Zika virus: new emergencies, potential for severe complications, and prevention of transfusion-transmitted Zika fever in the context of co-circulation of arboviruses

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Dear Sir,

We read with great interest the review article entitled "Zika virus and the never-ending story of emerging pathogens and transfusion medicine" by Marano *et al.*[1] This paper reviews data about Zika virus (ZIKV), an emerging arthropod-borne virus (arbovirus) with a special focus on its potential impact on blood transfusion. We would like to add complementary data to this manuscript about the spread of ZIKV, complications of Zika fever, and prevention of transfusion-transmitted Zika fever by nucleic acid testing (NAT) and pathogen inactivation (PI) in the setting of co-circulation of arboviruses.

As described by Marano *et al.*, autochthonous transmission of ZIKV in the Pacific was reported in Yap State, French Polynesia, New Caledonia, Cook and Easter islands. In 2015, ZIKV also emerged in Vanuatu, Fiji, Solomon and Samoa[2]. ZIKV was first detected in Brazil in May 2015 and subsequently spread in the Americas and re-emerged in Africa (Cape Verde)[2]. As of early February 2016, 31 countries and territories in the Americas, Caribbean, Pacific, Asia and Africa had reported active ZIKV circulation in the preceding 2 months[2]. In the Pacific area, ZIKV co-circulates with dengue (DENV) and chikungunya (CHIKV). The situation is more complex in some regions of the Americas because, in addition to DENV and CHIKV, ZIKV co-circulates with other arboviruses (such as those causing yellow fever, Mayaro fever, Oropouche fever), and some transfusion-transmissible bacteria and parasites (principally those causing American trypanosomiasis and malaria).

In most cases, ZIKV does not cause symptoms or is responsible for a mild disease. However, severe neurological complications were reported during the French Polynesian outbreak; the incidence rate of Guillain-Barré syndrome was approximately 20-fold higher than the established incidence rate of the syndrome in that country, and an increase in Guillain-Barré syndrome has now been reported in several American countries[2]. In October 2015, the Brazilian Ministry of Health reported a 20-fold increase in the incidence of microcephaly among neonates and, in November, declared a public health emergency in response to the dramatic increase over the expected incidence of microcephaly in some Brazilian states[2]. Contemporaneously, in November 2015, the Health Authority of French Polynesia also reported an increase of central nervous system malformations in foetuses and infants during 2014-2015[2]. The situation is rapidly deteriorating and, in early February 2016, the World Health Organisation declared a global heath emergency[2].

Transfusion-transmitted arboviruses are a challenge for blood transfusion. Possible preventive measures include NAT and pathogen inactivation. During the French Polynesian ZIKV outbreak in 2013-2014, we implemented both ZIKV NAT, using in-house tests, and a PI system based on amotosalen-ultraviolet A (UVA) illumination, which is licensed in France[3]. As ZIKV was co-circulating with DENV serotypes 1 and 3, we also performed NAT for DENV, in addition to NAT for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. In late 2014, after the ZIKV epidemic, a large CHIKV outbreak occurred in this country and we added CHIKV NAT to the previously mentioned NAT assays. NAT of blood donors' samples can be performed routinely in areas in which a single arbovirus is in circulation and when a licensed commercial test is available, as was done for West Nile virus in North America. In the setting of co-circulation of several arboviruses, testing all new pathogens requires the development and implementation of multiple licensed blood screening tests or preferably a cost-effective multiplex assay (including ZIKV, DENV and CHIKV) that can detect several arboviruses in the same reaction and can resolve the individual pathogen responsible for the infection. Home-made tests, such as the ones we employ in emergencies, are expensive and inconvenient.

In the meantime, PI can be used as an important safety measure. This strategy was found promising in the recent chikungunya epidemic in the French Caribbean, where contaminated blood products (identified after transfusion) that had been treated with amotosalen-

*Blood Transfus 2017; **15**: 272-3* DOI 10.2450/2016.0003-16

UVA illumination did not produce any evidence of post-transfusion infection in the ten recipients[4].

As an update to the manuscript by Marano *et al.*[1], we would like to highlight that inactivation of ZIKV by amotosalen-UVA illumination has recently been demonstrated[5]. Amotosalen combined with UVA light inactivated ZIKV in fresh-frozen plasma by 6.57 $\log_{10}$ $TICD_{50}$/mL for infectious particles and 10.25 $\log_{10}$ copies/mL for viral RNA. The magnitude of inactivation capacity in RNA load was higher than that found in 26 ZIKV-infected but asymptomatic French Polynesian blood donors (ranging from 3.40 to 6.91 $\log_{10}$ RNA copies/mL)[5]; amotosalen and UVA illumination could, therefore, inactivate viral loads typically found in asymptomatic donations. Since PI by amotosalen and UVA light was previously shown to inactivate other arboviruses such as DENV, CHIKV, and West Nile virus, it is now confirmed that this process is effective for the currently circulating arboviruses in plasma.

With regards to the rapid spread of ZIKV, the potentially severe complications of Zika fever, and the two possible cases of transfusion-transmission in Brazil[6], all countries with competent vectors for ZIKV (mosquitoes of the *Aedes* species), especially American and Caribbean countries, should be prepared for the introduction of this virus. Regarding blood donations, the European Centre for Disease Prevention and Control[2] and the Food and Drug Administration[6] issued recommendations to prevent transmission of ZIKV by blood transfusion. In areas without active circulation of ZIKV, the main recommendation is deferral of blood donors at risk of ZIKV infection. In areas with active ZIKV circulation, the main recommendations are to supply blood banks with blood products collected in areas without active circulation of ZIKV, or, if blood products are collected locally (especially for at-risk recipients: pregnant women and foetuses given intrauterine transfusion), deferral of blood donors at risk of ZIKV infection (although in endemic areas the whole population is at risk, except those people who have had ZIKV infection in the past), implementation of PI for platelets and plasma, use of NAT when a licensed test becomes available, and post-donation follow-up.

The rapid spread of ZIKV highlights the need to demonstrate the efficacy of PI when a new pathogen with the potential to be transmitted by blood transfusion emerges, as was done for ZIKV with amotosalen and UVA during the French Polynesian outbreak and to develop new NAT assays. In the context of global emergence of new pathogens, it also highlights the need to have PI technology suitable for inactivating pathogens in red blood cells or whole blood.

Disclosure of conflicts of interest

AS and JG are collaborating with Cerus Corporation, USA, in the field of research on pathogen inactivation.

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Arrived: 3 January 2016 - Revision accepted: 9 March 2016
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