who me? worry?

Should we be concerned about a **Zika** outbreak in Louisiana?

By **Claudia S. Copeland, PhD**

In February of this year, the Louisiana DHH announced two suspected cases of Zika virus infection, now confirmed by the CDC. The patients, just back from travel in the Caribbean, likely contracted the virus there, and presumably did not pass it on; as of the beginning of April, no further Zika cases have been seen here. How long, though, can a virus like Zika, which has spread explosively throughout Latin America, be held off? Could it take hold in Louisiana and become an epidemic? And if it did, how would that affect our residents?

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IMAGE BY CDC/ CYNTHIA GOLDSMITH (HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=20541) [PUBLIC DOMAIN], VIA WIKIMEDIA COMMONS

Zika virus is not a "new" virus–it was first isolated in the Zika Forest of Uganda in 1947. However, until last year, it has been a virus that few had ever heard of. This is partly due to its relative lack of symptoms–although it is related to the deadly viruses that cause yellow fever, dengue, Japanese encephalitis, and West Nile encephalitis, Zika fever is a very mild disease. In most patients, if symptoms are felt at all, they are those of a mild case of dengue–rash, fever, joint pain, conjunctivitis, muscle pain, and/or headache. In the vast majority of cases, there are no symptoms at all, and the person has no idea they were infected.

Recently, though, Zika virus has been implicated in serious neurological syndromes–most notably, thousands of cases of microcephaly in newborns in Brazil. In October of 2015, the Brazilian Ministry of Health reported an alarming increase in microcephaly cases, particularly in the hotter, more humid northeastern states. Whereas between 2010 and 2014, 150-200 cases of microcephaly had been seen in the country, that number jumped to over 3,000 in 2015. This rise was correlated with an epidemic of Zika virus, probably first introduced to Brazil from Southeast Asia or the South Pacific in late 2013.

While a causative link with Zika has not been proven, strong evidence is mounting in support of it, such as the finding of Zika virus particles in the brains of infants and fetuses with Zika-suspected microcephaly and in the amniotic fluid of Zika-exposed mothers. In addition, a team of neuroscientists and virologists, Tang et al., just reported in the March 2016 issue of *Cell Stem Cell* that Zika virus preferentially infects human neural progenitor cells, the cells that grow into the brain's cortex. Three days after exposure to the virus, 65–90% of their lab-grown cortical neural progenitor cells were infected, and the infection resulted in cell death for many of the cells, along with decreased expression of the genes that control cell division. Since these cells are stem cells from which other neurons are created, this sort of infection in a living brain would be expected to lead to the catastrophic results seen epidemiologically in Brazil. Further, Zika infection is correlated with other fetal neurological problems consistent with a virus that infects cells of the developing brain, including absent or poorly developed brain structures, defects of the eye, hearing deficits, and impaired growth, according to the CDC.

Over the years since the virus' discovery, Zika outbreaks in Africa, Asia, and Oceania have been felt by most patients as a mild febrile illness, if they get sick at all. One major exception, seen in a small minority of patients, is a serious neurological condition known as Guillain-Barré syndrome. Guillain–Barré syndrome, which affects adults more strongly than children, manifests as a progressive, symmetrical muscle weakness, often leading to temporary paralysis (and sometimes permanent damage). While the symptoms are temporary in most patients, it can be fatal: it can affect the muscles needed for breathing, and 5% of patients die from the syndrome, according to the CDC. A study by a team of French and French Polynesian researchers published in

Side-view illustration of a baby with microcephaly (left) compared to a baby with a typical head size

IMAGE BY CENTERS FOR DISEASE CONTROL AND PREVENTION [PUBLIC DOMAIN], VIA WIKIMEDIA COMMONS

February 2016 in *The Lancet* reported a significantly increased incidence of Guillain–Barré syndrome in patients in the 2013-14 French Polynesian outbreak. The patients suffered from a form of Guillain–Barré known as acute motor axonal neuropathy, with characteristic rapid onset but favorable long-term outcomes. Most patients eventually recovered (none died), although the recovery was slow, with a substantial number still unable to walk without assistance 3 months after discharge.

Zika virus in Louisiana?

So, how likely is it that Zika virus could take hold in Louisiana? According to DHH representative Samantha R. Faulkner, "we are unlikely to have a large outbreak in the state. It is possible that we could have some more imported cases, which could potentially lead to a few cases of local transmission, but this is unlikely to cause a large chain of transmission." If someone is concerned that they might have contracted Zika, their physician can determine if they need testing. As to prevention, the best way is to protect against mosquito bites: "make sure all screens on your house are intact, empty all containers with standing water on your property, and wear protective clothing and EPA-approved mosquito repellent." In short, while it's a good idea to minimize your contact with mosquitoes, according to the DHH, there really is no need to worry about a Zika epidemic here.

Despite this reassurance, though, several aspects of the Zika outbreak and characteristics of our region give cause for concern. First, there have been two confirmed cases here, and if up to 80% of infected people show no symptoms, it stands to reason that there could be more. Second, we have the mosquito. While the border areas of California, Arizona, New Mexico, and Texas all have large numbers of people entering from countries on the CDC Zika travel advisory, only the far south of Texas can support moderate populations of the Aedes aegypti mosquito, the main vector of Zika virus.

In contrast, the Gulf Coast regions, including southern Louisiana, have high populations of Aedes aegypti in the summer months. (While another common mosquito, Aedes albopictus, is capable of transmitting Zika, Tulane medical entomology professor Dawn Wesson points out that "given identical vector competence with Aedes aegypti, in the southern U.S., Aedes albopictus would be a less likely vector because it tends to feed less frequently on humans, and occurs in more peri-urban, suburban, and rural areas than does Aedes aegypti." She does concede, however, that in "high density urban areas in more temperate zones, Aedes albopictus may be the only species present of the two and could potentially be a vector.")

While Louisiana may not have the large influx of travelers/immigrants seen in other states, we have experienced epidemics of Aedes-transmitted diseases here, most recently West Nile virus. Over 1,600 Louisianans have contracted West Nile virus disease since 1999, with a peak of 335 cases in 2012. Last year, there were 36 cases of neuroinvasive West Nile disease (the more serious, and sometimes deadly, form of the disease), including 4 deaths. If West Nile could take hold here, why not Zika?

According to LSU epidemiology professor Susanne Straif-Bourgeois, the reason Zika virus will not take hold here like West Nile did lies in the absence of an animal reservoir. In order for a virus to maintain an infectious cycle, it needs to have a sufficiently large infected population with sustained viral transmission. Whereas West Nile virus maintains an active infection cycle in wild birds, "Zika virus has no animal reservoir in the U.S. so it will be very difficult to get established here. For an outbreak to occur, a lot of mosquitoes would have to be infected, a so-called 'epidemic threshold' ... Since we have no bird reservoirs where the virus could multiply and then reach the epidemic threshold, there is minimal risk. Unless we

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SYMPTOMS OF ZIKA


Headache


Fever


Joint Pain


Conjunctivitis


Muscle Pain


Rash

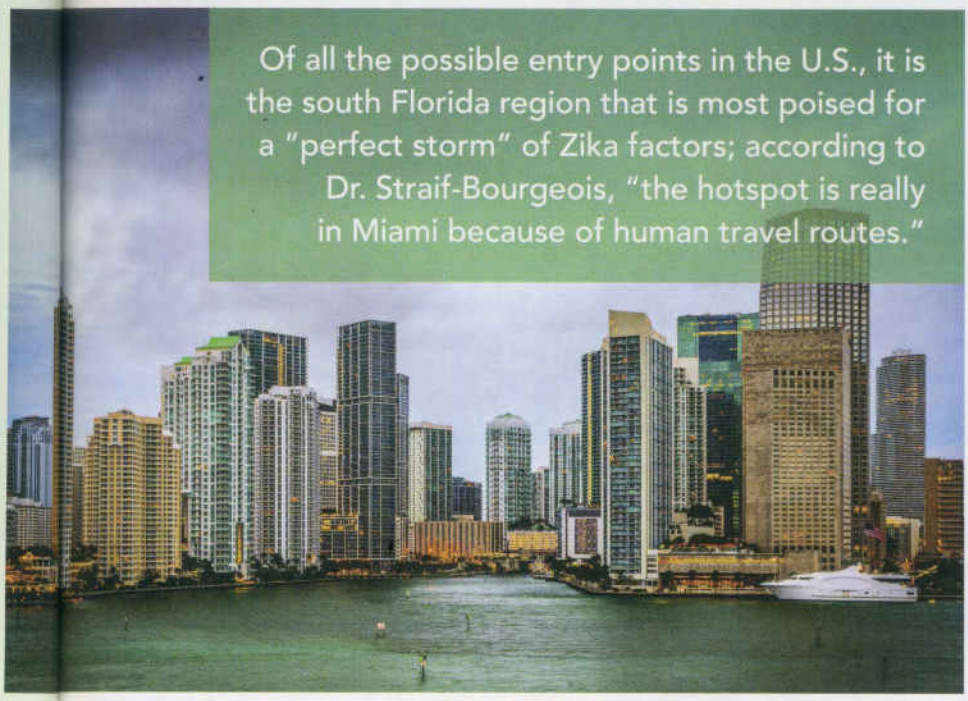
get a lot of currently infected people coming back with Zika virus in their blood it will be very difficult for Zika to become established here." (On the other hand, according to the European Centre for Disease Control and Prevention, rodents, alongside large African mammals, have been shown to harbor antibodies for the virus, indicating that they are carriers. It remains to be seen whether U.S. rodents could become animal reservoirs of Zika.)

Assuming there is no animal reservoir here capable of amplifying a Zika outbreak, what about the virus being maintained in the mosquitoes themselves? If the mosquito can pass this virus to her eggs, a process called transovarial transmission, could this alter the epidemiological prognosis? Probably not, according to Dr. Wesson: "We do not know if transovarial transmission of Zika virus by Aedes aegypti (or Aedes albopictus) can occur, but it is likely, given that both yellow fever and dengue (related flaviviruses) can be transmitted by transovarial transmission. That said, even if transovarial transmission is possible, it may not be important in the epidemiology of Zika." She explains that a recent review of dengue fever found that vertical transmission in mosquitoes was relatively unimportant in dengue virus transmission, compared with asymptomatic infection and movement of viremic dengue patients. That said, she points out that "Zika is not dengue" and highlights the need for specific data in this area.

So, the Gulf Coast has the main mosquito vector, but doesn't have the other elements that are probably necessary for an arboviral Zika epidemic to take hold. There is one U.S. region, though, that both harbors large numbers of Aedes mosquitoes and experiences regular, large influxes of travelers from Zika epidemic countries: southern Florida. Of all the possible entry points in the U.S., it is the south Florida region that is most poised for a "perfect storm" of Zika factors; according to Dr. Straif-Bourgeois, "the hotspot is really in Miami because of human travel routes." Also, in contrast to slightly more northern areas like Louisiana, Aedes aegypti mosquitoes in southern Florida maintain substantial populations not only during the summer but also over the winter. Several counties in southern Florida have already experienced local transmission of dengue and chikungunya, two other viruses that use Aedes aegypti as a vector. As of March 2016, there have been no confirmed locally acquired Zika virus infections anywhere in the U.S., but Florida has had, by far, the highest number of travel-associated infections (70 confirmed cases, out of a total of 273 in the U.S.).

It is important to remember that, if 4 out of 5 cases are too mild to report symptoms, the actual number of people infected may be five times the number of reported cases. With 70 confirmed travel-associated cases and therefore a reasonable estimate of 350 possible infections, south Florida is by far the most likely place for the emergence of local transmission in the U.S. As time moves forward, physicians might be wise to consider recent travel/residence in south Florida as a "light red flag" for Zika lab testing, along with the "dark red flags" of travel to Brazil and other countries already in the grips of the Zika pandemic.

Another factor to consider, adds Dr. Straif-Bourgeois, is the infectious period. Zika virus remains in a patient's blood for about one week after infection. This means that, for any traveler carrying the Zika virus, there is a window of about 7 days to get bitten by a mosquito and have that mosquito bite another person. Mosquitoes drink blood to support egg growth, and only need one blood meal per batch of eggs. Since this cycle takes 8-10 days, and mosquitoes only live for about a month, each mosquito can infect a maximum of about four people if they get full blood meals. (Current understanding of the threshold viremia needed for a mosquito to pick up the virus from an infected human is limited, but this is a factor that would further reduce viral transmission from a theoretical maximum.) Of



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course, if a mosquito is interrupted in the middle of a blood meal, she will bite again, but even in this case, the number of people a single mosquito can infect is quite limited. Considering the prevalence of screens, air-conditioning, and the relatively low population density of humans compared with other animal sources of blood here, the likelihood of an infected person passing the virus to another mosquito within the infectious period is low. Clearly, in Louisiana, any introduction of Zika virus via a traveler will most likely die out rather than become sustained in the population.

Brazil, in contrast, is characterized by densely populated cities with high Aedes aegypti abundance and poor infrastructure for protecting residents, such as screens on windows. In addition, shortly after the initial introduction of the virus into Brazil, there were several large sports events that brought thousands of people together in close proximity, further facilitating transmission. It is easy to see how thousands of mosquitoes could simultaneously infect thousands of people, who could then provide blood meals to different mosquitoes during the infectious period. (For perspective, the Brazilian Ministry of Health estimated that there were 0.4-1.3 million cases of Zika virus infection in Brazil in 2015.) While anyone who lives in Louisiana can attest to the large mosquito populations here, human populations are much less dense than in the large Brazilian cities and protective infrastructure is common. Louisiana is therefore not a likely place for a Zika epidemic to take root. It could, however, be where transmission is amplified–not through mosquito bites, but through unprotected sex.

Sexual transmission could cause the epidemiology of Zika to take an unexpected turn. Whereas infectious virus stays in the blood for only about a week, Zika can survive in semen for much longer. Researchers Musso et al. were among the first to detect Zika in semen, in a French Polynesian hematospermia patient. Originally infected with Zika during the 2013 French Polynesian outbreak, the patient's infection had long cleared, and no viral RNA could be detected in blood samples, but a high Zika virus RNA load and replicative Zika virus were detected in semen samples. While it's not clear how long an infected man can continue to transmit the virus through sex, British doctors Atkinson et al. detected Zika virus in semen 62 days after infection, with an RT-PCR signal stronger than that of the original serum diagnostic result. Of the 273 confirmed cases of Zika in the U.S., 6 were sexually transmitted, according to the CDC. Louisiana has some of the highest rates of STDs in the country, reflecting the prevalence of sexually risky behavior here (see Sex in the City is Risky Business; *Healthcare Journal of New Orleans*, Sept.-Oct. 2012). Further, the lack of symptoms in most people means that Zika, like the very common bacterial infection Chlamydia, could spread stealthily through the population, with most infected people having no idea they are carriers.

Clearly, the Zika epidemic is a complicated one, with many facets and many possible outcomes. Only time will tell whether the two confirmed Zika cases in Louisiana are the end of the story here, or whether we will see more of this epidemic, perhaps taking on a new face in our bon temps-loving, but often risk-ignoring, subtropical culture. ■

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