

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Zika and the Safety of the US Blood Supply



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H&O What exactly is the Zika virus, and when was it discovered?

MB The Zika virus was discovered in 1947 in the Zika Forest of Uganda as part of an early virologic discovery program. Sentinel Rhesus macaques were monitored for fever, at which point the animals were tested for viruses. The first human infection was seen in 1954 in Nigeria.

The Zika virus is a flavivirus, a category of RNA genome virus that has an envelope. It is similar to the dengue and Chikungunya viruses in structure and in genetic and antigenic cross-reactivity. These similarities make it challenging to develop accurate diagnostic tests.

The mosquito that is most likely to transmit the virus is the female *Aedes aegypti* mosquito, which is sometimes referred to as the yellow fever mosquito. These mosquitoes are found in numerous places around the world, including Africa, Asia, the Caribbean, Central and South America, and southern North America. An infected mosquito can bite and infect 5 or more people in a single day.

H&O How dangerous is infection with the Zika virus?

MB For the first 60 or so years that we knew about the Zika virus, there were only approximately 14 confirmed cases in humans, all in Africa or Asia. We first saw a major outbreak in 2007, on the island of Yap in Micronesia. The infection was relatively benign in these cases, causing a transient febrile-like illness with rash, arthralgia, and conjunctivitis in most people with clinical disease. We were not aware of any later effects. After French Polynesia experienced an outbreak in 2013, we saw cases

of Guillain-Barré syndrome in approximately 1 in 1000 people who had been diagnosed with Zika. We also realized that the majority of people who are infected have no symptoms—approximately 80% of people who are infected are completely asymptomatic.

The most alarming sequela was discovered after an epidemic began in northern Brazil in 2015. Astute clinicians linked the increased incidence of microcephaly in newborns with the epidemic that had occurred 9 months earlier. Since then, multiple studies have documented a causal relationship between Zika virus infection and congenital neurologic disease in the fetus via intrauterine transmission, especially if the mother is infected during the first trimester. It also has been documented that the mother does not need to develop symptoms in order for the fetus to be affected.

When infection occurs very early in gestation, it may cause spontaneous abortion. When infection occurs somewhat later, the baby may be born with microcephaly. In microcephaly, the virus causes extensive destruction of neurologic tissue that leads the brain to essentially disintegrate and the skull to collapse on itself. This damage can be seen on ultrasound, allowing women the option of abortion in countries where that is legal. The virus also may cause other neurologic diseases besides microcephaly in offspring.

We have gone from thinking for decades that this was a relatively benign virus in terms of long-term effects, to learning over the past 5 or so years that it can cause severe disease.

H&O What other routes of transmission are possible?

MB We know that mosquitos are responsible for the vast majority of infections. The virus is also found in semen, blood, urine, saliva, and breast milk, so it can be transmitted by sex and also by blood transfusions. Cases of sexual transmission have been documented, including male-to-female, male-to-male, and even female-to-male transmission. Sexual transmission has been documented primarily in countries where the risk of Zika is low, and may occur more often than we realize in Zika-endemic countries.

H&O How many cases of blood transfusion-related transmission have been documented?

MB At the peak of the outbreak in French Polynesia, 2.8% of blood donations were found to contain the Zika virus, according to a study by Didier Musso. We are now seeing that close to 2% of blood donations in Puerto Rico are positive for Zika RNA. But until the existing Brazil epidemic, we never had a confirmed case of transmission via blood transfusion. A total of 4 cases of blood transfusion transmission have now been documented in Brazil. All the recipients in those cases were asymptomatic with respect to Zika, with the cases identified when the donors called the blood bank several days after donation because they had subsequently developed symptoms and been diagnosed with Zika. Donor blood samples that the hospital had saved were found to contain Zika virus RNA, and the recipients were documented to have been Zika-negative prior to transfusion and Zika-positive after transfusion. Sequencing of the virus in the samples confirmed that the viral strains were identical between the donors and recipients.

H&O Is there a reason none of the recipients developed symptoms?

MB What is interesting is that there seems to be a difference in arbovirus disease outcomes following viral transmission from blood transfusion vs from a mosquito bite. A mosquito bite does more than just deliver a virus, it also induces an inflammatory process that allows the virus to actively replicate locally, and consequently to disseminate rapidly and extensively.

Another reason why blood transfusion recipients do not develop symptomatic Zika disease is that these patients are recovering from illness or trauma and are unlikely to be able to mount the robust immune response that occurs in healthy individuals and may be required for symptoms to develop. Patients who are elderly or are being treated for cancer, for example, are unlikely to have an active immune response following dengue or Zika infections that will lead to symptoms.

As a result of these 2 factors, transfused blood is

unlikely to cause people to develop Zika disease.

People with hemophilia A/B or von Willebrand disease are not at increased risk for infection because manufactured clotting factor concentrates are viral attenuated.

H&O Could blood transfusion to a pregnant woman cause microcephaly?

MB Although no case of transfusion-related transmission to a pregnant woman or a fetus has been documented, it is theoretically possible. As a result, Brazil has begun to test blood for Zika RNA or use blood from geographic areas where Zika is not present when the blood is to be transfused to a pregnant woman, including blood used for intrauterine transfusions.

H&O What steps are being taken to keep the Zika virus out of the US blood supply?

MB The US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) are extremely concerned about the blood supply in the US territories, especially in Puerto Rico, American Samoa, and the US Virgin Islands. These areas have experienced very large outbreaks of Zika this year—at least 5000 cases in 2015 and the first half of 2016—and in previous years they experienced large outbreaks of dengue and Chikungunya.

The FDA has been extremely aggressive about safeguarding the US blood supply from the Zika virus. The FDA policy, issued in February, requires that areas where Zika is present import blood from Zika-safe regions, test all blood for the Zika virus, or use pathogen-reduction technologies. In addition, people who have traveled to Zika-endemic regions are barred from donating blood for 1 month after their return to the continental United States. A sexual partner of a man who has traveled to a Zika-endemic region is barred from donating blood for 4 to 6 months because of evidence that the virus can persist in semen. We had a period in March 2016 in which Puerto Rico was required to import all of its blood from the continental United States. The exception was 1 blood center in Puerto Rico that adopted an FDA-licensed pathogen reduction technology for platelets as soon as the mandate was put in place; this allowed them to continue to collect and issue platelet apheresis components without Zika testing. The pathogen-reduction technology, Intercept from Cerus, inactivates a broad range of pathogens in platelets and plasma, including viruses, bacteria, and parasites. The company also is conducting clinical trials of technology to inactivate pathogens in red blood cells.

Then the FDA authorized emergency use of an experimental test from Roche Molecular Systems to screen all

blood donations, which allowed Puerto Rico to resume local collection, test the blood, and issue safe blood to patients by the first week of April. A second screening test from Hologic is also now in use.

Blood screening was implemented for donors in Puerto Rico beginning in April 2016, with detection of more than 150 Zika RNA–positive donors through July. The rate of infected donations approached 2%. In July, researchers determined that at least 14 people in Florida had been infected with the virus by autochthonous transmission, with the virus found in mosquitos in a small section of Miami–Dade County. The FDA subsequently ordered blood banks in Florida to implement Zika RNA screening. More infections have since been identified in Florida, and many southern states have expanded testing.

As Lyle Petersen and his CDC colleagues have reported, *Aedes* mosquitos are present throughout the southern United States. We used to think they were restricted to Florida and the Gulf Coast states, but now we know they are present all the way up to Washington, DC, and as far west as California. As a result, there is a potential for focal outbreaks of mosquito-transmitted Zika, seeded by travel-acquired infections, in most of the southern United States.

Screening blood donations is also a highly efficient way to detect spread of the virus in the continental United States. The American Red Cross and other organizations have started screening in some of the southern states. We already have screened tens of thousands of donations in the continental United States, with no infected donations seen as of early August. Hawaii also has made the decision to begin screening all donations, because officials wish to avoid the possibility of needing to import all their blood temporarily should any cases of Zika transmission occur.

All of the blood collection organizations belong to the AABB, and we are ready to respond to any changes in status. The FDA and CDC have provided a very aggressive response to the threat. The AABB and CDC websites provide up-to-date information on Zika around the world, including a map of all areas with active Zika virus transmission. We have learned from our experience with the human immunodeficiency virus, hepatitis, and the West Nile virus, and everyone is on high alert.

H&O How do you see the response to Zika evolving?

MB Although we are taking the approach of screening donor blood right now, a better strategy in the long term is pathogen inactivation. This is a proactive approach to preventing emerging infections, because new ones appear

every year. The federal government is investing hundreds of millions of dollars into developing pathogen inactivation technologies, especially for use in red blood cell products. Although these techniques will not completely sterilize the blood, they will dramatically reduce the transmission of new pathogens.

H&O Is there anything that you would like to add about Zika?

MB Although we take seriously the risk to the blood supply from the Zika virus, it is important to remember that blood transfusion is a small contributor to the spread of this disease and infectious diseases in general. Furthermore, we have yet to document clinical disease resulting from blood transfusion transmission of the Zika virus. So the current aggressive approach of deferral, testing, and pathogen inactivation may later be scaled back if studies establish that transmission and disease are rare outcomes in transfusion recipients.

I would also like to point out how different the response is between the United States, a wealthy country where the risk is minimal, and Brazil, a poorer country where the disease is widespread. Although the risk is far greater in Brazil, we are the ones screening donations in potentially at-risk states, not just those intended for pregnant women. This is just another example of the inequity in health care around the world, including in the arena of transfusion safety.

Disclosures

Dr Busch's laboratory receives funding to study the Zika virus and blood safety from the National Institutes of Health, the Centers for Disease Control and Prevention, and the commercial manufacturers of blood screening assays (Roche and Hologic) and pathogen reduction technologies (Cerus and Terumo). He does not receive personal compensation from or have financial interest in any commercial company involved in blood safety.

Suggested Readings

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