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Original Article

Zika Virus and the Blood Supply: What Do We Know?

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ABSTRACT

Zika virus (ZIKV), a mosquito-borne *Flavivirus* and emerging infectious disease, is the focus of an international public health emergency after its rapid spread through the Americas and the Caribbean. Although most ZIKV infections are subclinical or characterized by mild febrile illness, ZIKV has been implicated in severe complications, most notably microcephaly in babies born to incident infected mothers during pregnancy. As yet, the extent to which ZIKV is transfusion transmissible remains undefined. Nonetheless, a high prevalence of asymptomatic infection during outbreaks, the demonstration of ZIKV in blood donors, and 4 possible cases of transfusion-transmitted ZIKV in Brazil have raised concern for risk to the blood supply. Consequently, a proactive response is underway by blood collection agencies, regulatory bodies, national funding agencies, and industry alike. Mitigation strategies differ between endemic and nonendemic areas. In the continental United States, the American Association of Blood Banks and Food and Drug Administration guidelines recommend travel-based deferral for those returning from affected areas, and nucleic acid testing is being initiated under an investigational new drug application in Puerto Rico and selected areas of the United States. Options are less clear for countries where autochthonous vector–borne transmission is active. The burden of Zika falls in low-resource countries where high cost and technical barriers associated with testing and pathogen reduction pose barriers to implementation. Additional strategies include maintaining selective inventory for high-risk recipients (eg, pregnant women). We review the available data as of July 2016 on ZIKV in relation to the blood supply including risk, mitigation strategies, and barriers to implementation in addition to the research that is needed to address current uncertainty.

Contents

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Zika virus (ZIKV) is a mosquito-borne *Flavivirus* that is the focus of an international public health emergency after its rapid expansion through the Pacific and Americas and its implication in severe infant morbidity and mortality due to infection in pregnancy [1]. As of July 22, 2016, 56 countries or territories have reported locally transmitted ZIKV infections within the past 9 months [2], and an estimated 3 to 4 million people may be infected by the end of 2016 [1]. Cases of imported ZIKV infection have been described in countries that are still naive to autochthonous vector–borne transmission; this raises concern for further spread where competent vectors are already established (eg, *Aedes aegypti* and *Aedes albopictus* in the United States). Although congenital and sexual transmissions are now well described, evidence of transfusion-associated risk (infection and disease) is still preliminary. Nonetheless, ZIKV RNA has been detected in blood donors, and 4 likely cases of transfusion-transmitted ZIKV have been described [3]. Collectively, this has prompted a proactive response that has enlisted the support of blood collection agencies, regulatory and public health bodies, national funding agencies, and industry alike. Nonetheless, a balanced perspective is needed to guide decision making and allot resources appropriately.

Methods

A literature search was conducted as follows: PubMed and Medline databases were searched using a combination of the following terms: "Zika virus," "transfusion," "blood safety," "blood supply," "blood donor," "transfusion-transmission," "Dengue," "West Nile," "Chikungunya," "pathogen inactivation," "pathogen reduction" either alone or in combination. The search was extended to the Google Scholar database and included relevant data from the World Health Organization, Pan American Health Organization, Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control, Food and Drug Administration (FDA), and American Association of Blood Banks (AABB). Additional information (including unpublished data) was identified through direct contact with experts in the field as well as attendance at symposia (eg, AABB Zika Symposium, Washington, DC, June 10, 2016). The search was confined to English-language publications.

A total of 491 articles were identified using a combination of search terms, of which 225 were deemed relevant. After a thorough review of the full-text publications, a total of 80 articles fulfilled selection criteria and were included in this review. A total of 24 articles were identified relevant to Zika and the blood supply. Of these articles, 5 were original research studies, and the remaining were review articles (Table 1). This review incorporates available data that were reported up to and including July 22, 2016.

History and Epidemiology

Zika virus is an enveloped, icosahedral, single-stranded RNA virus belonging to the genus *Flavivirus*, family Flaviviridae. It is closely related to other flaviviruses of public health relevance including dengue virus (DENV), yellow fever, and West Nile virus (WNV) [4]. It was first identified in 1947 in rhesus monkeys in the Zika forest, near Lake Victoria in Uganda [5,6]. From its first description until 2007, only rare sporadic human cases were reported in Africa and Asia [7-9]. In April 2007, the first major ZIKV outbreak outside Africa and Asia occurred on the island of Yap in the Federated States of Micronesia. Although the outbreak was brief (~3 months), there is serologic evidence that 70% of the islands inhabitants were infected with the virus [8], demonstrating the high infectivity of ZIKV and its potential as an emerging infectious disease.

In October 2013, another major outbreak was recognized in French Polynesia. Subsequently, ZIKV spread to New Caledonia, the Cook Islands, and later to Easter Island [10]. The current ZIKV outbreak in the Americas began in early 2015 in Brazil. By October 2015, 56 318 suspected cases of ZIKV had been reported in Bahia, a state in northeast Brazil. The exact number of ZIKV cases is unknown; however, the Brazilian national authorities' estimate that up to 1.5 million (population of 200 million) cases of ZIKV infection have occurred since the outbreak began [11]. Furthermore, the outbreak has heralded continued spread to other countries and territories in South and Central America and the Caribbean. As of May 7, 2016, Colombia had reported the second largest outbreak of ZIKV with 80 793 (population of 48 million) reported cases in the 8 months since the country's first cases were described [12].

From 2007 up to the time of writing (July 22, 2016), vector-borne transmission has been documented in a total of 65 countries and territories [13]. Furthermore, imported cases have occurred in countries where autochthonous vector–borne transmission has not been described; most of these infections were acquired through travel to affected countries. For example, from 2015 to July 2016, a total of 1403 people in the continental United States were diagnosed with travel-related ZIKV; those infected were distributed across 47 states and Washington, DC [14] and include 400 pregnant women [15] and 15 cases of sexual acquisition [14]; 1 case of laboratory-acquired ZIKV has also been reported [14]. Complications that have been reported in the United States include 5 cases of Guillain-Barré syndrome (GBS) [14] and 3 cases of microcephaly [16-18]. This likely underestimates the true number of infected individuals among returning travelers to the United States given the high proportion of subclinical or mild infection. However, this may change given increased awareness and education, availability of diagnostic assays, and recommendation for diagnostic testing [19], along with ZIKV's designation as a nationally notifiable disease as of January 2016 [20].

Routes of Transmission

Zika virus is transmitted by the *Aedes* mosquitoes, of which *A aegypti* is considered the most common vector given its widespread distribution in the tropics and subtropics [21]. *Aedes* mosquitoes are also vectors for DENV and Chikungunya virus (CHIKV). Furthermore, both *A aegypti and A albopictus* are widespread in the United States, raising concern for ZIKV spread if introduced [22-24].

Zika virus has a sylvatic nonhuman primate cycle of transmission (mosquito-monkey-mosquito cycle) [25]. However, like DENV, humans can act as reservoirs for the virus after the bite of an infected mosquito; in so doing, humans serve as the primary vertebrate host in urban settings [25,26].

Despite there being competent vectors in the United States, the potential scale of an epidemic is unlikely to match that observed in Central and South America. Specifically, the United States has comparatively low rates of urban crowding, ubiquitous use of screens, air conditioning, and improved waste management. This was highlighted by a study, which demonstrated markedly different seroprevalences of DENV in 2 contiguous cities that straddled the US-Mexico border [27]. Furthermore, the United States has an established an ongoing arbovirus surveillance system (ArboNET), thus enabling early intervention using vector control (ie, reduction of breeding sites and use of pesticides/biological methods to control both mosquito larvae and adult mosquitoes) and public education [28].

The first case of sexual transmission of ZIKV was reported to occur in 2008: an American scientist transmitted ZIKV to his wife after his return to the United States after working in Senegal [29]. There are currently 15 reported cases of sexual transmission in the continental United States, several of which relate to pregnant women [14]. Importantly, ZIKV RNA has been reported to persist in semen up to 62 days after onset of febrile illness [30]; however, it is still unknown how its persistence correlates with rates transmissibility and how this might contribute to the broader epidemic; nonetheless, this is of particular concern for sexual partners of travel-related infection in nonendemic areas who are trying to conceive or already pregnant. In the majority of all known cases of sexual acquisition, transmission occurred from a male to his female or male sex partner [31,32]; thus far, only 1 case of transmission has been reported from an infected women to her male partner [33].The