Zika Virus Background

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Arboviruses
Viruses are not technically “living” creatures. They contain genetic information in the form of DNA or RNA wrapped in a protein shell that can inject the genetic material into a cell. The DNA or RNA can then take over the cell to reproduce copies of the virus. Eventually the cell explodes and releases new copies of the virus. Zika virus is a positive-sense RNA virus, which means it has the same orientation as mRNA (messenger RNA) and does not have to be “reverse-transcribed” using reverse transcriptase. This speeds up the process of virus replication in a cell. Zika virus is a flavivirus, in the family Flaviviridae. It is related to other RNA viruses like Dengue, West Nile, and St. Louis Encephalitis.

The Arbovirus Transmission Cycle
All of the previously mentioned viruses are Arthropod-borne Viruses or “Arboviruses” for short. Arboviruses originate in a “reservoir,” one or more species that are the “natural” host for the virus. Reservoir species usually do not get sick from the virus, so the virus is present in the population at low levels all of the time. An “arthropod vector,” such as a blood-sucking insect or tick, transmits the virus within the reservoir, but occasionally can transmit the virus to a “host species,” which may or may not become ill with the infection. The viruses previously mentioned are all transmitted by mosquitoes, but not all species of mosquitoes can transmit all types of arboviruses. A mosquito species that can transmit a particular virus is said to be a “competent vector.” When a host is infected by a particular virus transmitted by a competent vector, the virus will “amplify” as the host’s cells make more copies of the virus and it increases in concentration in the blood. This period is called the “viremic period” and usually occurs 3-14 days after infection. This can result in the host becoming ill and/or lead to a concentration in the blood which allows it to be picked up by another mosquito and transmitted to a reservoir species or host species. Some viruses like Zika can be transmitted from human to human by mosquitoes, while others like West Nile and St. Louis Encephalitis cannot. In the latter cases, humans are “dead-end hosts” because they do not circulate enough virus in the blood to infect additional vectors. West Nile and St. Louis Encephalitis epidemics can be maintained because birds are the reservoirs for these viruses.
Primates (monkeys, orangutans) are the likely reservoir for Zika virus. These species share a large percentage of the same DNA as humans.

Discovery of Zika Virus

Zika virus was first identified from a sentinel Rhesus monkey in the Zika Forrest in NE Uganda near Lake Victoria in 1943. The Rhesus monkey was not a primate native to the forest; it was placed in a cage on a tower in the rainforest canopy to attract primate-biting mosquitoes and be infected by viruses. Rhesus monkeys share about 93% of human DNA, so they are good “sentinels” for viruses that could potentially infect humans. The Rhesus monkey developed a fever for several days, but had no other symptoms. But the blood serum caused mortality in infant mice and a “filterable transmissible agent,” i.e., something smaller than a bacterium so it could not observed by a light microscope, when injected into another Rhesus monkey caused the same symptoms. The manifestation of human disease, a dense red rash on the body and limbs, fever, and conjunctivitis was not described in humans until a worker in the same lab developed a rash in 1956.

Epidemics

Sporadic cases of the rash associated with Zika were reported over the next 50 years. Tests for antibodies formed against Zika virus of populations from which the cases of rash emerged suggested that a very low percentage of people infected with the Zika virus develop any symptoms. Then in 2007 on the Pacific island of Yap, an outbreak of Zika generated 108 symptomatic cases. Later tests of islanders for Zika antibodies suggested a large percentage of the population was actually infected, almost 1/3 of the people, representing thousands of infections, but again, only a small proportion resulted in symptoms. Another epidemic occurred in French Polynesia (largest populations are on Tahiti and Moorea) between October 2012 and April 2014. In this case it is estimated that as many as 28,000 people sought medical attention for Zika-like symptoms. Documented infections totaled 2,686. Due to the excellent health care reporting system in French Polynesia, much retrospective analysis has been done which provides insight into Zika virus epidemiology. Subsequent Zika outbreaks on the Pacific Islands continue, including Vanuatu, the Solomon Islands, and New Caledonia so far. Then in April 2015, a large and sustained epidemic developed in Brazil. Thousands of symptomatic cases have been reported, but the rash and fever generally pass. Only 2 deaths have been reported in which Zika may have been a complicating factor. However, pediatricians began to suspect a correlation between a history of Zika infection in mothers who had given birth to microcephalic infants. Since microcephaly means a smaller than normal head, and therefore constrained brain development, and there are many things that can cause microcephaly, including malnutrition, drinking, smoking, etc., causation was not established. However, over 8,000 cases of microcephaly are being investigated in Brazil and a high percentage of them uncover a history of Zika-like symptoms. Recently, cases of Guillain-Barré syndrome have also been correlated with areas of Zika outbreak. The syndrome results when an agent (chemical or virus) binds with the myelin sheath of the nerve (which facilitates rapid nerve impulse transfer), and a person’s immune system attacks the invader and de-myelinates the nerves causing paralysis. In rare cases in which the breathing system becomes paralyzed, the patient can die. Unfortunately, exposure to chemicals like insecticides can also cause Guillain-Barré. Cases of Zika that are resulting from local transmission are now being reported from Puerto Rico.
Reservoirs
The presumed reservoir for Zika virus is primates. Antibodies to Zika virus have been detected in monkeys and orangutans in Africa and Asia, respectively. However, they have also been detected in large mammals like elephants, water buffalo, and zebra, and have also reported as being found in rodents. Whether the virus can be transmitted from mammals to humans has not been established. This is a fertile area for research. It is clear, however, that Zika virus can be transferred from human to human by mosquitos (we will discuss which ones next), but there are also examples of the virus being sexually transmitted. Visitors to Brazil during the recent ongoing epidemic have infected their partners when returning home. Humans are not technically a reservoir, but can be considered an “amplifying host.”

Vectors
The mosquitos which have been most strongly implicated in Zika virus transmission are species in the genus *Aedes*. In the Zika forest *Aedes africanus* was the likely vector. This species is a tree-dwelling species and rarely bites humans, which could account for the very sporadic cases in Africa. On the island of Yap the predominant mosquito species was *Aedes hensilli*. In French Polynesia *Aedes aegypti*, of yellow fever fame, is thought to have been the primary vector, with *Aedes polynesiensis* recently also implicated as a potential vector. The Brazilian epidemic is probably maintained by *Aedes aegypti*, though *Aedes albopictus* has also be implicated as a potential vector. *Aedes aegypti* does occur in the southern United States, but usually only as far north as central Kentucky because its eggs cannot survive freezing. *Aedes albopictus*, however, does occur in Illinois because it has a cold-hardy egg. *Aedes vexans*, the common floodwater mosquito, is widespread in the eastern United States and is a vicious biter; it is believed to be much less likely to transmit Zika virus than either of the previous two species. Nevertheless, a research program needs to be developed to assess the potential competency of all *Aedes* species in the eastern United States to transmit Zika virus. Perhaps the most alarming recent development was the report that mosquitos of the genus *Culex* allowed to feed on artificial blood containing Zika virus developed viral concentrations in their salivary glands typical of concentrations seen in competent *Aedes* vectors. *Culex* species are common in Illinois and maintain the West Nile virus transmission cycle already.

Human Hosts
The Zika rash, fever, and conjunctivitis associated with infection with the virus is not particularly dangerous. West Nile virus, in contrast, killed 1,100 Americans in the first 10 years after introduction to the United States; thousands more had serious post-illness symptoms such as polio-like muscle weakness. The correlation of Zika infection with cases of microcephaly and Guillain-Barré syndrome are much more alarming than the typical acute symptoms of the disease. Additionally, the evidence that Zika virus infections can cause Guillain-Barré has greatly increased recently. Using the excellent public
health records of French Polynesia, patients treated for Guillain-Barré during that epidemic were tested for Zika virus antibodies with almost a 100% correlation. This is not technically direct evidence of causation, but it is highly suggestive of causation. The evidence that Zika is at least a contributing factor in the development of microcephaly is also growing, in fact the Centers for Disease Control and Prevention (CDC) has recently announced that while the mechanism by which Zika causes microcephaly has not been discovered, the indirect evidence is now over-whelming.

The Illinois Situation

Current Scenario

To date (May 2016) all investigated cases of Zika virus in Illinois (and the continental United States) have been found to be travel related—with no local mosquito transmission suspected. It is important to understand that travel-related infections can result in sexual transmission to partners. The CDC originally recommended the use of condoms for 28 days after returning from an area with local Zika transmission. Recent studies have suggested the virus can persist in the semen at least 62 days after symptoms of Zika virus infection, so they have updated their travel advisory at: http://www.cdc.gov/media/releases/2016/s0315-zika-virus-travel.html. Women of child-bearing years who have the potential to become pregnant should avoid travel to areas where Zika is endemic. Zika infection during the first trimester of pregnancy carries the greatest risk for microcephaly, but at least two cases of microcephaly have been identified in which mothers reported third trimester rashes. If travel cannot be avoided, pregnancy tests should be taken before travel to ensure you are not pregnant and extreme measures to avoid pregnancy and to avoid exposure to mosquito bites should be taken (long clothing, repellants, permethrin-treated clothing, staying in air-conditioned indoors, bed netting, etc.). See the CDC website for further and most up-to-date recommendations at: http://www.cdc.gov/zika.

Anticipatory Scenarios

Control of Aedes aegypti and Aedes albopictus will depend on the resources available to local health departments and other local government agencies to conduct active vector control activities. If local transmission is established in the United States, Florida, Alabama, and Louisiana are the most vulnerable states due to the presence of Aedes aegypti and their near sub-tropical climates with the resultant potential for year-round mosquito production. While integrated mosquito control (surveillance, source reduction, and treatment) is more routine and sophisticated in the United States than many other countries, increased vigilance and more aggressive control measures particularly for Aedes aegypti and Aedes albopictus are warranted in these southern states. If local transmission of Zika virus in Illinois occurs, it will most likely be associated with Aedes albopictus populations. Illinois mosquito abatement districts (MADs) are quite familiar with the breeding habits of this species, and surveillance and source reduction efforts should be stepped up immediately where MADs are present. However, outside of municipalities with large populations, local mosquito control programs often provide very basic services or those services may not be provided because of limited local resources. More aggressive enforcement of used tire storage also needs to be implemented. These suggestions are problematic given that the state budget impasse is holding up dollars specifically earmarked for these purposes (Used Tire Management Fund and Emergency Public Health Fund). Research on the potential ability of Zika virus to survive overwintering is also needed. Assessment of whether rodents or other small mammals might be
serving as reservoirs in tropical areas where non-primates do not occur is needed. If they are serving as reservoirs, lab testing of the capacity of similar species in temperate regions to maintain Zika might also be warranted.

**Worst-case Scenario**

The worst-case scenario is Zika virus becoming locally established in the temperate regions of the United States. This would likely require a combination of low probability developments: 1) rodents or other small mammals serving as reservoirs, and 2) the competence of most *Aedes* species and/or *Culex* species, particularly those in the *C. pipiens* complex (northern and southern house mosquitoes), and 3) development of a mechanism for Zika to overwinter. This scenario would require a major increase in mosquito control measures and maybe even small mammal or rodent control. In such a case, the development of new genetic control measures will be needed, perhaps the use of “gene drives” (forcing a species to only produce males) or genetically engineered mosquito gut bacteria capable of intercepting and neutralizing viruses. The Illinois Natural History Survey in the Prairie Research Institute is currently assessing the potential for development of the latter technology.