Working document

Provisional recommendations for blood services in light of the Zika virus epidemic:

Potential impact on the spread of the infection and on the availability and safety of blood and blood components

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Methodology

This document was prepared with the collaboration and consensus of experts in transfusion medicine, based on recommendations from the 2014-2019 Regional Plan for Universal Access to Safe Blood (CD53.R6), the WHO 2008-2015 Strategy for the Safety and Availability of Blood, PAHO/WHO standards, and internationally published reference materials.

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Abbreviations

Abbreviation of Zika virus: ZIKV

I. INTRODUCTION

Human beings are often dead-end hosts for many identified arboviruses as they do not develop sufficient viremia to infect the vectors. However, West Nile virus, dengue, chikungunya, and Zika virus are important exceptions, since infected humans achieve a level of viremia that allows them to become the main vertebrate hosts in urban areas.[1]

ZIKV is spreading rapidly in the Americas and is considered a serious threat to health in our Region and globally.

Blood-borne transmission of a virus which is causing a public health emergency of international concern (PHEIC) means that preventive measures must be taken at blood banks. However, it is important to note that there is still insufficient clinical and scientific evidence to conclusively state that this virus is causing the neurological disorders attributed to it.

ZIKV, a *flavivirus*, is transmitted by mosquitoes of the *Aedes* genus and was isolated for the first time in 1947 in Rhesus monkeys in the Zika Forest of Uganda. Human infection was initially demonstrated by serological studies in Uganda and Tanzania in 1952, and the virus was isolated from human samples in Nigeria in 1968.[2]

The first autochthonous case in the Americas was reported in February 2014 by the Ministry of Health of Chile (Easter Island)[3], and since February 2015 a significant increase in the number of cases has been confirmed by the Ministry of Health of Brazil.[4] Since 2015 many countries and territories in the Americas have confirmed autochthonous circulation of Zika virus. http://www.paho.org/hq/index.php?option=com_content&view=article&id=11585&Itemid=41688&lang=en

Based on these various findings, since 7 May 2015 the Pan American Health Organization has published three epidemiological alerts (May, November, and December 2015),[2,5,6] and two epidemiological updates (October 2015 and January 2016).[7,8]

II. ZIKV INFECTION

1. Clinical considerations

After a bite from an infected mosquito, symptoms of the disease usually appear following a three- to twelve-day incubation period. Fatal cases rarely occur. Infection can be asymptomatic (70-80% of cases) or occur with the following clinical presentations[7]:

Table 1. Symptomatology of ZIKV infection

Main symptoms of Zika virus infection	
Fever between 37.2° C and 38° C	Myalgia and/or arthralgia
Pruritic maculopapular rash*	Malaise
Non-purulent conjunctivitis	Edema in limbs (hands and feet)
Headache	
Less frequent symptoms	
Retro-orbital pain	Anorexia
Vomiting, diarrhea	Abdominal pain

* This is one of the most distinctive symptoms of ZIKV infection; it should be taken into account for diagnosis and recorded in the clinical history. Symptoms last from four to seven days and tend to be self-limiting.[2]

In some countries of the Region where ZIKV is circulating, there are reports of an increase in neurological problems such as Guillain-Barré syndrome (GBS), meningoencephalitis, myelitis, and others. Although their causal relationship to ZIKV has not yet been established, this hypothesis cannot be ruled out.[7]

2. Diagnosis

The steps for diagnosis are set forth in PAHO's Epidemiological Update of 16 October 2015.[9]

2.1 Clinical diagnosis is suspected when one or more of the symptoms described above are present. Suspicion is stronger if in the past few days the patient was in an area where the vector is present, and it is even stronger if cases of ZIKV have been confirmed in that area. That is the strongest criterion for establishing a presumed diagnosis of ZIKV infection.

2.2 Differential clinical diagnosis is established in light of other infections that cause rash and fever, particularly *flavivirus* infections such as dengue, chikungunya, or West Nile virus, among others.

2.3 Confirmation of diagnosis requires a local or reference laboratory to perform the tests described below.

2.3.1 Virological diagnosis consists of identifying the viral nucleic acid through **reverse transcription followed by polymerase chain reaction (RT-PCR).** Selection of the type of sample to use is determined by the time that has elapsed since the onset of symptoms. The RNA of the virus can be found in serum until some five days after the onset of symptoms, while it can be found in urine for a few days longer. The RNA of the virus can also be detected in saliva or urine samples collected during the first three to five days from the onset of symptoms.

2.3.2 Serological diagnosis detects ZIKV-specific anti IgM antibodies through ELISA or immunofluorescence assays, starting five days after the onset of symptoms. Interpretation of the serological tests is especially relevant for ZIKV diagnosis. In primary infections (first infection with a *flavivirus*) cross-reactions with other genetically related viruses have been shown to be minimal. However, the sera of individuals with a history of previous flavivirus infection (especially dengue, yellow fever—including its vaccine—and West Nile virus) can cross-react.

More information can be found in: Pan American Health Organization, Zika Virus Surveillance in the Americas: Interim guidance for laboratory detection and diagnosis, http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=&gid=30176&lang=en

III. SAFETY OF BLOOD, BLOOD COMPONENTS, AND BLOOD PRODUCTS

Given the introduction of ZIKV in the Americas and its possible transmission through blood, blood components, and blood products, PAHO/WHO is contemplating the preparation of a document offering recommendations for the Region's blood supply system.

The risk has yet to be clearly established and further evidence is needed. However, in a study conducted in French Polynesia in the South Pacific, where a large outbreak of ZIKV infection occurred (28,000 estimated cases from November 2013 to February 2014—11% of the population), 42 people tested positive for the virus among 1,505 blood donors who were asymptomatic at the time of donation (3%). In order to avoid transmission through transfusion, several preventive procedures were established, including nucleic acid tests (NAT). The foregoing demonstrated that transfusion transmission of ZIKV is feasible. Among the positive blood donors, 11 of them (26.2%) reported having "fever similar to that of ZIKV 3-10 days after donating blood."[10]

The health authorities of Brazil have confirmed the first case of possible transfusion transmission of the virus.[11] The donor experienced symptoms three days after donating, whereas the recipient did not develop symptoms. Genetic sequencing tests on the viruses in the donor and the patient suggest a high likelihood of transfusion transmission.[12]

However, studies to assess the real prevalence of the virus and transmission through blood transfusion and through blood products are needed. Knowledge must also be expanded regarding possible reactions in recipients of these products.

IV. ZIKA'S IMPACT ON BLOOD SUPPLY SAFETY:

In order to reduce the risk of transfusion-transmitted infection, adoption of the guidelines in the 2014-2019 Plan of Action for Universal Access to Safe Blood is a priority. These will help strengthen national blood programs in the following ways:

1. Organize blood services well and concentrate processes;
2. Implement quality management programs throughout the transfusion chain and ensure GMP;
3. Ensure that blood donation is voluntary and repeatedly comes from low-risk populations, and that mandatory replacement donation is eliminated;
4. Ensure the appropriate use of blood and blood products;
5. Provide continuous training for blood services staff and blood products users; and
6. Provide health surveillance, hemovigilance, and risk management.

There is no doubt that the specific measures recommended to prevent ZIKV infection can only be properly implemented if they are a central part of the strategy.

Furthermore, to ensure blood supply availability, the following specific interventions are recommended in both affected and unaffected areas:

1. Affected areas:

a. Donors:

a.1 Deferral. Donors who during the pre-donation interview report having had a confirmed clinical or laboratory history of ZIKV during the previous 28 days, or who say they are currently experiencing hyperthermia or another two or more potential ZIKV symptoms (maculopapular erythema, muscle pain, conjunctivitis, etc.), should be deferred until 28 days after disappearance of the symptoms. It is also recommended that those who live in a household with people who have ZIKV, dengue, or chikungunya, should refrain from donating blood.

Deferral measures are important, despite the small impact they may have on reducing infection.

a.2 Post-donation information. Blood banks should provide information to donors on ZIKV infection, and encourage them to report any symptoms they might develop up to 14 days after donating blood. A blood bank that receives a report that a unit of blood collected came from a donor who subsequently had a clinical and/or laboratory diagnosis of ZIVK, should recall that unit and discard all unexpired products that were collected from that donor during the 14 days prior to onset of symptoms.

a.3 Counseling. All donors who are deferred due to the risk of transmitting ZIKV

infection should receive information on donor behavior and how to avoid spreading the virus in their communities.

b. Patients: It is important to monitor patients who receive transfusions from donors who develop symptoms or receive a laboratory diagnosis of ZIKV. It is recommended that hemovigilance be stepped up for transfusion patients who receive a clinical or laboratory diagnosis of ZIKV, in order to better understand the physiopathology of the disease and transfusion risk.

c. Laboratory: NAT should be conducted on donors for specific categories of patients (such as pregnant women) where possible. However, this will be very difficult to implement in our Region as the appropriate reagents (designed for blood banks) are not available.

d. Viral inactivation of the components: only applicable to plasma and blood platelets.

e. Quarantine of donated components: This measure is relevant in affected areas even though only 20% of those infected develop symptoms. Implementation of a 14-day quarantine period before release of blood products should be considered, to ensure that the donor does not develop ZIKV symptoms. Such a measure could prevent the transfusion of infected units.

f. Have an alternative blood supply (from unaffected areas, if possible). The capture, donation, and processing of blood from non-endemic or less affected areas should be increased, to supply blood banks experiencing critical shortages of safe blood.

It is essential that quarantine and alternative blood supply measures be implemented in response to the critical situation, and not to the blood supply. Each country, region, or city should establish measures tailored to the local epidemiological situation, and assess whether it is possible to use nucleic acid amplification tests or pathogen inactivation procedures for pregnant women and those who are immunosuppressed.

2. Unaffected or less affected areas:

a. Strengthen the capture, donation, and processing of blood in unaffected or less affected areas, to supply blood banks experiencing critical shortages of safe blood;
b. Defer donors who have visited affected areas for 28 days;
c. Conduct dissemination campaigns on ZIKV infection and issues related to the importance of blood donation; and

d. Monitor the status of the epidemic in the country to confirm whether the affected area is expanding.

For both affected and unaffected areas, it is important to consider that most people with ZIKV infection do not have clear symptoms, while 20% of those infected may have symptoms of mild illness lasting up to one week. This means that it is important to conduct a thorough interview prior to donation.

It is essential for blood banks to educate their personnel so that they are prepared to follow the recommended procedures, and incorporate them into the operational procedures manual that staff use when dealing with donors.

It is imperative that the national blood services have educational material incorporating the above recommendations.

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