Maintaining a safe and adequate blood supply during Zika virus outbreaks

Interim guidance

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1. Introduction

1.1 Background

These guidelines have been developed in recognition that infection with Zika virus may present a risk to blood safety, and in consideration of the declaration on 1 February 2016 by the WHO Director-General of a Public Health Emergency of International Concern with regard to clusters of microcephaly and other neurological disorders, potentially associated with Zika virus. Currently there is limited knowledge of Zika virus biology and lack of definitive evidence of a link between infection and potential complications. These guidelines will be regularly reviewed and updated as new information becomes available.

Zika virus is a mosquito-borne flavivirus, related to dengue. It is transmitted to humans through the bite of an infected mosquito from the *Aedes* genus. This mosquito also transmits dengue, chikungunya and yellow fever viruses [23].

Zika virus infection is followed by an incubation period prior to the development of clinical symptoms, which occur in only a minority of infected individuals. Asymptomatic infections are common, as described for other flaviviral infections such as dengue and West Nile fevers. It has been reported that only one in five individuals infected with Zika virus develops symptoms [4, 13]. The symptoms of Zika virus infection are similar to those of other arboviruses such as dengue, and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms are usually mild and typically last for 2–7 days. The incubation period is likely to be a few days to a week [4, 24], with some publications suggesting that it may be as long as twelve days [9]. Zika virus RNA has been detected in blood, urine, and saliva during the acute phase of the disease, and in seminal fluid after acute illness; infectious virus was detected in semen more than two, and possibly up to ten weeks, after recovery from clinical symptoms of Zika virus infection, and probable cases of sexual transmission have been described [7, 8, 14, 15].

A link between Zika virus infection during pregnancy and microcephaly in neonates is suspected and currently being investigated for causal association [12, 21]. An association of Zika virus with Guillain-Barré syndrome (GBS) and other autoimmune neurological complications was suspected during a 2013–2014 outbreak in French Polynesia and remains under investigation [6, 16].

During the Zika virus outbreak in French Polynesia between November 2013 and February 2014, a total of 1,505 healthy blood donors were tested by nucleic acid amplification technology (NAT) -based assays, with 42 (2.8 %) confirmed positive for Zika virus RNA. Blood donors positive for Zika virus RNA were contacted retrospectively to investigate the occurrence of 'Zika fever-like syndrome' (rash and/or conjunctivitis and/or arthralgia) after their blood donation. Of the 42 donors that tested positive, 11 declared that they had a Zika fever-like syndrome from 3–10 days after they gave blood. No transmission of Zika virus through transfusion was documented in this study [3, 13]. However, transmission of related flaviviruses (dengue and West Nile viruses) by blood transfusion has been documented [2, 18, 22]. Recently two probable cases of Zika virus transmission by blood transfusion have been reported from Campinas, Brazil [19].

1.2 Target audience

This guidance is intended for use by national health authorities and blood transfusion services, to provide a generic basis on which guidelines applicable to their own circumstances and local context may be developed.

2. Maintaining safe and adequate blood supplies in countries with ongoing Zika virus transmission

2.1 Ensuring blood supply through reinforcing blood collection in non-affected areas

Blood supply during a Zika virus outbreak should ideally be maintained by increasing blood collections in non-affected areas. In non-affected areas, consideration may be given to defer donors who have recently visited areas with ongoing transmission of Zika virus for a period of 28 days after their departure from the area (twice the assumed maximum incubation period [9]). It is crucial that public health authorities work with the blood transfusion service (BTS) to establish mechanisms to access regular, up-to-date

epidemiological information on Zika virus transmission in the country.

Effective public awareness campaigns on the need for blood donation, and education and motivation of potential blood donors are important elements in low risk areas, along with strategies to appropriately defer donors recently exposed to Zika virus in an affected area.

2.2 Measures to reduce risk to blood supply in areas with active transmission

Blood collection may need to continue in affected areas during a Zika virus outbreak in order to ensure ongoing and timely access to sufficient blood and blood components. This may be necessary when an outbreak affects most of or the entire country, or when it is logistically impossible to source blood from non-affected regions of the country.

The following measures for reducing the risk of Zika virus transmission through transfusion may be considered in areas with active Zika virus transmission.

a. Temporary donor deferral

The following donors should be deferred for a period not less than 28 days following the full resolution of symptoms:

i. donors with confirmed recent Zika virus infection; and

ii. donors with a recent clinical history consistent with Zika virus disease, for example a combination of fever or rash with conjunctivitis, or arthralgia, or headache or malaise [17].

Sexual partners of men with confirmed or suspected Zika virus infection in the last three months should be deferred for 28 days after their last sexual contact.

Blood donors must be informed and encouraged to provide post-donation information and asked to report to the BTS if they subsequently become unwell with signs and symptoms suggestive of Zika virus infection, or if diagnosed with Zika virus infection within 14 days after blood donation. Implicated blood components that have not been transfused should be recalled. Tracing of patients who have already received blood or blood components from implicated donations should be performed, and evidence for transfusion-related transmission collected.

b. Testing of blood donations

Blood donations may be tested for the presence of Zika virus by appropriate tests.

Viral RNA is the first detectable marker in Zika virus infection. NAT-based tests are therefore the most appropriate for donor screening. However, there are currently no commercially available NAT assays for Zika virus RNA detection designed to screen blood donors. Sensitive NAT tests designed for diagnostic purposes may be used for small-scale screening of blood donors after respective validation. In-house developed NAT tests may also be suitable, but should be properly validated for donor screening.

Theoretically, viral antigen is another marker potentially detectable in the viraemic period of incubation and during asymptomatic infections. However, antigen tests are generally associated with lower sensitivity when compared to NAT, and commercial Zika virus antigen tests are not yet available. Zika virus antibodies become detectable at the later stage of infection and are not estimated to be indicative for active infection. A potential problem is the cross reactivity of antibodies against related flaviviruses (e.g. dengue, yellow fever) in anti-Zika virus assays.

WHO is currently working on the provision of international reference preparations for Zika virus RNA and for Zika virus antibodies to be used for comparative evaluation of both diagnostic and screening assays.

c. Pathogen reduction of blood components

Pathogen reduction technology (PRT) may be implemented. PRT is currently available for plasma and platelets, but not for whole blood or red blood cells. Different PRTs have been shown to be effective against other flaviviruses (e.g. West Nile, dengue) [10,11,20] and, in the absence of Zika-specific information, are presumed as equally effective against Zika virus.

d. Quarantine of blood components

Blood components of appropriate shelf-life (e.g. red blood cells) may be quarantined for a period of 7–14 days, and subsequently released following confirmation from the donor that they have not experienced symptoms consistent with the acute phase of Zika virus infection during the quarantine period. Despite the majority of Zika virus infections taking an asymptomatic course, this measure could prevent at least a proportion of viraemic blood components from being transfused. As platelets are characterized by a more restricted shelf-life, a quarantine period of three days may be considered.

2.3 Selecting an appropriate risk-reduction strategy

The decision to stop donation activities in affected areas or to proceed with appropriate risk-reduction strategies should be based on epidemiology and risk assessment. In addition, a number of factors should also be taken into consideration in decision-making [1].

Donor deferral to reduce the risk of transmission of Zika virus has low sensitivity and specificity. The sensitivity of donor deferral procedures is a particular problem due to the high rate of asymptomatic infection [13].

Implementation of additional testing is expensive and is likely to be difficult for some countries. Development, validation and implementation of in-house developed RNA

tests will be challenging, particularly for countries with limited BTS laboratory infrastructure or capacity.

Pathogen reduction technology involves additional steps in processing which could lead to possible delays in release of components. Its impact will be very limited when most transfusions are whole blood or red cells. The benefit of this technology should be balanced against both cost and the overall risk of Zika virus infection in the area.

Quarantine of blood components is sometimes already in place for other pathogens, such as chikungunya. This measure could thus be easily adapted to quarantine for Zika virus infection. A quarantine period of 7–14 days for red blood cells is proposed, based on the limited scientific data currently available regarding the incubation period of Zika virus infection; however, a quarantine measure is expected to be less effective for Zika virus infection due to the relatively high proportion of asymptomatic infections.

2.4. Potential high-risk blood recipient groups

According to current evidence, Zika virus infection in pregnant women may be potentially associated to severe complications for the pregnancy and fetus. Until more is known and based on precautionary principles, risk-reduction strategies should be applied to pregnant women and other groups who may be at higher risk of severe complications following Zika virus infection.

3. Measures for blood transfusion services in countries without active Zika virus transmission

In countries without active Zika virus transmission, consideration may be given to the temporary deferral of potential donors who have recently visited areas or countries with ongoing Zika virus transmission, for a period of 28 days (twice the assumed maximum incubation period) after their departure from the affected area. A temporary deferral also should be considered for sexual partners of men previously infected or potentially exposed in the previous three months [15].

In some countries the existing donor deferral policy may already involve temporary deferral of donors who have travelled to countries with mosquito-borne pathogens associated with a transfusion-transmission risk, such as dengue virus or malaria parasites. Thus donors returning from many countries currently affected by Zika virus transmission will already be deferred by a pre-existing temporary donor deferral policy. Countries with many visitors to affected countries may need to assess the impact of deferral on blood supply availability and weight the risk-benefits of implementing this measure. Selective testing of blood donors returning from affected countries may be considered as an alternative to deferral.

BTS in all countries should monitor epidemiological information and strengthen haemovigilance to identify any potential transfusion transmission of Zika virus. It is recommended that countries with a likelihood of future Zika virus transmission (e.g. countries with *Aedes* mosquitoes) consider developing a preparedness plan to ensure maintaining safe and adequate blood supplies during a period of Zika virus transmission.

4. Guidance development

4.1 Acknowledgements

This interim guidance has been jointly developed by the WHO Departments of Service Delivery and Safety (SDS) and Essential Medicines and Health Products (EMP) Geneva and the WHO AMRO Medicines and Health Technologies, Health Systems and Services (MT/HSS).

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4.2 Guidance development methods

Drafts of this interim guidance were developed by WHO and circulated for feedback to external experts with recognized expertise and interest in the field, including members of the Blood Regulatory Network (BRN), Ibero-American collaborative group of transfusional medicine (G-CIAMT) and Ministries of Health/National Blood Programmes in affected countries.

There is currently limited available evidence on Zika virus biology, incubation period, viraemic period of infection, and causal link with potential severe complications. The evidence on the effectiveness of measures to ensure blood safety and supply during Zika virus outbreaks is limited and recommendations are drawn from best practice during

outbreaks of other mosquito-borne virus diseases (e.g. dengue, chikungunya and West Nile).

4.3 Declaration of interests

No conflicts of interest identified from any of the contributors.

4.4 Review date

These recommendations have been produced under emergency procedures and will remain valid until August 2016, unless revised earlier. The Department of Service Delivery and Safety at WHO headquarters in Geneva will be responsible for reviewing this guideline at that time, and updating it as appropriate to reflect the evolving knowledge base and development and availability of new technologies.

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