 2004). Recently a phase three trial of the
RTS,S/AT02 vaccine was carried out in African children between the ages of six to twelve weeks of age and five to seventeen months of age. The RTS,S/AT02 vaccine was found to be 50.4% efficacious in preventing malaria in the older age group one year after vaccination. When both age categories were pooled together, the vaccine was 34.8% efficacious in preventing severe malaria. The most common adverse effects including pain and fever were similar in the treated and the control groups. However, the incidence of generalized convulsive seizures among those in the older age group was 1.04 per 1000 persons in the RTS,S/AT02 group compared to 0.57 per 1000 in the control. This vaccine has the potential to reduce the risk of malaria among children in Africa (Agnandji et al., 2011). While more research is needed to evaluate the long-term immunity to \textit{P. falciparum} malaria, it is one step in the direction of controlling malaria in areas of targeted prevention.
**Dengue Fever**

Dengue virus is a single-stranded RNA virus of the Flavivirus genus and the Flaviviridae family. The virus is transmitted to humans by the bite of an infected *Aedes* species of mosquito that carries one of the four serotypes of the virus: DEN-1, DEN-2, DEN-3, and DEN-4 (WHO, Special Programme for Research and Training in Tropical Diseases {TDR}, 2009). Infection with dengue virus is characterized by abrupt onset of a high-grade fever as well as headache, retro-orbital pain, myalgias, and rash (Peters, 2008b). Illness can become complicated by plasma leakage leading to dengue hemorrhagic fever and can progress to dengue shock syndrome (WHO, 1997).

**Epidemiology**

Of all the mosquito-borne viral diseases throughout the world, dengue is the most rapidly spreading. The virus is endemic in over 100 countries. South-east Asia and the Western Pacific are two areas bearing most of the disease burden (Figure 5) (WHO, 2009, March). The incidence of dengue fever has increased 30-fold within the last 50 years (WHO, TDR, 2009). According to the WHO estimates, dengue poses a risk to two-fifths of the world’s population and causes as many as 50 million dengue infections worldwide every year (WHO, 2009, March). Within the United States, 796 cases of dengue infection were reported from 2001-2007 (WHO, TDR, 2009). The cases of dengue in the US increased from 81 cases in 2000 to 299 cases in 2007. During this time, there was an increase in hospitalizations (Streit, Yang, Cavanaugh, & Polgreen, 2011).

Many cases of dengue fever in the US are due to travel. Travel-related dengue fever was acquired in 14 of 33 American missionaries during a trip to the Dominican Republic in 2008. Those affected had symptoms of fever, weakness, chills, and body or joint pain. Only 2 of the 14
sought pre-travel advice and none were aware of dengue in the area of travel. The travelers did not take appropriate vector precautions. They all reported opening window screens and doors in the house for improved airflow and most denied use of insect repellant. None used insecticide on clothing or bedding and none used bed nets (CDC, 2010a).

More recently, dengue infections were identified in 7 of 28 missionary workers returning to the US from a trip to Haiti in 2010. Those with dengue infection had experienced fever, headache, arthralgias, and myalgias 3-7 days after returning home. All recovered from dengue infection, with 5 requiring hospitalization. Twenty-one missionaries participated in a survey to assess pretravel preparations and knowledge and mosquito-avoidance measures. Ninety percent of those surveyed had a pretravel healthcare appointment and 57% sought pretravel health advice from internet sources. While most (95%) were informed of the risk of infectious diseases in Haiti, only 48% reported receiving pretravel knowledge about dengue. Despite being informed of the risks of infectious diseases, only 24% used insect repellant throughout the day. Also less than 50% of the travelers wore long pants and 10% wore long sleeves more than one day during their stay in Haiti. There was no statistically significant association between pretravel advice or mosquito-avoidance methods and having dengue infection. Nonetheless, travelers should have pretravel health counseling 4-6 weeks before travel. Clinicians should educate their patients on mosquito avoidance measures and possible mosquito-transmitted infectious diseases prevalent in their travel destination (CDC, 2011).

While most cases of dengue in the US were acquired during travel to Asia, the Caribbean, or Central or South America, some are acquired locally along the Texas-Mexico border (WHO, TDR, 2009). In 1995 there were 4,758 suspected cases of dengue in Tamaulipas, a Mexican state bordering South Texas. During this time, there were 29 cases of dengue fever in Texas
residents. Eight patients reported recent travel to a dengue-endemic area other than Mexico and 21 reported recent travel to Mexico. However, 7 of the 29 reported no travel outside of Texas. This suggests indigenous dengue in parts of Southern Texas (CDC, 1996). Since then, cases of dengue fever have been seen in Texas during times of dengue outbreaks in Mexico. For instance, in 2005 there were 1,251 cases of dengue fever in Tamaulipas and over 129 cases in South Texas (CDC, 2007a).

Locally acquired cases of dengue fever were also seen in Key West, Florida in 2009-2010. The first case of dengue fever involved a New York resident who had recently returned from vacation in Key West and reported no recent travel to a dengue-endemic area. The patient presented to her primary care provider with fever, headache, chills, and malaise of one day. She was diagnosed with and treated for a urinary tract infection. Two days later, the patient returned to her PCP due to worsening symptoms of severe headache, retro-orbital pain, and lightheadedness. Upon physical exam the patient had a positive Romberg test and was referred to the emergency department. After testing, which included a CT scan of the head and a lumbar puncture, returned inconclusive, the patient’s lightheadedness resolved and the patient was discharged home. Four days later, the woman returned to her PCP and received consultation with an infectious disease specialist who suspected dengue infection. The patient was diagnosed with dengue fever one week after initially presenting to her PCP. After the appropriate health officials in Florida were notified, 28 cases of dengue fever in Key West were diagnosed (CDC, 2010b). This example demonstrates the importance of knowledge of infectious diseases as well as public health issues among clinicians.

In response to the cases of dengue in Florida, increased control measures were taken to prevent the spread of the disease. Truck and aerial mosquito sprayings were increased, as were
the efforts for the detection and elimination of breeding sites. A serosurvey of Key West residents revealed that 5.4% of participants were recently infected with dengue virus. Also, serum samples of patients who previously presented with signs and symptoms of dengue infection were re-evaluated. Forty three percent of the samples tested positive for dengue (CDC, 2010b). These results suggest that there may have been cases of dengue fever that were not diagnosed.

Lifecycle

Dengue virus is maintained in the urban lifecycle as it is transmitted from mosquito to human to mosquito. The primary mosquito vector of dengue virus is *Aedes aegypti* (Figure 6). However, *Aedes albopictus* also transmits the virus (Brooks, Carroll, Butel, Morse, & Mietzner, 2010). Dengue virus is transmitted from human to mosquito when a female mosquito feeds on a viremic human. The incubation period within the mosquito lasts 8-12 days and consists of the virus spreading systemically from the mid-gut. After this period of time, the virus can be transmitted to another human during any point in the remainder of the mosquito’s life (WHO, TDR, 2009).

Manifestations

Dengue virus infections can manifest in different ways. Those infected may be asymptomatic, or have manifestations consistent with classic dengue fever, or dengue hemorrhagic fever with or without dengue shock syndrome (Table 1). The WHO divides the course of dengue illness into 3 phases: febrile, critical, and recovery. After an incubation period of 4-10 days, the febrile phase of dengue fever begins. There is a sudden onset of high-grade fever, and patients often experience headache, retro-orbital pain, myalgias, arthralgias, and facial flushing. Many complain of nausea, vomiting, and loss of appetite. Less commonly, sore throat,
injected pharynx, and conjunctivitis are noted. There may be mild hemorrhagic manifestations such as petechiae, epistaxis and gingival bleeding and rarely gastrointestinal and vaginal bleeding. Also during this time, there may be hepatomegaly and a steady decrease in the white blood cell count. The febrile phase lasts 2-7 days. At this point, it cannot be determined which cases will become severe dengue fever (WHO, 1997; WHO, TDR, 2009).

The critical phase begins around days 3-7 when the temperature decreases to and remains at 37.5-38°C or less. During this time, there may be an increase in capillary permeability leading to an increase in hematocrit (WHO, TDR, 2009). An increase in capillary permeability and plasma leakage is considered dengue hemorrhagic fever (WHO, 1997). One point to note is that before plasma leakage occurs, there is a steady drop in total WBC count and a rapid drop in platelet count. If there is no increase in capillary permeability, the patient improves and is considered to have had non-severe dengue infection. Severe dengue occurs with the manifestation of at least one of the following: plasma leakage with or without shock, severe bleeding, or severe organ impairment (WHO, TDR, 2009). A chest X-ray or an abdominal ultrasound may be useful in identifying cases of severe dengue, as those with an increase in capillary permeability may develop pleural effusion and ascites (WHO, TDr, 2009). In addition to labs showing leucopenia and thrombocytopenia, there will be hemoconcentration as demonstrated by an elevation in hematocrit (WHO, 1997).

Dengue shock syndrome occurs when excessive amounts of plasma are leaked into the extravascular space. This may occur around day 4-5 or when the fever drops (WHO, TDR, 2009). Patients will exhibit signs of circulatory failure including cool, blotchy, and edematous skin, circumoral cyanosis, tachycardia, weak pulse, and a narrowing pulse pressure (WHO, 1997). It is important to note that the diastolic blood pressure rises as the systolic blood pressure
remains the same. This can be easily overlooked if the systolic blood pressure is within the normal range. However, the narrowing of the pulse pressure is a warning sign of shock and the patient needs prompt and adequate care. Shock is defined by a pulse pressure of less than or equal to 20mm Hg (WHO, TDR, 2009). If shock is treated, recovery can take place over 2-3 days (WHO, 1997). Multiple organ failure, metabolic acidosis, and disseminated intravascular coagulation can occur if shock is not recognized and treated aggressively. Lastly, severe hemorrhages and death may occur (WHO, TDR, 2009).

With proper monitoring and management, the recovery phase will commence consisting of resorption of the extravascular fluid within 48-72 hours. Symptoms improve and the patient returns to hemodynamic stability. The hematocrit, WBC count, and platelet count reach normal levels (WHO, TDR, 2009).

The prognosis of dengue fever is good. There is the potential for the sequelae of prolonged fatigue and depression in some cases. In DHF, the case fatality rate is less than 1% (WHO, 1997). Rare but severe complications of dengue fever that can occur even without plasma leakage and shock are hepatitis, encephalitis, myocarditis (WHO, TDR, 2009). CNS manifestations of convulsions, spasticity, altered consciousness, and transient paralysis have been seen in some cases. Acute renal failure and hemolytic uremic syndrome are other rare findings (WHO, 1997).

**Diagnostic Modalities**

Along with malaria, dengue fever should be considered in the differential diagnosis when a patient presents with a febrile illness, especially with a recent travel history. If the patient presents within 5 days of the onset of symptoms, the virus is usually present in the bloodstream and therefore, detectable by tests including virus isolation, nucleic acid amplification tests
NAATs, or antigen detection tests. Virus isolation in cell culture is very specific. However, the test must be performed by an experienced technician and results take at least one week. NAATs such as RT-PCR are very sensitive and specific for dengue virus infection. Results are available in 24-28 hours. A disadvantage is that an experienced technician at a facility with proper equipment must carry out this test. The NS1 antigen detection kit detects the presence of the non-structural protein 1 of dengue virus using ELISA. This test is less expensive than RT-PCR and virus isolation and results are ready in a few hours (WHO, TDR, 2009).

After five days from the onset of symptoms, the tests to order are serology for detection of antibodies to dengue virus. These tests include IgM ELISA, IgM rapid test, and IgG (paired sera) by ELISA, H1, or neutralization test. The advantages of these tests are that they are the least expensive and easiest to perform. Also, the tests can distinguish between primary and secondary infections. The disadvantage is that two serum samples are required, which delays the diagnosis. For diagnosis of dengue virus infection it is preferred if laboratory results detect both the virus and the antibodies (WHO, TDR, 2009).

**Therapy**

The clinical course of dengue virus infection varies, and therefore, treatment is determined individually depending on a patient’s status. The most important aspects of treating a patient with DF are to recognize early signs of plasma leakage and to begin fluid therapy. A healthcare provider (HCP) must also recognize dengue shock syndrome and aggressively address the issues of shock, bleeding, and organ impairment (WHO, TDR, 2009).

The decision to send a patient with DF home can be made if the patient is able to maintain adequate levels of fluid intake and output. The patient must also have stable hematocrit levels and show no warning signs of severe dengue. A treatment plan consists of fever control
and drinking plenty of fluids containing electrolytes and sugar. NSAIDs are contraindicated due to the potential for hemorrhagic manifestations. Patients must meet with their HCP on a daily basis to be assessed for signs of illness progression. It is essential for HCPs to educate their patients on warning signs that necessitate prompt medical attention. These warning signs include shortness of breath, a fast pulse, severe abdominal pain, persistent vomiting, jaundice, cool and clammy extremities, lethargy, irritability, convulsions, significant bleeding (i.e. coffee-ground emesis or black stools), and no urine output for 4-6 hours (WHO, TDR, 2009).

Patients may be admitted if warning signs are present, if there are co-existing conditions, or if they do not have a caregiver at home or means of transportation to a hospital should they experience warning signs. Pregnant women as well as infants with dengue virus infection should also be admitted. For a patient with warning signs, first the hematocrit must be measured and then IV fluids should be aggressively administered. The patient’s status and hematocrit levels must be reevaluated and IV infusion rates may be adjusted accordingly. Vital signs and peripheral perfusion should be monitored until the patient has advanced to the recovery phase. Urine output, blood glucose, and organ function should also be monitored. In a patient who is admitted without warnings signs of severe dengue, IV fluid therapy should only be started if the patient cannot tolerate oral fluids. HCPs should watch for warning signs of severe dengue and measure the patient’s temperature, fluid intake and urine output, hematocrit and WBC and platelet counts (WHO, TDR, 2009).

The last category of treatment is for those in the critical phase of dengue fever. Patients in the critical phase need emergency hospitalization. Those in this category have one or more of the following manifestations: dengue shock and/or fluid accumulation leading to respiratory distress, severe hemorrhage, and severe organ impairment. IV fluid resuscitation is essential and
usually is the only intervention necessary for treatment of this phase. The goals of fluid resuscitation are to improve central and peripheral circulation and organ perfusion. If a patient is in shock, IV fluid resuscitation should be started and the patient must be monitored closely. If there is no improvement, the hematocrit must be measured. If the hematocrit is still high, a second bolus of fluids should be given. In a patient with shock refractory to treatment, a hematocrit that is lower than the initial reference hematocrit is indicative of bleeding. In this instance, a blood transfusion is needed immediately (WHO, TDR, 2009).

**Prevention**

The Dengue Vaccine Initiative (DVI) was established in 2010 and on February 10, 2011, the International Vaccine Institute (IVI) announced its collaboration with the Sabin Vaccine Institute and the Johns Hopkins University (JHU), and the World Health Organization to support research on the development of a safe, affordable, and effective dengue vaccine. The initiative is funded by a grant from the Bill and Melinda Gates Foundation. The DVI works with researchers and policy makers to develop a dengue vaccine and a plan for its distribution to those in need of the vaccination (Sabin Vaccine Institute, 2011, February 10)
Chikungunya Fever

Chikungunya virus (CHIKV) is a single-stranded RNA virus of the Alphavirus genus and the Togaviridae family. It is transmitted to humans via the bite by an infected mosquito of the *Aedes* species (WHO, 2008a). The virus was first isolated from human sera and mosquitoes in 1953 in Tanzania during an epidemic in Africa (Ross, 1956). The clinical features were first described during an outbreak in villages on the Makinde Plateau in the Southern Province of Tanganyika in October of 1952. Those infected displayed unusual postures as a result of the severe joint pain, a distinguishing symptom of chikungunya viral infection. The name “Chikungunya” (of the Makonde dialect) describes this posturing and means, “that which bends up” (Robinson, 1955).

Epidemiology

Chikungunya is endemic in countries in Africa and Asia. Recently the virus has caused epidemics in previously unaffected regions of the world (Figure 7). In March of 2005 the WHO reported on the first known epidemic of chikungunya in the southwestern Indian Ocean region. The virus affected people of the Comoro Islands and then spread to other islands in the Indian Ocean including Mayotte and Mauritius. Next the epidemic spread to Reunion Island, a French district east of Madagascar, and lasted from March of 2005 to April of 2006. There were 244,000 confirmed cases of CHIKV infection during this time. The attack rate was 35% (Renault et al., 2007).

In 2006, chikungunya virus spread to India where there were 1.39 million reported cases with an attack rate as high as 45% in some areas. Over 37,000 cases were reported the following year (CDC, 2007b).
Then in 2007, there was an outbreak in the villages of Castiglione di Cervia and Castiglione di Ravenna in northeastern Italy. The virus is thought to have been introduced to the local *A. albopictus* mosquito population by an infected man who traveled from India on June 21, 2007 and became symptomatic 2 days later. From July to August of 2007 there was an unusually high number of febrile illnesses in the two villages. From July 4th -September 27th there were 205 reported cases of chikungunya fever. The attack rate was 5.4% in Castiglione di Cervia and 2.5% in Castiglione di Ravenna. PCR analysis of the CHIKV sequence showed an Ala226Val mutation in the E1 protein, which was also present in the Indian Ocean variant of the African genotype. This reinforces the theory that someone who was infected in India introduced the epidemic to the villages in Italy (Rezza et al., 2007).

Between 2005 and 2009, there were 107 reported cases of chikungunya fever in the US (Gibney, et al., 2011). Four cases reports of CHIK among travelers returning to the US were presented by the CDC. The areas of travel included Zimbabwe, Somalia, Kenya, Reunion Island, and India. Based on onset of symptoms and time of return to the US, three of the four travelers probably posed no threat of transmitting the virus to local mosquito populations. The other traveler, however, was likely to be viremic upon return to the US (CDC, 2006a). Since *Aedes* species of mosquitoes are present in the US, there is the potential for introduction of chikungunya to the local mosquito population.

**Lifecycle**

During non-epidemic periods chikungunya virus is maintained in a sylvatic lifecycle in Africa by the *Aedes* species of mosquitoes, nonhuman primates, rodents, cattle, birds, and squirrels. The virus is transmitted to humans by the bite of an infected *A. aegypti* (Figure 6) or
A. albopictus and is maintained in the urban lifecycle (Diallo, Thonnon, Traore-Lamizana, & Fontenille, 1999; Peters, 2008a; WHO, 2008a).

**Manifestations**

Chikungunya virus has an incubation period of 2-4 days (range of 1-12 days) after which abrupt onset of fever is seen (Staples, Fischer, & Powers, 2009; WHO, 2008a). The most common symptoms of chikungunya fever as described by the WHO include fever, arthralgia, backache, and headache (Table 1). The fever can be as high as 39-40°C and usually lasts 24-48 hours. The joint pain is severe and debilitating. It is worse during the morning and mild exercise provides some relief. Other symptoms of CHIK that the WHO classifies as occurring infrequently are maculopapular rash, stomatitis, oral ulcers, hyperpigmentation, and exfoliative dermatitis (WHO, 2008a). Other studies, however, report a maculopapular rash in 32.5-76.5% of patients (Beltrame et al., 2007; Borgherini et al., 2007; Renault, et al., 2007; Rezza, et al., 2007). The rash occurs after the fever breaks (Staples, et al.) and usually covers the trunk and limbs but can involve the palms, soles, and face (WHO, 2008a). Other studies described myalgias in only 46-61.6% of patients (Renault, et al.; Rezza, et al.). The WHO describes the following symptoms as rare in adults but sometimes seen in children: photophobia, retro-orbital pain, vomiting, diarrhea, meningeal syndrome, and acute encephalopathy. Other studies, however, reported gastrointestinal symptoms in 47.1% of patients, diarrhea in 23% of patients, and vomiting in 19% of patients (Borgherini, et al.; Rezza, et al.), although these studies did not classify symptoms according to age. Conjunctivitis, pruritus, and non-severe bleeding from the nose and gums have been described in a very small percentage of cases of CHIK (Beltrame, et al.; Borgherini, et al.; Rezza, et al.; Taubitz et al.). Rare but serious complications include myocarditis, ocular disease (uveitis and retinitis), hepatitis, and neurological symptoms.
(peripheral neuropathy, parasthesias, and entrapment syndromes) (Staples, et al.). The WHO advises health care providers to consider chikungunya infection when a patient presents with the triad of fever, rash, and joint manifestations (WHO, 2008a). The CDC advises the consideration of CHIK among returning travelers presenting with fever and arthralgias or arthritis (CDC, 2006a).

Arthralgias observed with chikungunya infections may resolve in some cases and persist in others. The sequelae of persistent arthritis have been the topic of several studies. One study contacted 107 people of northern Transvaal (modern day South Africa) who were seropositive for chikungunya virus in 1975, 1976, and 1977. The participants were queried 3-5 years after infection about arthralgias. The majority of participants (87.9%) reported complete recovery. Only 3.7% reported occasional joint stiffness and discomfort, 2.8% reported persistent residual joint stiffness without pain, and 5.6% still suffered from joint pain, stiffness, and frequent effusions. (Brighton, Prozesky, & de la Harpe, 1983). Another study of 88 people who suffered from chikungunya virus infection during the outbreak on Reunion Island (March 2005-April 2006) found persistent arthralgia to be much more common. While 32 patients (36.4%) recovered from the joint pains caused by CHIKV in a mean of 2.9 months (+/- 2.4 months), 56 patients (63.8%) reported persistent arthralgia up to a mean of 18 months after the onset of chikungunya fever. Those with persistent arthralgia reported it as being polyarticular and over half had continuous joint pain. The most commonly affected joints were the metacarpophalangeal joints, knees, wrists, metatarsal joints, and ankles. Upon physical exam, the shoulders, ankles, metacarpophalangeal joints, and metatarsal joints more commonly produced pain. This study differed from the Brighton et al., study in terms of patient’s age and the length of time studied after acute illness. This could account for the significant differences
found by each study and further studies are needed to investigate the persistence of arthralgia. One major limitation of this study was that it did not account for the 44% of participants who had reported a history of arthralgia before CHIKV infection (Borgerini et al., 2008).

Another study also investigated the morbidity from chikungunya infection and looked into other areas of health rather than only arthralgia. A telephone interview of 1,094 people who had been tested as either seropositive or seronegative for chikungunya virus during the 2005-2006 La Reunion outbreak was conducted. Questions centered on current symptoms including musculoskeletal/rheumatic, fatigue, cerebral, sensorineural, digestive, and dermatological manifestations. It was found that on an average of 24 months after acute CHIK, those who actually had the infection were twice as likely to have musculoskeletal pain. They were also more likely to complain of light cerebral disorders including attention difficulties, memory trouble, mood disturbance, and depression. Infection was also associated with sensorineural impairment 24 months later. This study suggests that 33% of rheumatic symptoms, 10% of neurological complaints, and 7.5% of sensorineural complaints were due to chikungunya infection (Gerardin, et al., 2011). Overall 43-75% of those infected still suffered from the sequelae of chikungunya virus infection on average 24 months later.

**Diagnostic Modalities**

Diagnostic testing for chikungunya in the US is limited to the CDC, the Wadsworth Center of the New York State Department of Health, and Focus Diagnostics (commercial) (Gibney, et al., 2011). Chikungunya virus infection can be detected by virus isolation, RT-PCR, detection of IgM antibodies, or a rising titer of IgG antibodies (the second sample collected 2-4 weeks after the first). While levels of IgM antibodies are usually detectable in blood samples
within 2 weeks of acute illness, the WHO suggests waiting 1 week after onset of symptoms to perform the ELISA for IgM (WHO, 2008a).

The goal of one study by Panning et al was to compare the usefulness of chikungunya diagnostic tests. They showed RT-PCR to be 100% positive up to day 4 of infection and IgG and IgM antibody tests to be 100% positive from day 5 and on. Virus isolation was less useful in diagnosis, as the virus was successfully isolated in only 23.4% of RT-PCR confirmed positive serum samples. Their method of choice for clinical virus detection was RT-PCR (Panning, Grywna, van Esbroeck, Emmerich, & Drosten, 2008).

Another study also investigated the usefulness of diagnostic tests. Taubitz et al found that RT-PCR was sensitive during the first week of infection while antibody tests were very reliable, mainly after the first week. The earliest IgM and IgG were detectable were 3 and 6 days after the onset of symptoms, respectively. Because antibody tests may be normal during the first week, RT-PCR appears to be more sensitive for diagnosing chikungunya infection early on (Taubitz, et al., 2007).

If hematological tests are ordered, there is often leucopenia with lymphocyte predominance. Also, the erythrocyte sedimentation rate and C-reactive protein levels may be elevated. Thrombocytopenia or a positive rheumatoid factor test is very rarely seen (WHO, 2008a).

**Therapy**

The treatment of chikungunya fever is completely symptomatic as there is no antiviral drug for chikungunya infections. Acetaminophen is the drug of choice for relief of symptoms. Those recovering from CHIKF and experiencing joint manifestations may benefit from mild exercise and the application of cold compresses (WHO, 2008a).
Patients who are well enough to recover at home should get plenty of rest and drink water supplemented with electrolytes. Adults should take in two liters of fluids and maintain a urine output of at least 1 liter, all within 24 hours (WHO, 2008a). Patients should be educated on the importance of seeking medical care if they experience any of the following: fever lasting more than 5 days, pain refractory to treatment, postural dizziness, cold extremities, decreased urine output, bleeding, or persistent vomiting (WHO, 2008a).

Once a patient experiences any of the above symptoms, the healthcare provider should evaluate the patient’s hydration status and order blood tests to rule out other diagnoses such as malaria, dengue fever, and leptospirosis. A patient demonstrating hemodynamic instability, oliguria, altered sensorium, bleeding, severe arthralgia refractory to treatment and people over the age of 60 as well as infants will require in-patient therapy. (WHO, 2008a).

People suffering from the sequelae of chikungunya virus can receive some benefit from interventions. Those suffering from osteoarticular problems can continue with NSAIDs and cold compresses for relief. Exercise and physiotherapy should be used to prevent the formation of contractures. Because the chronic manifestations may be caused by an immunologic response, a short course of steroids should be considered. Steroids should also be considered in those with uveitis and retinitis with changes in their vision. Chronic dermatological issues should be cared for by a dermatologist who may use zinc-oxide cream or calamine lotion for hyperpigmentation and papular eruptions. Patients with psychosomatic problems should be assessed and be given psychosocial support (WHO, 2008a).

**Prevention**

There currently is no vaccine to protect against chikungunya virus, although research is being directed at the possibility of vaccines. A DNA vaccine is being developed that contains
CHIKV capsid and envelope consensus sequences. When tested in mice, the vaccine was shown to elicit both T-cell and humoral immune responses (Muthumani et al., 2008). More research is needed in the development of this vaccine before it could be considered for testing in humans. Another group constructed a virus-like particle (VLP) vaccine that was shown to produce neutralizing activity in rhesus macaques. Upon CHIKV challenge of vaccinated monkeys, the immunized monkeys were protected against viremia (Akahata et al., 2010). While more research is needed in the development of a chikungunya vaccine, these studies show some promise in this area of research.
**Differential Diagnosis**

The differential diagnosis for malaria, dengue fever, and chikungunya fever includes influenza, typhoid fever, viral hepatitis, visceral leishmaniasis, bacterial meningitis, septicemia, pneumonia, amebic liver abscess, babesiosis, leptospirosis, relapsing fever, and rheumatic fever (WHO, 2008a, 2010; Zeiger R. F., 2006). Other infectious diseases that cause fever including rickettsial diseases, measles, enteroviruses, and the viral hemorrhagic fevers should be considered (WHO, TDR, 2009). Flavivirus infections such as Yellow Fever, Japanese encephalitis, St Louis encephalitis, and West Nile present with similar manifestations (WHO, TDR, 2009). Also included in the differential diagnosis are alphavirus infections that cause persistent arthritis such as Ross River, Barmah Forest, O’nyong nyong, Sindbis, Mayaro viruses, and Semliki (Beltrame, et al., 2007; Taubitz, et al., 2007).
**Vector Control**

The key aspect of the prevention of malaria, dengue, and chikungunya infection rests on controlling the vector population. This includes discarding containers that collect water, such as birdbaths, flowerpots, and discarded tires and containers. Environmental control also includes screens placed over windows and doors and bed nets. Larvicides and adulticides may also be used as an adjunct to control larval habitats and the adult vectors (WHO, TDR, 2009).

To minimize exposure to mosquitoes, travelers are urged to wear long sleeves and long pants and sleep under an insecticide-treated bed net (CDC, 2010, February 8d). Insect repellants containing DEET, IR3535, or picaridin and household insecticides should also be used to control exposure (WHO, TDR, 2009). For adults, the CDC recommends a repellant that contains no more than 50% DEET. Children two months of age and older may use a repellant with up to 30% DEET. An insect repellant, however, should not be used in infants less than two months of age. Rather, a mosquito netting should be draped over the infant’s carrier for protection against mosquitoes (CDC, 2011, May 2).

Another important aspect involved in prevention of malaria, dengue, and chikungunya is global surveillance. The goals of surveillance are early detection of epidemics, determining the burden of the disease within the community, recording data pertaining to the distribution of the disease, and evaluating prevention and control programs. Monitoring for localized disease events, such as unexplained fevers, followed by timely reporting to local health officials are critical components of prevention (WHO, TDR, 2009). It is important to note that while malaria and dengue fever are notifiable diseases in the US, chikungunya is not. However, the CDC urges clinicians to report suspected cases of CHIK to local and state health officials as well as to the CDC (CDC, 2006a). Also, emergency preparedness and response systems should be in place in
the event of an outbreak of disease. The plans differ among countries depending on the risk level of the given area as well as the financial resources and political will. Regardless, it is the clinicians, nurses, and laboratory personnel trained in recognizing, diagnosing, and treating malaria, dengue, and chikungunya infections who are the integral components of the response system (WHO, TDR, 2009).
Summary

Malaria, dengue fever, and chikungunya fever are three emerging mosquito-transmitted infectious diseases that pose a threat to the US. Because the US harbors the *Aedes* and *Anopheles* species of mosquitoes, these three diseases could potentially become endemic in the US. If travelers are infected with these microbes upon return to the US, they could introduce the parasites and viruses to the indigenous mosquito population. These autochthonous outbreaks have occurred within the US in the past with malaria (CDC, 2010, February 8b). Dengue virus is gaining a foothold in Florida as there have been locally acquired cases of dengue fever in the recent years (CDC, 2010b). Chikungunya virus has already demonstrated its ease of transmission with the outbreak in Italy in 2007 (Rezza, et al., 2007). Any of these infectious diseases could become established within the US. Ultimately, prevention of disease transmission is of utmost importance.

Vaccine development is a key component in prevention of disease. Research is currently being conducted for malaria, dengue virus, and chikungunya virus with some promising results. Until a vaccine is developed, vector control, personal protective measures, and early public health notification of disease activity is essential. This along with surveillance of infected mosquitoes in high-risk areas could prevent an epidemic.

Another important factor in controlling the transmission of these diseases is the prompt recognition and diagnosis by healthcare professionals. To ensure adequate education, healthcare institutions should provide their students as well as their healthcare professionals with a strong background in these diseases as well as other emerging infectious diseases. While healthcare providers may be somewhat familiar with malaria and dengue, they may have never heard of chikungunya virus. In fact, the WHO identified chikungunya as an emerging vector-borne
disease that has not received sufficient coverage in the medical curriculum around the world (WHO, 2008a). Healthcare providers who possess a strong knowledge base of these diseases are invaluable to the prevention of autochthonous transmission and a malaria, dengue, and chikungunya epidemic.
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### Table 1: Comparisons of the key points regarding malaria, dengue virus, and chikungunya virus infections

<table>
<thead>
<tr>
<th>Malaria</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vector</strong></td>
<td><em>Anopheles</em> species</td>
<td><em>Aedes aegypti</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Aedes albopictus</em></td>
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<tr>
<td><strong>Distribution</strong></td>
<td>The Americas, Africa, Asia,</td>
<td>The Americas, Africa, Eastern</td>
</tr>
<tr>
<td></td>
<td>Eastern Europe, Caribbean,</td>
<td>Mediterranean, Western</td>
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<tr>
<td></td>
<td>South Pacific</td>
<td>Pacific, South-east Asia</td>
</tr>
<tr>
<td><strong>Incubation Period</strong></td>
<td>7-30 days</td>
<td>4-10 days</td>
</tr>
<tr>
<td><strong>Clinical Manifestations</strong></td>
<td>Fever, shaking chills,</td>
<td><em>Dengue Fever</em>: Sudden high-grade fever, headache, retro-orbital pain, myalgias, arthralgias, weakness, rash, nausea, vomiting, petechiae, epistaxis, gingival bleeding</td>
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<tr>
<td></td>
<td>headache, myalgias, fatigue,</td>
<td></td>
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<tr>
<td></td>
<td>nausea, vomiting,</td>
<td><em>Dengue Hemorrhagic Fever</em>*: Fever lasting 2-7 days, hemorrhagic manifestation, thrombocytopenia, increased vascular permeability</td>
</tr>
<tr>
<td></td>
<td>orthostatic hypotension</td>
<td><em>Dengue Shock Syndrome</em>: DHF plus hypotension, pulse pressure ≤ 20 mm Hg, or frank shock</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Blood smear (Giemsa stain)</td>
<td>Within day 5 of symptom onset: virus isolation, RT-PCR, antigen detection via ELISA</td>
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<tr>
<td></td>
<td>RDT</td>
<td>After day 5 of symptom onset: IgM ELISA, IgM rapid test, IgG ELISA</td>
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<tr>
<td></td>
<td>PCR</td>
<td></td>
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<tr>
<td><strong>Treatment</strong></td>
<td>***Artemisinin-based</td>
<td><em>Dengue Fever</em>: Supportive</td>
</tr>
<tr>
<td></td>
<td>combination, chloroquine,</td>
<td><em>DHF and DSS</em>: ICU hospitalization</td>
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<tr>
<td></td>
<td>primaquine, atovaquone,</td>
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<tr>
<td></td>
<td>proguanil, quinine,</td>
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<td></td>
<td>quinidine, doxycycline,</td>
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<tr>
<td></td>
<td>clindamycin</td>
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<tr>
<td><strong>Prognosis</strong></td>
<td><strong>Uncomplicated malaria</strong>:</td>
<td><em>DHF</em>: mortality rate &lt; 1%</td>
</tr>
<tr>
<td></td>
<td>mortality rate of 0.1%</td>
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<td></td>
<td><strong>Severe malaria</strong>:</td>
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<td></td>
<td>mortality rate of 10-20%</td>
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</table>

* Epidemic
** Need all four for diagnosis
*** Selection of the appropriate anti-malarial is based upon the species of malaria, the clinical status of the patient, and the susceptibility of the parasite
Key: DHF (dengue hemorrhagic fever), RDT (rapid diagnostic test), PCR (polymerase chain reaction), RT-PCR (reverse transcriptase polymerase chain reaction), ELISA (enzyme linked immunosorbent assay), ICU (intensive care unit)
Table 2: Guidelines for the treatment of malaria

<table>
<thead>
<tr>
<th>Species of <em>Plasmodium</em></th>
<th>Considerations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated <em>P. falciparum</em> malaria</td>
<td>Region in which the infection was acquired.</td>
<td>Any of the following ACTs: artemether plus lumefantrine (AL), artesunate plus amodiaquine (AS+AQ), artesunate plus mefloquine (AS+MQ), artesunate plus sulfadoxine-pyrimethamine (AS+SP), and dihydroartemisinin plus piperaquine (DHA+PPQ) Treat for at least 3 days</td>
</tr>
<tr>
<td>Severe <em>P. falciparum</em> malaria</td>
<td>Treatment should be initiated as soon as possible after a positive diagnostic test. When the patient is well enough to tolerate oral medications, a full course of an appropriate ACT should be initiated.</td>
<td>First line therapy: IV artesunate Alternative: cinchona alkaloids (quinine and quinidine) or other artemisinin derivatives (artemether and artemotil)</td>
</tr>
<tr>
<td>US travelers returning home with uncomplicated <em>P. falciparum</em> malaria</td>
<td>Need prompt and effective treatment to prevent development of severe malaria</td>
<td>Atovaquone plus proguanil, AL, DHA+PPQ, or quinine plus doxycycline or clindamycin</td>
</tr>
<tr>
<td>US travelers returning home with severe <em>P. falciparum</em> malaria</td>
<td>Admission to the ICU</td>
<td>Treatment is the same as outlined for severe <em>P. falciparum</em> malaria</td>
</tr>
<tr>
<td>Uncomplicated <em>P. vivax</em> malaria</td>
<td>Primaquine is used to prevent a relapse of malaria</td>
<td>Chloroquine combined with primaquine (if there is no known resistance). If chloroquine resistance, treat with ACTs (except AS+SP) along with primaquine for at least 14 days</td>
</tr>
<tr>
<td>Severe <em>P. vivax</em> malaria</td>
<td>Same as for severe <em>P. falciparum</em> malaria</td>
<td></td>
</tr>
<tr>
<td><em>P. ovale</em> malaria</td>
<td>Usually sensitive to chloroquine. Primaquine is used to prevent a relapse of malaria.</td>
<td>Chloroquine and primaquine</td>
</tr>
<tr>
<td><em>P. malariae</em> malaria</td>
<td>Usually sensitive to chloroquine</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Mixed malaria infection</td>
<td>ACTs Also use primaquine if <em>P. vivax</em> or <em>P. ovale</em> malaria</td>
<td></td>
</tr>
</tbody>
</table>
Figures

*Figure 1.* A female *Anopheles albimanus* mosquito during a blood meal. This species transmits malaria mainly in Central America. Reprinted from the Centers for Disease Control and Prevention Public Health Image Library, Image 7862, by J. Gathany, 2005. Retrieved from http://phil.cdc.gov/phil/home.asp
Figure 2: Parts of the world in which malaria transmission occurs. Adapted from “Malaria: Where Malaria Occurs,” by the Centers for Disease Control and Prevention, February 8, 2010. Retrieved from http://www.cdc.gov/malaria/about/distribution.html
Figure 3: Lifecycle of the malaria parasite. Adapted from “Malaria: Biology,” by the Centers for Disease Control and Prevention, February 8, 2010. Retrieved from http://www.cdc.gov/malaria/about/biology/index.html
Figure 6: A female *Aedes aegypti* taking a blood meal. This mosquito transmits dengue and chikungunya viruses. Adapted from the Centers for Disease Control and Prevention Public Health Image Library, Image 9261, by F. H. Collins and J. Gathany, 2006. Retrieved from http://phil.cdc.gov/phil/home.asp
Countries where people have become infected with chikungunya virus:

<table>
<thead>
<tr>
<th>Country</th>
<th>Country</th>
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<tbody>
<tr>
<td>Benin</td>
<td>Mauritius</td>
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<td>Burundi</td>
<td>Mayotte</td>
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<tr>
<td>Cambodia</td>
<td>Myanmar</td>
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<tr>
<td>Cameroon</td>
<td>Nigeria</td>
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<td>Central African Republic</td>
<td>Pakistan</td>
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<td>Comoros</td>
<td>Philippines</td>
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<td>Congo, DRC</td>
<td>Reunion</td>
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<td>East Timor</td>
<td>Senegal</td>
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<td>Equatorial Guinea</td>
<td>Seychelles</td>
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<td>Guinea</td>
<td>Singapore</td>
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<td>India</td>
<td>South Africa</td>
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<td>Sudan</td>
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<td>Italy</td>
<td>Taiwan</td>
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<td>Kenya</td>
<td>Tanzania</td>
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<td>Laos</td>
<td>Thailand</td>
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<td>Madagascar</td>
<td>Uganda</td>
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<td>Malawi</td>
<td>Vietnam</td>
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<td>Malaysia</td>
<td>Zimbabwe</td>
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<tr>
<td>Maldives</td>
<td></td>
</tr>
</tbody>
</table>

Figure 7: Global distribution of CHIKV (a) and the countries where CHIKV has infected humans (b). The list does not include countries where only imported cases had been reported. Adapted from “Chikungunya: Chikungunya Distribution and Global Map,” by the Centers for Disease Control and Prevention, April 14, 2010. Retrieved from http://www.cdc.gov/ncidod/dvbid/Chikungunya/CH_GlobalMap.html
Abstract

**Objective:** Malaria, dengue, and chikungunya are mosquito-transmitted infectious diseases with similar clinical manifestations. This review compares the signs and symptoms, diagnostic modalities, and treatments for these infectious diseases. **Methods:** Searches were performed in MEDLINE and PubMed using the key words: “malaria,” “dengue,” “chikungunya,” “infectious disease,” “travel,” “clinical manifestations,” “diagnostic tests,” and “vaccination.” Websites of relevant organizations including the CDC and WHO were also utilized. **Results:** Malaria, dengue, and chikungunya should be considered in a febrile patient returning from an endemic area. These illnesses may also be considered in a patient without a history of recent travel because of the presence of the mosquito vectors in the US as well as previous reports of autochthonous cases of malaria and dengue. **Conclusion:** This review will assist healthcare professionals in the recognition and diagnosis of malaria, dengue, and chikungunya, which is essential for the timely reporting to public health authorities.