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HUMAN DISEASE CAUSING VIRUSES VECTORED BY MOSQUITOES

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Introduction

There are a number of disease-causing viruses transmitted to people primarily through the bite of infected mosquitoes. Female mosquitoes take blood meals to produce eggs (Fig. 1). A mosquito that bites an infected animal may pick up a virus within the blood meal. If the mosquito is the appropriate species, and conditions inside the insect and the surrounding environment are supportive, the virus reproduces within the mosquito. Later, the mosquito may pass the virus on to other animals (including humans) as they feed again. Not all mosquitoes vector (transmit) viral diseases to humans, and specific mosquito species vector specific viruses. The successful replication and transmission of viruses in mosquitoes depends on several factors, the most important being the compatibility of the vector, ambient temperature and humidity (higher temperatures often accelerate virus replication), and mosquito life span.

Figure 1. *Aedes aegypti* female taking a blood-meal. Alex Wild, alexanderwild.com

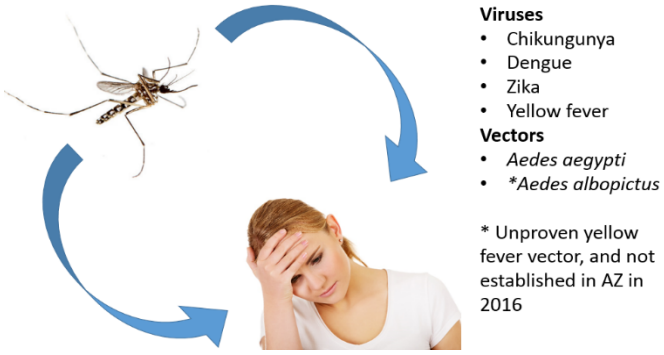

Figure 2. Humans are primary hosts for a number of important mosquito transmitted diseases.

Some **arboviruses** (arthropod-borne, primarily by insects and ticks) such as St. Louis encephalitis virus and western equine encephalitis virus have been present in the United States for many years. Others are relatively recent introductions, such as West Nile virus, and many more are emerging as public health threats, including dengue virus, chikungunya virus, and Zika virus. The increasing circulation of arboviruses that threaten human health (Fig. 2) may be due to many factors including: climate change; wildland-urban interface population increases; globalization trends; widespread use of plastic containers and packaging (which provides habitat for species that breed in manmade water-holding containers); decreased funding for research and vector control; the development of pesticide resistance; and a lack of new management tools.

Vector-borne diseases are among the most complex of all infectious diseases to prevent and control (Centers for Disease Control and Prevention, 2016).

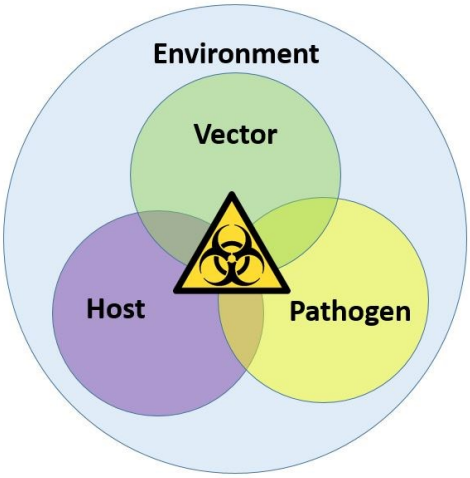

Figure 3. For a disease epidemic to occur a host, vector, and pathogen must occur concurrently, under supportive environmental conditions.

In order for a disease epidemic to occur, a susceptible host, a competent vector, and a pathogen must be together in the same place, at the same time, and under supportive environmental conditions (Fig. 3). While children and the elderly are most severely impacted by mosquito-borne pathogens, in some instances life-threatening illness or permanent debilitation can occur in hosts of any age.

Key Mosquito Arboviral Vectors in Arizona

All mosquito species go through four distinct stages during their life cycle: eggs (Fig. 4a, 4b), which hatch when exposed to water; larvae (Fig. 4c), which live in water, feed on organic matter, and develop through four stages (instars) of increasing size; pupae (Fig. 4d), which live in water as a non-feeding stage; and winged adults (Fig. 4e). Only the adult female mosquito bites and feeds on the blood of humans or other animals.

For more information about mosquito biology, ecology and management go to https://extension.arizona.edu/sites/extension.arizona.edu/files/pubs/az1706-2016.pdf

Figure 4a. *Aedes aegypti* eggs. Chris Bibbs, Anastasia Mosquito Control District

Figure 4b. *Culex* egg raft. Sean McCann, ibycter.com

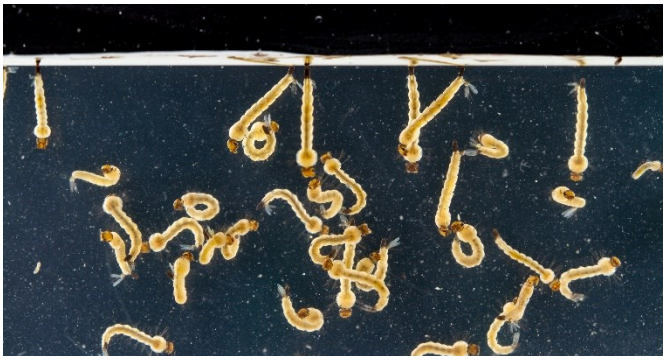

Figure 4c. *Aedes aegypti* larvae. Alex Wild, Alexanderwild.com

Figure 4d. *Aedes aegypti* pupae. Alex Wild, Alexanderwild.com.

Figure 4e. *Aedes aegypti* adult female. Alex Wild, Alexanderwild.com

Although there are about 180 species of mosquitoes in the United States, only a few are a problem for humans. Of the forty plus species found in Arizona, *Aedes aegypti* and two *Culex* species are the critically important arbovirus vectors impacting human disease incidence. The notably aggressive human-feeding *Aedes albopictus* (Asian tiger mosquito) is expanding its range in California and may soon establish in Arizona.

Important *Culex* vector species in Arizona

Culex tarsalis (Western encephalitis mosquito) and *Culex quinquefasciatus* (Southern house mosquito), both vector West Nile and St. Louis encephalitis viruses. These mosquitoes feed on a wide range of animals but can only contract the viruses by feeding on infected birds.

Culex tarsalis is a North American species found in many environments, but particularly common in arid regions where irrigation has made formerly inhospitable land ideal for breeding (sunlit standing freshwater). The species range spans the entire continental United States from northern Mexico to southern Canada and from the Pacific to the Atlantic coast.

Culex quinquefasciatus exists throughout the southern United States and can utilize a wide variety of breeding sites including water-holding containers, old tires, unmanaged swimming pools, wetlands and drainage ditches. This mosquito is commonly found around homes and human activity.

The exact distribution of either species within Arizona varies year to year, but both have been reported in all counties.

For images and more information about *Culex* go to https://extension.arizona.edu/sites/extension.arizona.edu/files/pubs/az1706-2016.pdf.

After a mosquito feeds on the blood of a virus-infected bird, the virus undergoes a short incubation period before it can be retransmitted to humans or other animals. This is called the extrinsic incubation period, and can be as short as four days in some mosquito species in Arizona. The infected mosquito, full of virus and ready to feed again, will look for an animal for its next blood meal. This is the basic transmission cycle of the virus as it moves from bird (reservoir host) to mosquito (vector) and then, on to humans or other animals. (Fig 7).

Important *Aedes* vector species in Arizona

Aedes aegypti (yellow fever mosquito, Figs. 1, 4, & 5), is responsible for transmitting several disease causing viruses between human hosts. Diseases include, yellow fever, Mayaro virus disease (neither of which occur in the United States at this time), dengue fever, chikungunya and Zika (none are locally transmitted in Arizona at the time of this writing). Originally from Africa, it is now found in all southern states.

Figure 5. *Aedes aegypti* female engorged with a blood meal. Alex Wild ,Alexanderwild.com

Aedes aegypti has spread into many populated areas of Arizona and lives in very close association with human habitations. This mosquito is found in cities and towns in southern and central Arizona. As of this writing, the range in Arizona extends from the Verde Valley in the north, throughout Maricopa County, west to Yuma, east to Cochise County and south to the border with Sonora, Mexico.

All three important vector species are closely monitored by several county vector control and abatement districts in coordination with the Arizona Department of Health Services http://azdhs.gov/preparedness/epidemiology-disease-control/mosquito-borne/index.php.

Aedes albopictus the Asian tiger mosquito (Fig. 6) is not established in Arizona at this time, but was introduced into the United States in tire casings imported from Asia during the 1980s. The species has since spread to more than 20 states including most southern states and many west coast and east coast states. In the United States, it has been found carrying La Crosse encephalitis and West Nile viruses. However, it is presently unclear whether the Asian tiger mosquito is a significant vector of disease in the United States. This mosquito is a potential vector of Zika virus.

Figure 6. Adult *Aedes albopictus*. Alex Wild Alexanderwild.com

Aedes albopictus has been recorded from Arizona at least twice (in Tucson and Chandler, Arizona), but failed to become established. Both sightings were associated with plants purchased from internet sites (Frank Ramberg, personal communication).

Viruses Causing Human Diseases of Concern Spread by Mosquitoes in Arizona

West Nile virus is vectored by *C. tarsalis* and *C. quinquefasciatus*, the latter being the predominant vector in Arizona. Mosquitoes become infected when they feed on infected birds, and can transmit the virus to other birds during later blood meals, the virus may be injected into humans and other animals, where it can cause illness. Of all the arbovirus disease cases, West Nile Fever has the highest case counts in Arizona to date. Infected mosquitoes are found throughout the state.

The virus can affect people of all ages, with 20-30% of those infected developing West Nile fever, and the rest showing mild or no symptoms. The incubation period (the time from infected mosquito bite to onset of illness) is 3 to 14 days if symptoms develop at all. The virus may also be transmitted through contact with bodily fluids from other infected animals. Human infections have also occurred through organ transplant, blood transfusions and breast milk. There are very few reports of transplacental (mother to developing fetus) transmission. To date, no human-to-human transmission through normal contact has been reported.

West Nile fever symptoms include: fever, headache, body aches, swollen lymph glands, tiredness and rash on the trunk of the body. About one out of every 150 people infected with the West Nile virus will develop a severe infection resulting in encephalitis (inflammation of the brain), or meningitis (inflammation of the lining of the brain and spinal cord). Unlike West Nile fever, which develops with equal likelihood in persons of any age, the *severe* neuroinvasive form tends to occur more in people over 50 years of age. Symptoms of encephalitis or meningitis include high fever, neck stiffness, disorientation, muscle weakness, paralysis, headache, stupor, tremors, convulsions and coma. Death can result.

While there is no vaccination against West Nile virus for humans, there are a number of vaccinations for equine use. Some protect specifically against West Nile virus, while some vaccinate against a number of equine pathogens. Veterinarians highly recommend horses receive West Nile vaccinations as the virus causes fatal disease in a third of infected horses, and annual boosters are required to maintain immunity.

St. Louis encephalitis virus is another disease-causing virus vectored by *C. tarsalis* and *C. quinquefasciatus* mosquitoes in Arizona. Birds again are the primary hosts, but humans can also be infected (Fig. 7). Infected mosquitoes are commonly found in Phoenix, Tucson, Yuma and other cities.

The incubation period for St. Louis encephalitis disease ranges from 5 to 15 days. Fatal human cases are uncommon but a significant number of human clinical cases were recorded in Arizona during 2015. Less than 1% of St. Louis encephalitis virus infections are clinically

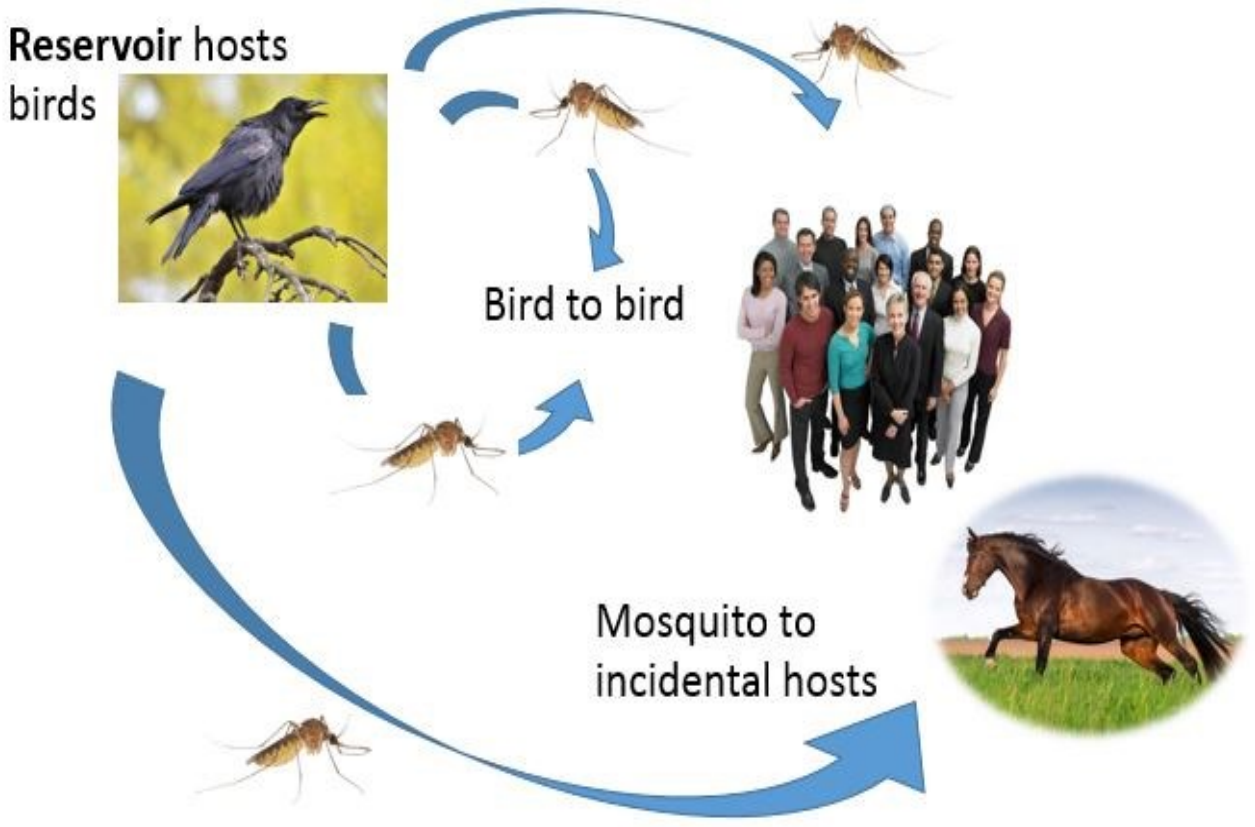

Figure 7. West Nile virus and St. Louis encephalitis virus transmission cycle.

apparent most infections going undiagnosed. However, St. Louis encephalitis virus generates a higher incidence of neuroinvasive cases compared with West Nile virus, and children and the elderly are the most severely impacted. About 40% of children and young adults with St. Louis encephalitis disease develop a fever, headache or aseptic meningitis, and about 90% of elderly with St. Louis encephalitis disease develop encephalitis. The risk of fatal disease increases with age. Unfortunately, there is no vaccination available for St. Louis encephalitis virus.

Western equine encephalitis virus is a disease-causing virus vectored by *C. tarsalis* throughout Arizona. Birds again are the primary hosts, and humans are rarely affected (Fig. 7), but the virus is also known to occur generally in Arizona wildlife. Outbreaks in equine or bird populations often precede human cases. Arizona state livestock officials periodically warn horse owners to update their horse vaccinations against the potentially fatal equine sleeping sickness or western equine encephalitis. The Arizona Department of Health Services occasionally finds mosquitoes carrying the virus, but very few human cases have occurred during the last 20 years.

The incubation period ranges from 4 to 10 days, and most people infected with Western equine encephalitis virus will have very mild or no symptoms. Infants and the elderly are at highest risk of developing encephalitis. Approximately 5-15% of encephalitis cases are fatal, with 50% of surviving infants having permanent brain damage. Most severe human cases begin with a sudden high fever, headache, stiff neck, vomiting, and lethargy. Within four days, the illness may progress to convulsions, disorientation, irritability, seizures and coma. Cases of Parkinson syndrome have been reported in adults after Western equine encephalitis infection. If symptoms occur, seek medical attention quickly. There is no human vaccination available.

Symptoms of western equine encephalitis in horses include neurological signs such as depression and lack of coordination. A sick horse may collapse and not be able to stand back up. The illness is fatal in 20-50% of infected horses. There is an effective vaccine for equines only.

Exotic viruses that if introduced could be vectored by Arizona mosquito species

None of the exotic viruses listed here are endemic (naturally transmitted) within Arizona at the time of this writing, but given that we have one of the vector mosquitoes, and travelers contracting the virus and returning to Arizona regularly, this situation may change at any time. In all cases, humans are the primary host and *Ae. aegypti* and *Ae. albopictus* (Figs. 5 & 6) are potential vectors.

When infected, early recognition and prompt supportive treatment can substantially lower the risk of medical complications and death.

Chikungunya virus is transmitted rarely from mother to newborn around the time of birth but this virus is not spread from person to person.

Outbreaks of chikungunya have been reported from countries in Africa, Asia, Europe, Indian and Pacific Ocean islands. The virus arrived in the Americas in late 2013 on the island of St. Martin and local transmission spread it quickly through the Caribbean and into South and Central America (CDC 2015). Local transmission (Fig. 8) means that mosquitoes in the area have been infected with the virus and are spreading it within the local population. Beginning in 2014, chikungunya disease cases were reported among United States travelers returning from affected areas in the Americas and local transmission was identified in Florida, Puerto Rico, and the Virgin Islands (CDC 2015). During 2016, travel-related chikungunya cases were reported in 37 of the continental states, including Arizona, but no local transmission has occurred in Arizona to date (CDC 2017).

The majority of people infected with chikungunya virus will develop some symptoms which develop 3–7 days after being bitten by an infected mosquito.

People infected with chikungunya virus typically develop fever and joint pain, which can be extremely severe as the virus cases arthritogenic disease (causing joint pain). Other symptoms can include muscle aches, headaches, nausea, vomiting, joint swelling and rash. Travelers returning from areas with local transmission of chikungunya virus should seek medical care if they experience any of these symptoms. Healthcare providers in areas with reported cases should be on the alert for local transmission.

Infection with chikungunya virus is rarely fatal, but the joint pain can often be severe and debilitating. Patients recover in about a week,

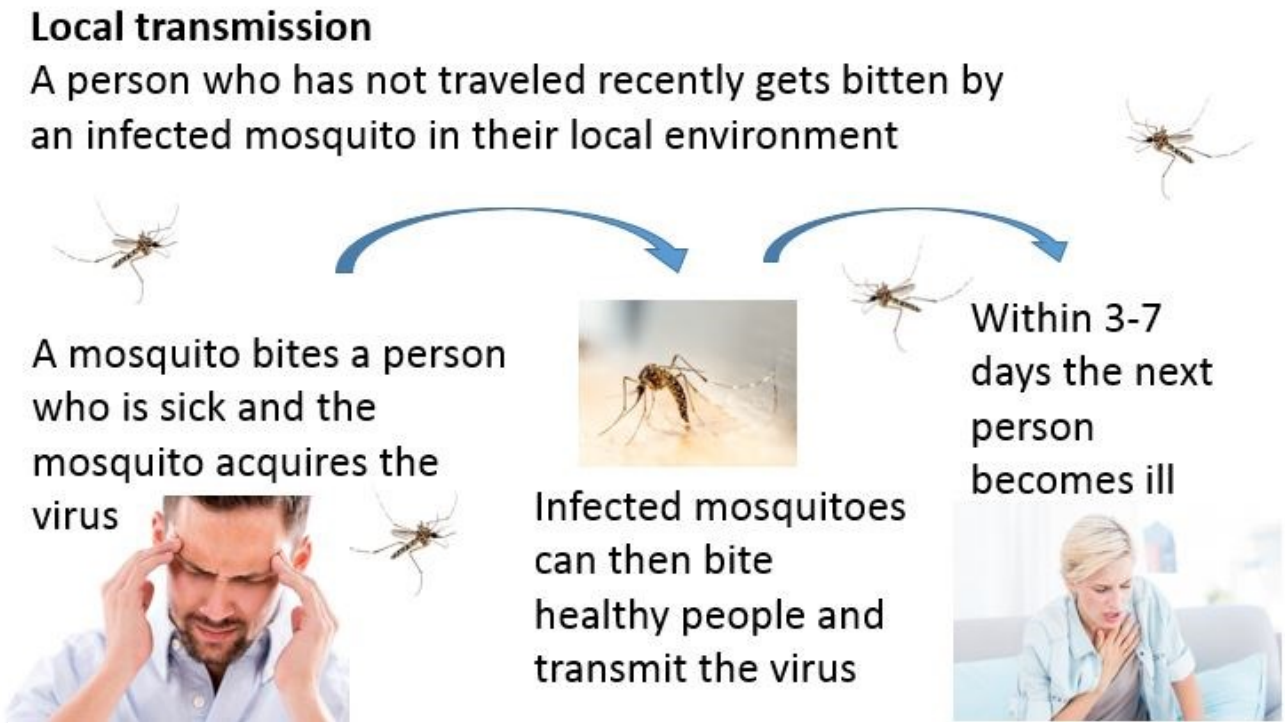

Figure 8. What is local transmission?

although long-term joint pain occurs in some people. According to the CDC, infection is thought to provide lifelong immunity.

During 2016, researchers developed the first chikungunya vaccine that may be approved for use at some point in the future.

Dengue virus causes dengue fever (Fig. 9), an infectious disease caused by any one of five related dengue virus serotypes (variations). Dengue virus is currently endemic (regularly transmitted) in more than 100 countries including many popular tourist destinations in Mexico, Puerto Rico, Latin America, Southeast Asia, Africa and the Pacific Islands. Cases occur regularly in southern Gulf States of the United States (Texas, Louisiana, Mississippi, Alabama, and Florida).

More than one-third of the world population live in areas with the virus and its vector, and dengue is a leading cause of illness and death in the tropics and subtropics, with estimates of 400 million people infected annually (CDC 2016a). Dengue can be transmitted in organ transplants and blood transfusions from infected donors, and between an infected pregnant mother and her fetus.

The incubation period is 4–7 days and the majority of people infected develop symptoms lasting between 3–10 days. It has been established that even asymptomatic infections (infected people with no symptoms of illness) generate a high enough level of viremia (virus particles) in their blood to provide feeding mosquitoes with virus, which can sustain high levels of transmission.

Symptoms of dengue fever include high fever, rash, severe headache, severe muscle and joint pains, mild bleeding from the skin, nose, and gums, and vomiting (Fig. 9). Most people recover from dengue infections within a few weeks. Dengue fever results from infection by one of the dengue serotypes, but infection by one serotype does not generate an immunity to the others, and ongoing infections put people at greater risk for the far more serious forms of the disease dengue hemorraghic fever, and dengue shock syndrome. Both severe forms of the disease can be fatal, and children and the elderly are the most at risk.

Dengue fever mortality rate is typically less than 1% of symptomatic cases. When treated, dengue hemorrhagic fever has a mortality rate of 2-5%, but if left untreated, the mortality rate may be 50%.

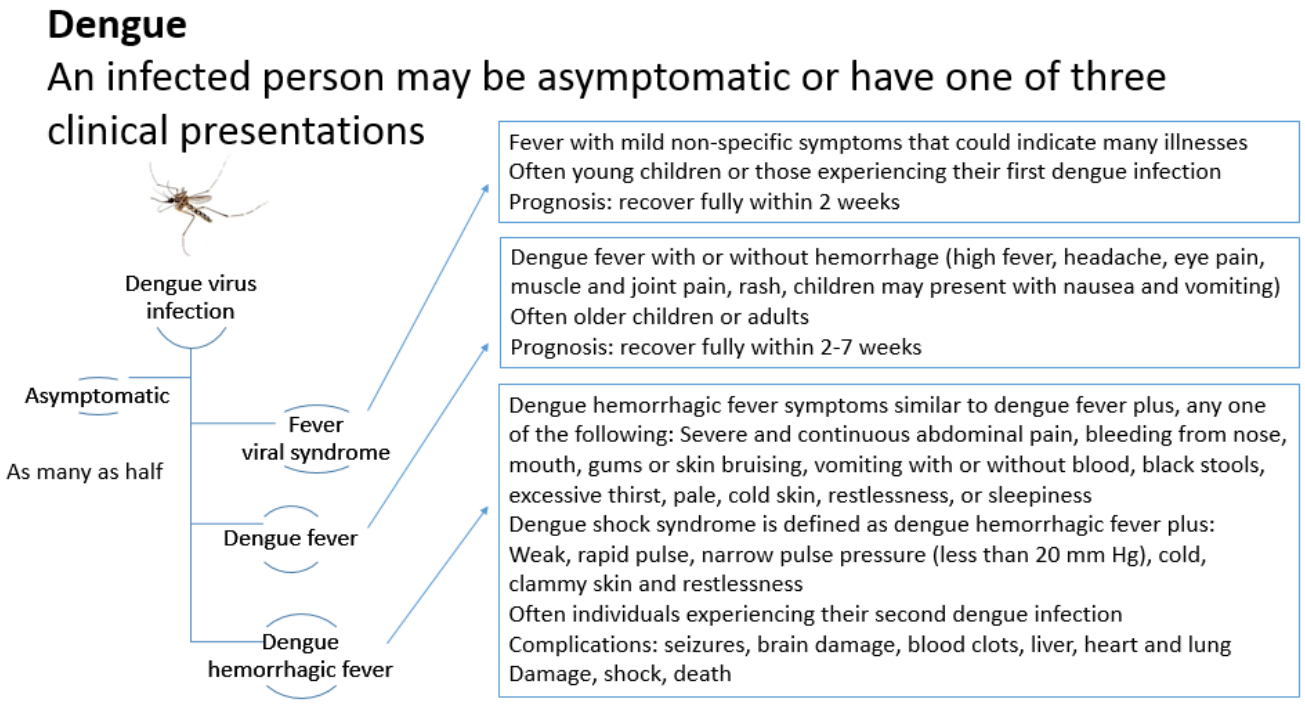

Figure 9. The course of infection and symptoms resulting from various stages of dengue.

There are no vaccines to prevent dengue virus infection available in the United States currently, but the DENGVAXIA® vaccine has been approved in Mexico and many other countries.

Zika virus infections in humans have been documented since 1952, but the first large outbreak of Zika was reported on the Island of Yap in 2007. Zika was identified as a global health concern in 2015 when an outbreak in Brazil was linked to a dramatic increase in cases of babies born with microcephaly (Fig. 10). Microcephaly is a neurological condition in which the brain develops abnormally in the womb, and an infant's head is smaller than the heads of other babies of the same sex and age. Currently, locally acquired Zika disease cases have been reported in many countries, several United States territories, Texas, and Florida. For up to date information on Zika cases reported around the world go to https://www.cdc.gov/zika/geo/.

As well as transmission via the bite of a mosquito, Zika virus can also be transmitted from mother to fetus during pregnancy, through blood transfusions, bodily fluids, and by sexual contact. At this point three *Aedes* species have been found capable of vectoring the Zika virus (*Aedes vexans*, in addition to *Ae. aegypti*, and *Ae. albopictus*).

The incubation period is typically 2-7 days, and about 20% of people infected with Zika virus become ill and develop Zika symptoms. The most common symptoms are fever, rash, joint pain, and/or conjunctivitis (red eyes) (Fig. 11). Other symptoms include muscle pain and headache.

The illness is usually mild, with symptoms lasting for a few days to a week. Severe disease symptoms requiring hospitalization are uncommon. Death due to the virus is rare. The main health concerns are related to pregnant women and impacts on the developing fetus.

Congenital Zika syndrome is a pattern of birth defects occurring when babies are infected with Zika virus during pregnancy. Birth defects include: severe microcephaly where the skull is partially collapsed, decreased brain tissue, damage to the back of the eye, joints with limited range of motion, muscle abnormalities restricting body movement. Some infants with congenital Zika virus infection who do not have microcephaly at birth may later develop postnatal microcephaly.

Recognizing that Zika is a cause of certain birth defects does not mean that every pregnant woman infected with Zika will have a baby with a birth defect.

However, infection with Zika during pregnancy increases the chances of birth defects, and infection during the first trimester is particularly problematic. The CDC does not believe that a woman who has fully recovered from a past Zika virus infection (and who no longer has Zika virus in her blood) is at greater risk for birth defects in future pregnancies. However, there is still much we need to learn about this virus and the pathology of Zika infection. Check https://www.cdc.gov/zika/pregnancy/index.html for the latest information.

Figure 10. Microcephaly is a condition that develops during pregnancy when a baby's brain does not develop properly or stops growing after birth. These babies therefore have a smaller head size than expected. CDC 2016b

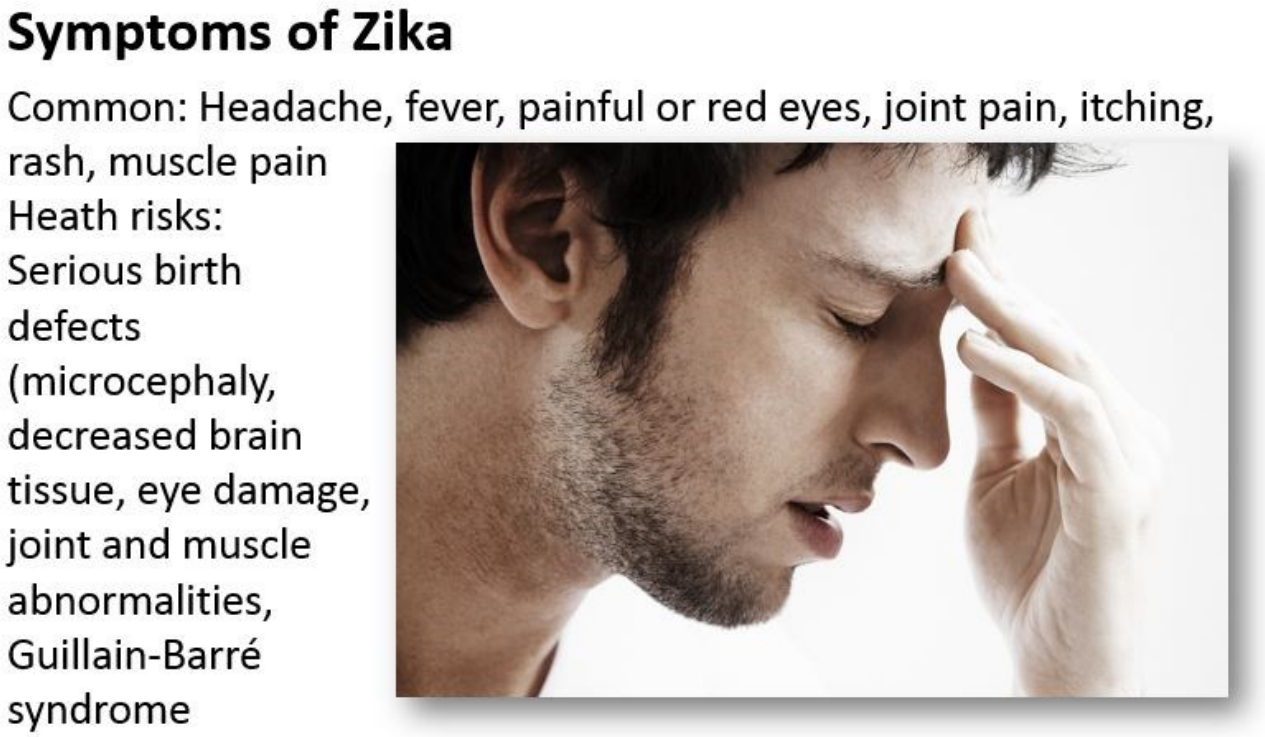

Figure 11. The most common symptoms of Zika are: fever 99.5 – 101.3°F (37.5 - 38.5°C), rash (maculopapular), joint pain (arthralgia), and red eyes (conjunctivitis). Other symptoms include: muscle pain and headache.

See a healthcare provider if you develop symptoms, particularly if you have visited an area where Zika is common: http://wwwnc.cdc.gov/travel/page/zika-travel-information. If you have recently traveled, tell your healthcare provider where and when you traveled.

Your blood may be tested for Zika virus and other viruses that cause similar symptoms like dengue and chikungunya viruses.

Work on a Zika vaccine is underway, but it could be several years before one is available.

CDC issues Zika updates at: https://www.cdc.gov/zika/index.html.

Significant efforts by mosquito abatement teams are underway to prevent local transmission of exotic disease causing arboviruses for as long as possible.

Integrated Mosquito Management (IMM) – Fight the Bite!

The most effective way to avoid arbovirus illness is to avoid mosquito bites.

It is particularly important for women of childbearing age to avoid mosquito bites – cover up, use insect repellents, and keep indoor living space free of mosquitoes.

People infected with any of the arboviruses should protect themselves from additional mosquito bites by wearing insect repellents, using air conditioning, or window and door screens to keep mosquitoes out of homes and buildings. Wearing long pants and long-sleeved shirts when possible is also advisable. **Protecting yourself and others from mosquito bites during the first few days of illness can help prevent other mosquitoes from becoming infected and reduce the risk of further spread**.

For more information about managing mosquito vectors around your home go to: https://extension.arizona.edu/sites/extension.arizona.edu/files/pubs/az1706-2016.pdf

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