

# Maintaining a Safe Blood Supply in an Era of Emerging Pathogens

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Coming shortly after outbreaks of dengue and chikungunya virus in related locations, the recent outbreak of Zika virus in the southern part of the western hemisphere is yet another reminder that infectious pathogens continue to emerge rapidly and can adversely affect public health, including the safety of the blood supply. In response to Zika virus, public health measures that rely largely on donor deferral and sourcing of blood from non-outbreak areas until a blood donor screening test becomes available have been implemented to address the safety of the blood supply in the United States. However, a more universal approach to ensuring blood safety in the setting of rapidly emerging infectious diseases is needed.

**Keywords.** blood safety; donor screening tests; emerging pathogens; pathogen-reduction; Zika virus.

Recent episodes of arboviral disease in the western hemisphere have included large outbreaks of infections due to West Nile virus, dengue viruses, chikungunya virus, and, most recently, Zika virus [1]. An arbovirus from the *Flaviviridae* family, genus *Flavivirus*, Zika virus is transmitted to humans primarily by the *Aedes aegypti* mosquito, although it may also be transmitted by other *Aedes* species [2]. It was first isolated in 1947, from a rhesus monkey in the Zika Forest of Uganda, and later isolated from a human, in 1968, in Nigeria [3]. Epidemiological studies showed that the virus has circulated in humans between 1951 and 1981 in African and Asian countries, and illness was first recognized outside of Africa, in Asia, during an outbreak on Yap Island, Micronesia, in 2007 [4]. Zika virus reached the western hemisphere in early 2015, with local transmission first reported in Brazil, and now there are about 30 countries and territories worldwide with active local mosquito-borne transmission of the virus [5].

Although there is still much to be learned about the pathogenesis of Zika virus, its current association with an increased number of cases of microcephaly, Guillain-Barré syndrome, and other complications is quite concerning, despite the fact that most people have a relatively mild illness and 4 of 5 are asymptomatic [6]. In addition, there is compelling evidence to indicate that Zika virus is transmissible via sexual activity and transfusion [7]. Relevant to the potential for transmission via transfusion, in French Polynesia, 2.8% of samples from asymptomatic blood donors contained detectable Zika virus RNA during an outbreak there in 2013 to 2014 [8]. More recently, in 2016, 2 instances of probable transmission via transfusion were described in Brazil, and reports of confirmed sexual transmission are increasing [9].

The relatively rapid emergence of Zika virus has led to the urgent need for accurate clinical diagnostic tests to detect acute and recent infections in certain potentially exposed individuals, particularly pregnant women. Development of blood donor screening tests poses special challenges, as very high sensitivity is needed, yet high specificity is also desirable to avoid an excess number of false-positive test results, which lead to unnecessary donor deferral, counseling, and follow-up testing. In addition, these tests need to

be optimized for use in high-throughput systems. In principle, nucleic acid tests targeted to Zika virus RNA would be best suited for this purpose. It would be ideal for nucleic acid tests to be used on mini-pools of 6–16 samples, as this facilitates the necessary volume of screening of the many millions of units of whole blood collected each year in the United States. However, as in the case of West Nile virus, individual donation testing may be needed to detect low levels of virus that may be present in the blood of asymptomatic donors. Although nucleic acid screening tests for detection of Zika virus in the blood supply are not yet licensed by the Food and Drug Administration (FDA), it is in the public domain that they are under development. In the meantime, to protect public health, the FDA has issued guidance to reduce the transmission of Zika virus [10].

In areas where there is no active transmission of Zika virus, the FDA recommends that donors at risk for Zika virus infection be deferred for 4 weeks. Individuals considered to be at risk include those exposed in an area of local transmission who have had symptoms suggestive of Zika virus infection (such as fever, arthralgia, maculopapular rash, and conjunctivitis), those who have had sexual contact with a man who has traveled to or resided in an area with active Zika

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virus transmission during the prior 3 months, and those who have traveled to or resided in areas with active transmission of Zika virus during the past 4 weeks.

In areas with active transmission of Zika virus, as defined by the Centers for Disease Control and Prevention [5], the FDA is recommending that whole blood and blood components for transfusion be obtained from areas of the United States without active transmission. Blood-collection establishments may continue collecting and preparing platelets and plasma if an FDA-approved pathogen-reduction device is used. The eventual implementation of a licensed screening test is anticipated in the guidance, as blood collection will be permitted in areas with active transmission once Zika virus-infected units can be identified and prevented from entering the blood supply.

At this time, Puerto Rico, the US Virgin Islands, and American Samoa are the only areas of the United States and its territories with active transmission of Zika virus. However, if some predictions are accurate and Zika virus is able to take hold in southern parts of the continental United States, having highly accurate blood donor screening tests available for high-throughput use will greatly facilitate blood supply management. Implementing one more screening test will come at a significant additional cost for the blood supply.

Over the past decade there has been an increased strain on the blood industry in the United States. Paradoxically, this has been caused, at least in part, by medical progress. Improved patient management and blood-conserving surgical advances have substantially reduced the need for transfusion [11]. Additionally, a number of large randomized controlled clinical trials have demonstrated equivalent benefit in most populations of lower transfusion thresholds (hemoglobin level, 7–8 g/dL) than those previously used in clinical

practice [12]. At the same time, the list of nucleic acid screening tests and antibody screening tests that have been developed and need to be developed to detect emerging infectious pathogens potentially transmitted via transfusion has grown longer, and new-test implementation has added measurably to the cost of screening the blood supply. Zika virus happens to be the latest pathogen to threaten blood safety, but others will undoubtedly follow over the coming years. As certain of these pathogens emerge rapidly, they initially cause disruption to the blood collection system because of the donor deferrals that must be implemented while screening tests are developed. Widespread or universal implementation of robust pathogen-reduction technology for all blood components could remarkably change this reactive blood safety paradigm. At this time, there are FDA-approved devices for use in the preparation of plasma and platelets only, and whole blood and red blood cell pathogen-reduction technologies are under investigation [13]. Since existing pathogen-reduction technologies act on nucleic acids, suitably robust methods should protect the blood supply against the large majority of existing and emerging pathogens. Although the protection derived from implementing pathogen-reduction technologies would initially come at a high cost, over time, the reduction in the need for blood donor screening tests could potentially more than make up for this added cost.

In the meantime, as blood donor screening tests for Zika virus are developed and implemented and pathogen-reduction technologies for whole blood and red blood cells are further evaluated, the FDA will work with its federal partners to address the emergence of Zika virus and to protect public health. Making use of lessons learned from previous outbreaks of infections with West Nile virus, dengue viruses, chikungunya virus, and other pathogens, the FDA will do whatever it

can to ensure the safety of the blood supply while facilitating further development of pathogen-reduction technologies as a more universal approach to emerging pathogens.

## Note

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